

**A RANDOMIZED MULTI-CENTER COMPARISON OF AN  
ULTRATHIN STRUT BIODEGRADABLE POLYMER SIROLIMUS-  
ELUTING STENT WITH A DURABLE POLYMER EVEROLIMUS-  
ELUTING STENT FOR PATIENTS WITH ACUTE ST-SEGMENT  
ELEVATION MYOCARDIAL INFARCTION UNDERGOING  
PRIMARY PERCUTANEOUS CORONARY INTERVENTION**

**BIOSTEMI TRIAL**

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**CLINICAL STUDY PROTOCOL**

**Version 5 – 11.05.2016**

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**Study Categorisation:** Risk category A

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**Investigational Product:** Orsiro® Hybrid DES (Biotronik AG, Bülach, Switzerland)

**Protocol Version and Date:** Version 5 – 11.05.2016

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Study number Study registry and registration number

Study Title A RANDOMIZED MULTI-CENTER COMPARISON OF AN ULTRATHIN STRUT BIODEGRADABLE POLYMER SIROLIMUS-ELUTING STENT WITH A DURABLE POLYMER EVEROLIMUS-ELUTING STENT FOR PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

The Coordinating Investigator, co-investigators and trial statistician have approved the protocol version 3, dated 10.02.2016, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Coordinating Investigator: Prof. Dr. Thomas Pilgrim

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Place/Date

---

Signature

**Local Investigator at study site\*:**

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site

Local Investigator

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Place/Date

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Signature

*\*Note:* In multicentre studies, this page must be individually signed by each participating Local Investigator.

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## STUDY SYNOPSIS

<b>Study Title:</b>	A randomized multi-center comparison of an ultrathin strut biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent for patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.
<b>Short Title / Study ID:</b>	BIOSTEMI trial
<b>Protocol Version and Date:</b>	Version 5 – 11.05.2016
<b>Trial registration:</b>	The trial is registered at <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> and Swiss supplementary federal database (SNCTP).
<b>Study category and Rationale</b>	Clinical trials of medical devices risk category A as the devices used for the purpose of the study bear a conformity (CE) marking and will be used in accordance with their indications and instructions.
<b>Sponsor:</b>	Bern University Hospital, Inselspital, Department of Cardiology, 3010 Bern
<b>Objective:</b>	The purpose of the study is to compare the safety and efficacy of a novel biodegradable-polymer sirolimus-eluting stent (Orsiro <sup>®</sup> ) with a durable-polymer everolimus-eluting stent (Xience Xpedition or Xience Alpine <sup>®</sup> ) in a superiority trial among patients presenting with acute STEMI and undergoing primary PCI.
<b>Primary endpoint</b>	Target lesion failure (TLF), a composite of cardiac death, target vessel myocardial infarction (Q-wave and non-Q-wave), or clinically driven target lesion revascularization within 365 days.
<b>Secondary endpoint</b>	<ol style="list-style-type: none"> <li>1. Clinically indicated and not clinically indicated target lesion revascularization (TLR) at 30 days, 1, and 2 years;</li> <li>2. Clinically indicated and not clinically indicated target vessel revascularization (TVR) at 30 days, 1, and 2 years;</li> <li>3. Target vessel failure (TVF) at 30 days, 1, and 2 years;</li> <li>4. Cardiac death at 30 days, 1, and 2 years;</li> <li>5. All-cause death (cardiac and non-cardiac) at 30 days, 1, and 2 years;</li> <li>6. Myocardial infarction (Q-wave and non-Q-wave) at 30 days, 1, and 2 years;</li> <li>7. Definite stent thrombosis at 30 days, 1, and 2 years;</li> <li>8. Definite and probable stent thrombosis at 30 days, 1, and 2 years;</li> <li>9. Device, lesion and procedural success.</li> </ol>
<b>Study design:</b>	<p>Prospective, randomized, multicenter, investigator-initiated, assessor-blind, superiority trial to be conducted at interventional cardiology centers in Switzerland and Italy. Patients with STEMI will be randomized in 1:1 randomization fashion to undergo primary PCI with either an ultrathin strut biodegradable-polymer sirolimus-eluting stent (Orsiro<sup>®</sup>) or a durable-polymer everolimus-eluting stent (Xience Xpedition or Xience Alpine<sup>®</sup>). All patients will be followed for up to 2 years for clinical endpoints.</p> <p>Evidence from a previous trial (BIOSCIENCE) was used in designing the current BIOSTEMI trial and results from the previous trial (BIOSCIENCE) will be combined with the results of the current trial (BIOSTEMI) using a robust Bayesian approach.</p>

<b>Inclusion criteria:</b>	<ol style="list-style-type: none"> <li>1. Age <math>\geq</math>18 years;</li> <li>2. ST-segment elevation acute myocardial infarction, defined as: <ul style="list-style-type: none"> <li>- ST-segment elevation <math>&gt;</math>1 mm in <math>&gt;</math>2 contiguous leads, or</li> <li>- New (or presumably new) left bundle branch block, or</li> <li>- Posterior myocardial infarction with ST depression <math>&gt;</math>1 mm in <math>&gt;</math>2 contiguous anterior leads).</li> </ul> </li> <li>3. Primary PCI occurring within 24 hours of symptom onset;</li> <li>4. Presence of <math>\geq</math>1 acute infarct artery target vessel with one or more coronary artery stenoses in a native coronary artery from 2.25 to 4.0 mm in diameter that can be covered with one or multiple coronary stents.</li> </ol>
<b>Exclusion criteria</b>	<ol style="list-style-type: none"> <li>1. Known allergy to aspirin, Ticagrelor, Prasugrel, Clopidogrel, Sirolimus, Everolimus or contrast media;</li> <li>2. Planned surgery within 6 months of primary PCI, unless dual antiplatelet therapy could be maintained throughout the peri-surgical period;</li> <li>3. Currently participating in another trial before reaching the primary endpoint;</li> <li>4. Missing informed consent or missing consent from an independent physician;;</li> <li>5. Non-cardiac comorbid conditions with life expectancy of less than 1 year;</li> <li>6. Mechanical complication of acute myocardial infarction;</li> <li>7. Acute myocardial infarction due to stent thrombosis.</li> </ol>
<b>Measurements and procedures:</b>	<ul style="list-style-type: none"> <li>• Eligible patients with acute STEMI presenting within 24 hours of symptom onset will undergo primary PCI.</li> <li>• The use of manual or mechanical thrombus aspiration and pre-dilatation of the culprit lesion is left to the discretion of the operator.</li> <li>• The randomly allocated stent has to be implanted in the culprit lesion of the target vessel.</li> <li>• Complete revascularization of all non-culprit lesions within the target infarct vessel has to be performed with the randomly allocated study stent, at the discretion of the operator.</li> <li>• Staged procedures for the treatment of non-culprit vessels are permitted within 3 months with the uniform use of the randomly allocated study stent in all lesions.</li> <li>• Non-culprit vessels treated by the randomly allocated study stent at baseline or during follow-up will not contribute to the primary endpoint.</li> <li>• Dual antiplatelet therapy consisting of acetylsalicylic acid (<math>\geq</math>250 mg loading dose, <math>\geq</math>75 mg qd) and a P2Y<sub>12</sub> receptor inhibitor (Ticagrelor 180 loading dose, 90 mg bd, or Prasugrel 60 mg loading dose, 10 mg qd) according to local STEMI protocol will be prescribed in all patients for 12 months.</li> <li>• Unfractionated heparin will be routinely administered with a minimal dose of 5'000 IU or a dose of 70 to 100 IU/kg to maintain an activated clotting time <math>\geq</math>250 seconds.</li> <li>• The use of glycoprotein IIb/IIIa inhibitors is left to the discretion of the operator.</li> </ul>
<b>Study stent</b>	Orsiro <sup>®</sup> Hybrid DES system with biodegradable polymer (Biotronik AG, Bülach, Switzerland).
<b>Control stent</b>	Xience <sup>®</sup> (Xience <sup>®</sup> Xpedition and Xience <sup>®</sup> Alpine) DES system with durable polymer (Abbott Vascular, Santa Clara, USA).

<b>Number of Participants with Rationale:</b>	1'250 patients (625 per treatment arm) will be enrolled. Patients included in the STEMI subgroup of the BIOSCIENCE trial (n=407) will be included in the primary analysis of the BIOSTEMI trial using a robust Bayesian approach based on individual patient data. A total of 1'657 patients will be finally analyzed in the combined robust Bayesian meta-analyses of both trials.
<b>Study Duration:</b>	<ul style="list-style-type: none"> <li>- The estimated duration for the inclusion period is 12 months.</li> <li>- Patients will be followed-up at 12 months (including ECG and physical examination).</li> <li>- Patients will also be followed-up for clinical endpoints by telephone at 30 days and 2 years.</li> </ul>
<b>Study Schedule:</b>	<ul style="list-style-type: none"> <li>- Initial Enrollment: March 2015</li> <li>- Last Enrollment: December 2017</li> <li>- Last 1 Year Follow-up: January 2019</li> <li>- Last 2 Year Follow-up: January 2020</li> <li>- Study completion: June 2020</li> </ul>
<b>Principal investigators:</b>	<p>Prof. Dr. Thomas Pilgrim (Coordinating Investigator)  Head of Heart Valves Diseases  Department of Cardiology, Bern University Hospital  Address: 3010 Bern, Switzerland  Phone: +41 31 632 21 11  E-mail: thomas.pilgrim@insel.ch</p> <p>Dr Juan F. Iglesias, MD (Co-Principal Investigator)  Invasive Cardiology  Department of Cardiology  Lausanne University Hospital  1011 Lausanne, Switzerland  Phone: +41 79 556 30 84  Fax: +41 21 314 00 13  e-mail: juan-fernando.iglesias@chuv.ch</p> <p>PD Dr Olivier Muller (Co-Principal Investigator)  Invasive Cardiology  Department of Cardiology  Lausanne University Hospital  1011 Lausanne, Switzerland  Phone: +41 79 556 54 96  Fax: +41 21 314 00 13  e-mail: olivier.muller@chuv.ch</p>

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<b>Study centres:</b>	Multi-centre trial, starting with 2 centres in Switzerland and to be expanded to up to 16 interventional cardiology centers in Switzerland as well as 2 in Italy.
<b>Statistical Considerations:</b>	Clinical outcomes from BIOSTEMI subjects (N=1'250) will be combined using a robust Bayesian approach with historical individual subject information from the STEMI subgroup of the BIOSCIENCE trial used as prior information (N=407, henceforth called BIOSCIENCE STEMI). The primary endpoint, incidence rate of target lesion failure at 1 year, will be analysed with log-Poisson models applied to the primary endpoint from BIOSTEMI with a robustified historical prior that incorporate historical information from the BIOSCIENCE STEMI trial. The Rate Ratio (RR) will be reported as the median of the posterior distribution with two-sided 95% Credibility Intervals (CrI). Superiority of BP-SES will be declared if the upper limit of this CrI is $\leq 1$ . The BIOSTEMI trial is powered for superiority on the primary endpoint at 1 year using the robust Bayesian approach as described above. Power calculation was based on a Monte Carlo simulation where historical primary endpoint results of the BIOSCIENCE STEMI patients were included via a Robustified Historical Prior and the new primary endpoints to be acquired from the BIOSTEMI patients were simulated from a binomial distribution. In BIOSCIENCE STEMI trial, a rate ratio of 0.38 was associated to the experimental arm BP-SES. To be conservative, a less pronounced rate ratio of 0.60 was assumed for the BIOSTEMI trial for the present sample size calculation. Thus, we assumed an event rate for the primary endpoint of 4.2% in BP-SES and of 7.0 % in DP-EES in the BIOSTEMI trial. Drop-out rate was assumed to be 5% at 1 year in the BIOSTEMI trial. With a 1:1 allocation ratio and a two-sided $\alpha=0.05$ we found that enrolment of a total of 1'250 patients (625 per arm) in the BIOSTEMI trial would provide over 80% power to detect a rate ratio of 0.60 in the BIOSTEMI trial.
<b>GCP Statement:</b>	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

## ABBREVIATIONS

AE	Adverse Event
BMS	Bare-Metal Stent
CA	Competent Authority (e.g. Swissmedic)
CAD	Coronary Artery Disease
CEC	Competent Ethics Committee
CRF	Case Report Form
DES	Drug-Eluting Stent
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
Ho	Null hypothesis
H1	Alternative hypothesis
ISO	International Organisation for Standardisation
ITT	Intention to treat
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
RHP	Robustified Historical Priors
STEMI	ST-Elevation Myocardial Infarction
SAE	Serious Adverse Event
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization

## STUDY SCHEDULE

STUDY EVENTS	SCREENING	INTERVENTION PERIOD				
		PROCEDURE	POST-PROCEDURE TO HOSPITAL DISCHARGE	30 DAYS ± 7 DAYS	1 YEAR ± 30 DAYS	2 YEARS ± 30 DAYS
Type of contact				Telephone interview	Office visit	Telephone interview
Patient information and Informed consent	X					
Demographics	X					
Medical history	X			X	X	X
Inclusion/exclusion criteria	X					
Physical examination	X				X	
Vital signs: blood pressure, heart rate, weight, height	X	X	X		X	
<sup>1</sup> Laboratory tests: complete blood count, blood chemistry, lipids, glucose	X		X			
<sup>2</sup> Laboratory Tests: CK, CK-MB	X		X			
<sup>3</sup> Laboratory Tests: Troponin	X					
<sup>4</sup> 12-lead ECG	X		X		X	
Randomisation		X				
Coronary angiography		X				
Assessment of the primary endpoint					X	
Assessment of the secondary endpoints		X		X	X	X
Assessment for concomitant medical therapy	X	X	X	X	X	X
Adverse Events and severe adverse event monitoring		X	X	X	X	X

<sup>1</sup> Within 24 hours prior to or immediately after the index procedure.

<sup>2</sup> CK, CK-MB are determined prior to PCI and every 6-8 hours until CK maximum level has been reached.

<sup>3</sup> Troponin T/Troponin I/high sensitive troponin, whichever is clinical routine.

<sup>4</sup> ECG prior to primary PCI, 24 hours post-procedure and at discharge.

## 1. STUDY ADMINISTRATIVE STRUCTURE

### 1.1 Sponsor

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BIOSTEMI is an investigator-initiated study supported by Biotronik AG (Bülach, Switzerland).

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### **1.7 Clinical Event Committee**

The Clinical Event Committee, consisting of cardiologists not participating in the trial, will review and classify all major adverse cardiac events. The members of the Clinical Event Committee will be blinded, i.e. unaware of the patient's treatment allocation and trial results. The Clinical Event Committee will retrospectively determine the percentage diameter stenosis by QCA of all revascularization procedures. The investigator's prospective clinical assessment and the Clinical Event Committee measurement of percentage diameter stenosis will be combined to form the classification of clinically or non-clinically driven target lesion revascularization in the primary endpoint analysis. If the prospective clinical assessment by the investigator is missing, the Clinical Event Committee will make this assessment based on relevant source documents obtained from the clinic.

### **1.8 Data Safety Monitoring Board**

The present study aims at comparing the efficacy and safety of two medical devices with CE marking approval and used according to their respective indications for use. Therefore, a Data Safety Monitoring Board will not be required for the purpose of this trial. Serious adverse events (events leading to serious disability or admission to hospital, life-threatening events or death) will be periodically reviewed and analyzed by the Clinical Event Committee. Members of this Committee will be blinded, i.e. unaware of the patients' treatment allocation, not affiliated with any interventional cardiology site enrolling patients into the trial, not participating in the trial, and will declare any conflicts of interest should they arise. Based on the safety data, the board may request a non-blinded review of the data or recommend modifications to the protocol and advise the Steering Committee.

## 2. ETHICAL AND REGULATORY ASPECTS

### 2.1 Study registration

The trial is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and the Swiss National Clinical Trials Portal (SNCTP).

### 2.2 Categorization of study

The present clinical trial including medical devices (DES systems) comes under the risk category A as the devices used for the purpose of the trial bear a conformity (CE) marking and will be used in accordance with their indications and instructions.

### 2.3 Competent Ethics Committee (CEC)

The responsible local investigator at each site will ensure that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the present clinical study. No changes to the study protocol will be made without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants. Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report will be submitted within one year after study end. Amendments will be reported according to section 2.9 of the present study protocol.

### 2.4 Ethical Conduct of the Study

Due to the particular situation of patients suffering from a heart attack with STEMI and the emergency need for treatment two specific points need to be addressed:

**Vulnerable subjects:** to handle with the emergency requirement for the treatment and to enable the potential inclusion of unconscious patients, a specific informed consent process has been developed, see 2.6.

**Women and potential pregnancy:** patients with STEMI will be treated according to the current ESC guidelines as “emergency treatment with no delay until revascularization”. The use of new generation DES is preferred over BMS as the default option [1]. This treatment is recommended independently of the sex.

- The requirement of a specific pregnancy test prior to a potential inclusion for women in childbearing age (e.g. below 60 years of age, who did not undergo tubal ligation, ovariectomy or hysterectomy and last menstruation within the last 12 months) would *de facto* mean an exclusion of all women below 60 years of age. This would discriminate this specific population group.
- In the BIOSCIENCE trial, 79% of the included patients with STEMI were male. The mean age of women with STEMI was 68.8 (standard deviation 12.9, range 36.3-88.1). The likelihood of the potential inclusion of a pregnant woman is extremely low.
- A pregnancy may only affect the medical treatment for congestive heart failure potentially resulting from myocardial infarction. This medication is independent from the BIOSTEMI trial and is left to the discretion of the treating cardiologist.
- Previous trials were also conducted without such a specific exclusion criteria<sup>1,2</sup>.

For these reasons and to prevent a bias in the trial, pregnancy is not an exclusion criteria.

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

### 2.5 Declaration of interest

The principal investigators and co-investigators of the study have no conflict of interest to disclose in relation with the present clinical trial.

### 2.6 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved,

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<sup>1</sup> TOTAL Trial, Jolly SS, Cairns JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med* 2015;372:1389-98. DOI: 10.1056/NEJMoa1415098

<sup>2</sup> TASTE Trial, Lagerqvist B, Fröbert O, Olivecrona GK, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med* 2014;371:1111-20. DOI: 10.1056/NEJMoa1405707

the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Enough time will be given to the participant to decide whether to participate or not to the trial. The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The participant will read and consider the statement before signing and dating the informed consent form, and will be given a copy of the signed document. The consent form will also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

Due to the particular situation of patients suffering from a heart attack with STEMI and the emergency need for treatment, the following informed consent process will be applied:

- If the patient is conscious and in a position to take an informed decision, the patient will be asked for consent prior to the randomization.
- If the patient is conscious but, according to the treating cardiologist, not in position to read, interpret and sign the informed consent form, an oral consent will be asked for. This oral consent will be documented in the clinical report. As soon as possible after the intervention, the patient will be asked to confirm his/her decision by signing the informed consent form. If the consent is revoked, the health-related personal data of the patient collected up to the time of withdrawal will be anonymized after data evaluation has been completed. In case of death after oral consent but prior to the signed informed consent, the collected data will be anonymized after data evaluation has been completed.
- If the patient is unconscious and there is no indication that the patient is opposed to participate in such a project, an independent physician not involved in the study will be called in to safeguard the interests of the patient and to decide about the involvement of the patient in the study. As soon as possible after the intervention, the patient will be asked to confirm his/her decision by signing the informed consent form. If the patient is still unconscious after the intervention, a relative / person authorised to act as a representative will be asked for an assumed consent of the patient. Should the patient or the relative / person authorised to act as a representative revoke the presumed consent, the health-related personal data collected up to this time will be anonymized. In case of death of the patient prior to the signed consent, the health-related personal data collected up to this point will be anonymized.

Both stents used in this trial are approved for PCI in patients with acute myocardial infarction. Both stents are used in a routine way in the institution. From a patient's point of view, the main question about the potential participation to the trial concerns his/her willingness to enable the medical data related to the intervention (and during the follow-up) to be used for this research project. In case of unconscious patients the results obtained up to a potential withdrawal of the consent by the patient or a relative / person authorised to act as a representative will be anonymized and not destroyed. The use of the anonymized data will enable the complete rendering of periprocedural events and avoid survivorship bias. Thus, it is a measure required in order to preserve the validity of the clinical trial (HRA, Art. 17, 4).

The different options listed above for the informed consent process will ensure that, independently for the emergency intervention, enough time, is given to the participant to decide whether or not to participate to the trial.

## **2.7 Participant privacy and confidentiality**

The investigator will affirm and uphold the principle of the participant's right to privacy and will comply with applicable privacy laws. Especially, anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual subject medical information obtained as a result of this study will be considered as confidential and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files. For data verification purposes, competent authorities or the ethics committee will have direct access to parts of the medical records relevant to the study, including participants' medical history.

## **2.8 Early termination of the study**

The Investigators may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns;
- insufficient participant recruitment;
- when the safety of the participants is doubtful or at risk, respectively;
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise;
- early evidence of benefit or harm of the experimental intervention.

## **2.9 Protocol amendments**

Substantial amendments will only be implemented after approval of the CEC. Under emergency circumstances, deviations from the study protocol to protect the rights, safety and well-being of the trial participants may proceed without prior approval of the CEC. Such deviations will be documented and reported to the CEC as soon as possible. All non-substantial amendments will be communicated to the CEC within the Annual Safety Report (ASR).

# **3. BACKGROUND AND RATIONALE**

## **3.1 Background**

Primary percutaneous coronary intervention (PCI) is considered nowadays as the reperfusion strategy of choice for patients with acute ST-segment elevation myocardial infarction (STEMI) [1], owing to a lower risk of myocardial re-infarction and improved short- and long-term survival compared to fibrinolysis [2]. However, STEMI is still associated with poorer clinical outcomes after PCI, compared to stable CAD (CAD), with higher rates of stent thrombosis and an increased risk myocardial re-infarction persisting throughout long-term follow-up [3-5].

STEMI is most frequently caused by a ruptured coronary artery plaque and is considered as a heightened state of thrombogenicity. Compared to stable CAD lesions, culprit lesions in STEMI are characterized by larger lipid-laden necrotic core, thinner fibrous cap, presence of thrombus, and increased fibrin deposition [6]. Moreover, compared to non-culprit sites, culprit lesions in STEMI after primary PCI are characterized by reduced neo-intimal thickness and increased percentage of uncovered struts, struts with inflammation and struts with fibrin [6]. Therefore, STEMI has been associated with delayed arterial healing after PCI, which has been shown to be a risk factor for device-related adverse outcomes, including late stent thrombosis [6-8], even with newer-generation DESs (DES) [9]. Late adverse clinical events have been linked to a chronic inflammatory reaction [6], at least in part due to the presence of durable polymer coatings, which has been recently also described with newer-generation DES [10]. The large amount of intracoronary thrombus during primary PCI may also predispose to stent malapposition secondary to stent undersizing and later thrombus resolution [6], potentially increasing the likelihood of either stent thrombosis or in-stent restenosis [11]. Consequently, the choice of the optimal stent therapy in patients undergoing PCI for STEMI still remains unresolved.

BMSs have been shown to reduce the risk of infarct-vessel re-occlusion compared with balloon angioplasty alone, but have been associated with in-stent restenosis due to neo-intimal hyperplasia in up to 20% of patients [12,13]. Furthermore, BMS have not been shown to reduce the rate of mortality and myocardial re-infarction among patients with STEMI [12,13].

First-generation DESs releasing sirolimus or paclitaxel from durable polymers reduce in-stent restenosis and the need for repeat revascularization among patients with STEMI [14-18], but delay vessel healing due to chronic inflammation induced by the presence of a durable polymer [6]. Limus analogues have been shown to be more effective as site-specific agents than paclitaxel to reduce neo-intimal growth and repeat revascularization procedures [19-20]. However, late stent thrombosis remains more frequent with first-generation DESs compared to BMSs, owing to delayed healing and re-endothelialization [19-20]. Furthermore, hypersensitivity reactions from the polymers may further increase the risk of stent thrombosis [21]. These effects may be particularly pronounced in ruptured plaques of STEMI patients due to the direct contact with the necrotic core [6]. Several potential mechanisms for delayed arterial healing and increased risk of stent thrombosis after PCI with first-generation DESs for STEMI have been suggested, including high affinity of the highly lipophilic drugs for the lipid-rich plaques following penetration of the stent struts into the necrotic core, reduced coverage of the lipid-rich avascular necrotic core by migrating and proliferating cells, absence or reduced number of smooth muscle cells in ruptured fibrous caps, delayed smooth muscle cell proliferation and endothelial regrowth with higher drug concentrations, and increased drug uptake by thrombus [6,22].

Second-generation DESs with more biocompatible permanent polymers represent an important breakthrough technology for the treatment of patients with CAD and are associated with improved clinical outcomes, including death, myocardial infarction, stent thrombosis and repeat revascularisation, as compared with BMSs and first-generation DESs in a broad spectrum of patients with CAD [23-24]. Nevertheless, newer-generation DESs with durable polymer have been recently associated with persistent inflammatory reaction and neoatherosclerosis, similar to first-generation DESs, resulting in persistent late adverse clinical events, including an increased risk of thrombosis [10]. Second-generation DESs have been shown to offer better efficacy and safety outcomes, compared to BMSs in patients with STEMI. The EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArction) trial compared the durable polymer EES with BMS in 1'498 patients with STEMI and showed reduction in target lesion revascularisation (3.7% vs 6.8%,  $p=0.008$ ) but no difference in the composite endpoint of all-cause death, MI and target lesion revascularisation (11.9% vs 14.2%,  $p=0.19$ ) at 1-year follow-up [25].

Several clinical trials have compared the efficacy and safety of second-generation DESs with more biocompatible permanent polymer with first-generation DESs with permanent polymer in patients with STEMI [26-32]. However, these studies have not been able to show a convincing superiority of second-generation DESs, eluting either zotarolimus or everolimus from a permanent polymer, over first-generation DESs in patients with STEMI. ZEST-AMI compared the efficacy and safety of zotarolimus-eluting stents ( $n=108$ ) against first-generation SES ( $n=110$ ) and paclitaxel-eluting stents ( $n=110$ ) in patients with STEMI [26]. At 12 months, cumulative incidence rates of primary endpoint (MACE, composite of death, MI and ischaemia-driven target vessel revascularisation) in the zotarolimus-eluting, sirolimus-eluting and paclitaxel-eluting stents were 11.3%, 8.2% and 8.2%, respectively ( $p=0.834$ ). XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial has compared EES against the first-generation SES and reported a lower rate of MACE (composite of cardiac death, AMI or any target vessel revascularisation) with EES (4.0% vs 7.7%,  $p=0.048$ ) but no significant difference in cardiac mortality (1.5% vs 2.7%,  $p=0.36$ ) or the incidence of definite/probable stent thrombosis (1.2% vs 2.7%,  $p=0.21$ ) at 1 year [27]. However, at 3-year follow-up, there was no difference in EES and SES groups for MACE (EES 8.0% vs SES 10.5%,  $p=0.30$ ), cardiac death (2.5% vs 2.7%,  $p=0.86$ ) and definite/probable stent thrombosis (2.3% vs 3.2%,  $p=0.60$ ) [28]. RACES-MI (Randomized Comparison of Everolimus Eluting Stents and Sirolimus Eluting Stent in Patients With ST Elevation Myocardial Infarction) is a prospective, single-center, randomized trial evaluating the benefits of the second-generation EES versus the first-generation SES in 500 patients undergoing primary PCI for acute STEMI ) [29]. The primary endpoint was a major adverse cardiac event at 3-year follow-up. Interestingly, no significant difference was observed between the everolimus eluting-stent and the SES with durable polymers in terms of major adverse cardiac events (16% vs. 20.8%, adjusted hazard ratio [HR]: 0.75 [95% confidence interval (CI): 0.5 to 1.13],  $p=0.17$ ), cardiac death (4.4% vs. 5.6%, adjusted HR: 0.77 [95% CI: 0.35 to 1.71],  $p=0.53$ ), recurrent MI (6.4% vs. 10%, adjusted HR:0.62 [95%CI: 0.33 to 1.16],  $p=0.13$ ), and target vessel revascularization (4.8% vs.4.8%, adjusted HR: 1.00 [95%CI:0.45 to 2.32],  $p=0.99$ ). However, EES was associated with a significant reduction in stent thrombosis (1.6% vs. 5.2%, adjusted HR: 0.3 [95% CI: 0.1 to 0.92],  $p= 0.035$ ). STEMI substudies of other trials comparing EES against SES, including Basket-PROVE (the BASKET-Pro prospective Validation Examination) [30], EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting) [31], and SORT-OUT IV (The Scandinavian Organization for Randomized Trials with Clinical Outcome IV) [32], have also shown no significant advantage of EES over SES in patients with STEMI. These data were confirmed in a recent mixed treatment comparison analysis of trial level data from 34'068 patient-years of follow-up from 28 randomized trials [9] demonstrating no significant difference between first- and second-generation des with durable polymer (EES and zotarolimus-eluting stent) in terms of target lesion revascularization among patients with STEMI, despite a reduction in the risk of stent thrombosis, particularly with EESs. In conclusion, second-generation DESs with durable polymer failed to demonstrate in previous studies a clear significant superiority in terms of efficacy and safety, compared with first-generation DESs with durable polymer, in patients with STEMI.

Third-generation DESs with biodegradable polymers have been developed to overcome limitations of second-generation DESs with the potential advantages to be more biocompatible, reduce the risk of late adverse clinical events, including late and very late stent thrombosis, cardiac death, and myocardial infarction and shorten the duration of dual antiplatelet therapy. Newer-generation DESs with biodegradable polymers have been shown to improve long-term clinical efficacy and safety outcomes, as compared to first-generation DP-DES in a broad patient population [33]. However, the potential benefit of BP-DES over new-generation DP-DES for the management of patients with acute STEMI remains debated.

The COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute STEMI) trial, comparing BES against BMS, demonstrated the superiority of the biodegradable

polymer BES to BMS with the identical metallic platform in terms of a significant reduction in the primary endpoint of MACE defined as the composite of cardiac death, target vessel-related MI and ischaemia-driven target lesion revascularisation (4.3% vs 8.7%,  $p=0.004$ ) and POCE (8.4% vs 12.2%,  $p=0.04$ ) at 1-year follow-up [34]. Definite stent thrombosis was numerically lower in the BES group (0.9% vs 2.1%,  $p=0.10$ ), and there was no difference in mortality (2.9% vs 3.5%,  $p=0.53$ ). Two-year follow-up results were recently reported, showing persistent benefit of BES over BMS [35]. A pooled analysis of the EXAMINATION and COMFORTABLE-AMI trials also showed that newer-generation DES improve safety and efficacy compared with BMS at 1-year follow-up [36]. However, further follow-up is awaited to evaluate the long-term impact of durable polymer newer-generation DES on very late stent thrombosis and its associated clinical impact.

LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) was a 10-center, assessor-blind, non-inferiority, 'all-comers' trial randomizing 1707 patients to treatment with either biodegradable polymer BESs (BES) ( $n=857$ ) or durable polymer SESs (SES) ( $n=850$ ) [33]. The primary endpoint was a composite of cardiac death, myocardial infarction (MI), or clinically indicated target vessel revascularization at 9 months. At 5 years, BES was non-inferior to SES for the primary endpoint but was associated with a significant reduction in the patient-orientated composite endpoint of all-cause death, any MI, and all-cause revascularization (35.1% vs. 40.4%, RR: 0.84 [95% CI: 0.71 to 0.98],  $p$  for superiority = 0.023). A significant reduction in very late definite ST from 1 to 5 years was evident with the BES (0.7% vs. 2.5%, RR: 0.26 [95% CI: 0.10 to 0.68],  $p=0.003$ ), corresponding to a significant reduction in ST-associated clinical events (primary endpoint) over the same time period. In the post-hoc analysis of the subgroup of patients with acute STEMI ( $n=275$ ) [37], PCI with BES was associated with a significant reduction of Patient-Oriented Composite Endpoint (POCE, composite of all-cause death, all myocardial infarction and all revascularizations; 24.4% vs 39.3%; RR 0.55, 95% CI 0.36 to 0.85,  $p=0.006$ ), major adverse cardiac events (MACE, composite of cardiac death, MI and clinically indicated target vessel revascularization; 12.6% vs 25.0%; RR 0.47, 95% CI 0.26 to 0.83,  $p=0.008$ ) and cardiac death (3.0% vs 11.4%; RR 0.25, 95% CI 0.08 to 0.75,  $p=0.007$ ), along with a trend towards reduction in definite stent thrombosis (3.7% vs 8.6%; RR 0.41, 95% CI 0.15 to 1.18,  $p=0.088$ ) at 5-year follow-up, compared with first-generation SES with permanent polymer. This subgroup analysis demonstrated, for the first time, that primary PCI with BES with biodegradable polymer, compared with the durable polymer SES, reduced cardiac death as well as stent thrombosis in a STEMI population at 5-year follow-up.

These data were recently confirmed by the results of a pooled analysis of individual patient data from three randomised trials [38], comparing clinical outcomes of patients with acute STEMI ( $n=497$ ) undergoing primary PCI with either a biodegradable polymer BES (BES) or a durable polymer SESs at four years. The primary endpoint was a composite of cardiac death, myocardial, or target lesion revascularization. At four years, the primary endpoint was significantly reduced following primary PCI with BES (hazard ratio [HR] 0.59, 95% CI: 0.39-0.90;  $p=0.01$ ) driven by reduced rates of target lesion revascularization (HR 0.54, 95% CI: 0.30-0.98;  $p=0.04$ ). Trends towards reduction were seen for cardiac death or MI (HR 0.63, 95% CI: 0.37-1.05;  $p=0.07$ ) and definite or probable stent thrombosis (3.6% vs. 7.1%; HR 0.49, 95% CI: 0.22-1.11;  $p=0.09$ ), suggesting superior clinical outcomes following primary PCI with a third-generation DES with biodegradable polymer at four years, compared to first-generation DES with durable polymer.

BIO SCIENCE [39], was a large, prospective, multi-center, single-blind, non-inferiority trial that randomized 2119 patients with chronic stable CAD or acute coronary syndrome to treatment with the third-generation Orsiro<sup>®</sup> SES with a biodegradable polymer or the second-generation Xience<sup>®</sup> EES with a durable polymer. In the pre-specified stratified analysis of the primary endpoint of target lesion failure (cardiac death, target vessel myocardial infarction, clinically-indicated target lesion revascularization at 12 months), the Orsiro<sup>®</sup> DES was associated with favourable clinical outcome, compared with the Xience<sup>®</sup> DES in the subgroup of patients with acute STEMI ( $n=407$ ) with 62% relative risk reduction and 5.4% absolute risk reduction (3.3% vs 8.7%, RR 0.38, 95% CI 0.16-0.91,  $p=0.024$ ,  $p$  for interaction=0.014). Thus, recent data from randomized controlled trials and meta-analyses demonstrate a consistent and strong signal towards a significant reduction in major adverse cardiac events among patients with STEMI undergoing primary PCI with third-generation DESs, compared with both first-generation [33], and second-generation [39], DESs with durable polymer. Importantly, this signal suggesting superiority of third-generation DESs in patients with STEMI has never been demonstrated with second-generation DESs. Third-generation DESs with enhanced biocompatibility may therefore have a particular clinical benefit in high-risk subgroups of patients with delayed vascular healing but these data warrants confirmation in appropriately designed randomized controlled trials. The present trial aims at filling the current gap of evidence by providing randomized data to establish the superior clinical outcome with an ultrathin strut third-generation DES with biodegradable polymer designed to improve vascular healing in patients with STEMI undergoing primary PCI, compared to the current state-of-the art second-generation DES with permanent polymer.

### 3.2 Study stent

The Orsiro® Hybrid DES system is manufactured and marketed by Biotronik AG (Bülach, Switzerland), and is currently available in most major European and Asian-Pacific countries. The Orsiro® Hybrid DES system is a combination product comprised of two regulated components:

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

#### 3.2.1 PRO-Kinetic Energy Stent

The backbone of the Orsiro® Hybrid DES is the PRO-Kinetic Energy stent, the BMS platform which is left in the vessel wall after the biodegradable polymer has dissolved. It is a tubular, balloon-expandable stent sculpted by laser from a single tube of L-605 Co-Cr alloy. The stent consists of circular segments at each end, followed by a transition zone and helicoidally arranged struts in the middle. Each loop of the helix is connected to the next loop by 3 longitudinal struts. The stent surface is fully coated with a layer of amorphous silicon carbide (PROBIO®). The PRO-Kinetic ENERGY stent received CE marking in September 2008. The PRO Kinetic Energy stent has been evaluated in a multicenter, prospective, non-observational registry (ENERGY Registry) to determine the long-term safety and clinical performance of the Co-Cr PRO-Kinetic Energy Coronary Stent System in a large patient population. The primary endpoint for the ENERGY registry is 6-month MACE rate, which includes cardiac death, clinically-driven target lesion revascularization (TLR) and MI/acute MI (ST-elevated/non-ST-elevated). A total of 1'016 subjects with 1'074 lesions in 48 centers were enrolled from April to November 2010. Clinical follow-up was scheduled at 6 and 12 months. Six-month clinical data were available for 986 enrolled subjects and 12-month data were available for 916 subjects. At 6 months, MACE rate was 6.3% (62/986), including a 3.7% (36/986) rate of TLR; no probable stent thrombosis; and a 0.9% (9/986) rate of definite and possible stent thrombosis. At 12 months, MACE rate was 8.8% (81/916), including a 4.6% (42/916) rate of TLR; no probable stent thrombosis; and a 1.1% (10/916) rate of definite and possible stent thrombosis. Major adverse cardiac events at 12 months in pre-defined subgroups included 11.4% (17/149) for subjects with diabetes, 7.0% (16/229) for small vessels, and 9.5% (40/419) for subjects with acute coronary.

#### 3.2.2 Passive coating (PROBIO®)

The entire surface of the underlying BMS is coated with a thin layer of amorphous silicon carbide that is saturated with hydrogen (a-SiC:H), referred to as PROBIO® coating, in a physical vapor deposition process. The coating has a transparent appearance with a thickness in the range of 100 nm. The silicon carbide material encapsulates the stent and minimizes interaction between the metal stent and surrounding tissue. Finally, the release of potentially allergenic ions from a silicon carbide-coated stent is reduced in comparison to an uncoated metal stent. The PROBIO® coating has semiconducting properties that efficiently prevent the electron transfer from fibrinogen to the metal surface in vitro. Thereby the conversion from fibrinogen to fibrin and its deposition at the stent surface is reduced. [40] Additionally, aSiC:H-coated stents exhibit a lower adhesion and activation of blood platelets and leucocytes. [41] 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. [42-46].

#### 3.2.3 Active coating (BIOLute®)

Poly-L-lactic acid (PLLA) is the polymer used as the excipient in the Orsiro® Hybrid DES. The Orsiro® Hybrid DES body surface is completely coated by a matrix consisting of the carrier PLLA and the drug substance Sirolimus (BIOLute). The matrix has a maximal thickness on the abluminal surface of 25 µm. The largest stent design has a maximal coating mass of 42.6 µg per millimeter of stent length. PLLA is a highly biocompatible material. There is existing published experience with PLLA as a stent and stent coating material in humans [46-48]. Previously, this material was used in osteosynthesis and assuture material. This highly biocompatible polymer gently degrades over 3 years, avoiding increased inflammation, and ultimately metabolizes into CO<sub>2</sub> and H<sub>2</sub>O via the Krebs cycle. Studies in mini pigs have shown no residual PLLA and benign histology at 3 years. The first successful in-human experience with a fully biodegradable stent was described in 2000 [49]. The study included 15 subjects with 19 lesions treated with a monopolymer poly-L-lactic acid Igaki-Tamai stent with a zigzag helical coil pattern. No death, MI or stent thrombosis occurred for up to 6 months, and only one subject with two lesions underwent repeat revascularization. Another fully biodegradable stent using PLLA is the everolimus eluting ABSORB stent. Two-year outcomes of the first-generation, first-in-man trial involving 30 subjects were

encouraging, with only one myocardial infarction and no cardiac death, stent thrombosis or ischemia-driven target lesion revascularization (TLR), resulting in a MACE rate of 3.6% [50]. For the second-generation ABSORB stent, the MACE rate at 12 months was 7.1% (7 of 101 subjects) [51]. Other stent systems using poly-L-lactic acid as biodegradable polymers, such as the BioMATRIX and Nobori stent, have also been proven safe and effective [44,48].

### **3.2.4 Sirolimus**

Sirolimus is the drug substance utilized in the Orsiro® Hybrid DES system. It is an immunosuppressive drug, which has been approved by the FDA for the prevention of renal transplant rejection. It has also potent antiproliferative and antimigratory effects on vascular smooth muscle cells in vitro and has been shown to reduce angiographic and clinical restenosis in patients with CAD.

The RAVEL study was a prospective multi-center, randomized, double-blind, trial comparing a SES with a bare metal stent of identical design in humans [52]. 238 patients with low-risk lesions in native coronary arteries were randomized to receive either a Sirolimus-coated stent (n=120) or an uncoated steel stent (n=118). Follow-up at 1 year revealed a remarkable difference in the primary clinical endpoint of MACE (major adverse cardiac events) between the Sirolimus-eluting and the uncoated stent groups (5.8% versus 28.8%). The difference in the MACE rates between the two groups was primarily due to a difference in rates of percutaneous revascularization of the target lesion. Angiographic follow-up at 6 month also revealed a significant difference in the primary angiographic end-point of luminal late loss ( $-0.01 \pm 0.33$  mm versus  $0.80 \pm 0.53$  mm in the control group,  $p < 0.001$ ). No edge effect or delayed stent thrombosis occurred in the Sirolimus group.

The SIRIUS trial [53] was a multi-center study that randomized 1'101 patients to implantation of a bare metal stent or its Sirolimus-eluting counterpart. The primary endpoint of target vessel failure (death, myocardial infarction, target vessel revascularization) at 9 months was significantly less frequent among patients treated with the SES (8.6%) than those treated with the bare metal stent (21%). This was due to a higher need for target lesion revascularization in the bare metal stent group (16.6% vs. 4.1%,  $p < 0.001$ ). The degree of in-lesion restenosis suppression was profound (late lumen loss 0.24 mm versus 0.81 mm,  $p < 0.001$ ).

### **3.2.5 Delivery system**

The delivery system of the Orsiro® stent is a fast-exchange PTCA catheter compatible with a 5F guide catheter, with a working length of 140 cm. The stent is securely crimped on a nylon balloon situated at the distal tip of the catheter between two radiopaque markers made of a platinum-iridium alloy. The proximal shaft of the delivery system is a hypotube composed of polyamide-covered 304 or 304L stainless steel; it has a single luer port for connecting an inflation/deflation device to inflate/deflate the balloon. The distal section of the catheter comprises the inflation/deflation (balloon) lumen and the 29-cm-long guide wire lumen, which starts at the catheter tip and ends at the guide wire exit port. It accepts guide wires of 0.014" diameter. The stent delivery system is compatible with guiding catheters with a minimal inner diameter of  $\geq 0.056$ " (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.

### **3.2.6 Contraindications**

The Orsiro® Hybrid DES System is contraindicated for use in subjects with:

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

## **3.3 Clinical Evidence to Date**

The development of the Orsiro® Hybrid DES system has been supported by an extensive clinical trial program (Table 1) designed to collect data on over 3'000 Orsiro-treated subjects in studies using the Xience® EES system as a stent 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, randomized all-comers study against the Xience Prime™ stent. Table 1 summarizes the key design elements of each Orsiro study. A brief description of the studies, its status and results is provided in this section.

BIOFLOW I trial was a prospective, multi-center, non-randomized, first-in-man trial including 30 patients and designed assess the safety and clinical performance of the Orsiro® hybrid drug eluting stent in patients with single de-novo coronary artery lesions. The primary endpoint was late lumen loss at 9 months. The primary endpoint was  $0.05\pm 0.22$  mm for in-stent late lumen loss and  $0.05\pm 0.26$  mm for in-segment late lumen loss despite a high rate of diabetic patients and complex coronary artery lesions despite being a first-in-man study.

BIOFLOW II [54] was a prospective, multicenter, assessor-blind, randomized, controlled, non-inferiority trial including 452 patients with stable or unstable CAD undergoing percutaneous coronary intervention who were randomly assigned 2:1 to treatment with the Orsiro® DES (298 patients, 332 patients) or Xience® EES (154 patients, 173 lesions). The primary endpoint was in-stent late lumen loss at 9 months. The Orsiro® DES was noninferior to the Xience® drug-eluting-stent for the primary end point ( $0.10\pm 0.32$  versus  $0.11\pm 0.29$  mm; difference= $0.00063$  mm; 95% confidence interval,  $-0.06$  to  $0.07$ ;  $p$  non-inferiority $<0.0001$ ). Clinical outcome showed similar rates of target-lesion failure at 1 year (6.5% versus 8.0%, respectively; hazard ratio= $0.82$ ; 95% confidence interval,  $0.40$ – $1.68$ ; log-rank test:  $P=0.58$ ) without cases of stent thrombosis. A subgroup analysis of patients ( $n=55$ ) who underwent serial optical coherence tomography at 9 months, demonstrated similar neointimal thickness among lesions allocated to Orsiro® and Xience® DESs ( $0.10\pm 0.04$  mm versus  $0.11\pm 0.04$  mm;  $-0.01$  [ $-0.04$ ,  $-0.01$ ];  $P=0.37$ ). Another subgroup of patients ( $n=56$ ) underwent serial intravascular ultrasound at baseline and 9 months indicating a potential difference in neointimal area at follow-up ( $0.16\pm 0.33$  mm<sup>2</sup> versus  $0.43\pm 0.56$  mm<sup>2</sup>, respectively;  $P=0.04$ ).

BIOFLOW III [55] registry was a prospective, non-randomised, multi-centre, observational all-comers registry including 1'356 patients. The study was designed to evaluate the safety and performance of the Orsiro® DES in a large series of patients under real-world conditions with treatment according to standard of care and follow-up assessments up to 60 months. The primary endpoint was target lesion failure, a composite of cardiac death, target vessel myocardial infarction, CABG and clinically driven target lesion revascularisation at 12 months. The primary endpoint occurred in 5.1% (95% CI: 4.0-6.4) of patients in the overall population with mainly complex CAD, and in 7.7% (95% CI: 5.5-10.9), 5.8% (95% CI: 4.2-8.1), 1.8% (95% CI: 0.2-11.8) and 7.2% (95% CI: 5.1-10.0) of patients with diabetes mellitus, small vessels, chronic total occlusion and acute myocardial infarction, respectively. The BIOFLOW II study confirmed the favourable clinical outcomes following PCI with the Orsiro® DES system in an all-comers population, even in predefined high-risk subgroups.

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

1. Randomized controlled trial (RCT) at up to 50 sites in Japan and Europe, which will enroll 555 subjects with up to two *de novo* lesions  $\leq 26$  mm in length in native coronary arteries 2.5–3.75 mm in diameter. Subjects will be randomized in a 2:1 fashion to receive the Orsiro® stent or the Xience Prime™/Xpedition™ stent.
2. Concurrent, non-randomized pharmacokinetic (PK) sub-trial at 3–5 sites in Japan, which will enroll 20–30 subjects with up to two *de novo* lesions  $\leq 26$  mm in length in native coronary arteries 2.5–3.75 mm in diameter. The primary endpoint for the main RCT is the 12-month TVF rate, defined as any clinically-driven TVR, target vessel Q-wave or non-Q-wave MI, emergent CABG or cardiac death. There is no primary endpoint for the PK sub-trial.

Enrollment into the BIOFLOW-IV trial has been completed.

BIOSCIENCE [39], was a large, prospective, multi-center, single-blind, non-inferiority trial that randomized 2'119 patients with chronic stable CAD or acute coronary syndrome and minimum exclusion criteria to treatment with the Orsiro® SES with a biodegradable polymer or the Xience® everolimus-eluting stent with a durable polymer. The rate of the primary endpoint of target vessel failure (cardiac death, target vessel myocardial infarction, clinically-indicated target lesion revascularization) at 12 months was similar in both treatment arms (6.5% in the Orsiro® group vs. 6.6% in the Xience® group). No significant differences were found in rates of definite stent thrombosis, confirming the safety of the newer-generation DESs with ultrathin struts and biodegradable polymer.

Finally, the one-year results of the SORT-OUT VII trial, an investigator-initiated, randomized, multicenter, two-arm, non-inferiority study comparing the Orsiro® ultrathin-strut SES with biodegradable polymer ( $N=1'261$ ) and the Nobori® (Terumo Corp., Tokyo, Japan) thick-strut BES with durable polymer ( $N=1'264$ ) in an all-comers

population of patients undergoing PCI, were recently presented [56]. The rate of the primary endpoint of target lesion failure, defined as a composite of cardiac death, myocardial infarction, or target lesion revascularization at 12 months, occurred in 3.8% of patients in the Orsiro<sup>®</sup> group compared to 4.6% of patients in the Nobori<sup>®</sup> group (*p* for non-inferiority <0.0001). Importantly, patients in the Orsiro<sup>®</sup> arm had a significantly lower rate of definite stent thrombosis (0.4% versus 1.2%, respectively; *p* = 0.03).

### 3.4 Explanation for choice of the stent comparator

The Xience<sup>®</sup> DES system is manufactured and marketed by Abbott Vascular (Santa Clara, California, USA). The Xience<sup>®</sup> DES system is currently available in most major European and Asian-Pacific countries, as well as the USA. The safety and efficacy of the Xience<sup>®</sup> DES system has been extensively investigated in several clinical trials.

The feasibility of using everolimus on a DES was demonstrated in the earlier FUTURE-I [57, 58] and FUTURE II [59, 60] studies and more recently in the SPIRIT FIRST [61] study, using the EES. The SPIRIT FIRST study (N=60) was a multi-center, single blinded controlled study conducted to assess the feasibility and efficacy of the EES in the treatment of patients with de novo native coronary artery lesions compared to the metallic, uncoated MULTI-LINK VISION RX<sup>®</sup> Coronary Stent System. This feasibility trial showed clinical safety and the angiographic in-stent late lumen loss observed was 0.10mm, a reduction of 88% relative to the bare metal stent at six months and a late lumen loss of 0.24mm at 12 months, which was a reduction of 71% [61,62].

The SPIRIT-II trial was a continuation of the assessment of the safety and performance of the XIENCE<sup>®</sup> V everolimus-eluting stent versus the TAXUS<sup>®</sup> paclitaxel-eluting stent in the treatment of patients with a maximum of two *de novo* native artery lesions. A total of 300 patients were randomized to treatment with either an everolimus-eluting stent (n=223) or a paclitaxel-eluting stent (n=77). At 6 months, the in-stent late loss (the primary endpoint) was 0.11 ± 0.27 mm in the EES arm, as compared to 0.36 ± 0.39 mm in the paclitaxel-eluting stent arm (*p*<0.0001). Hierarchical ischemia-driven MACE was 2.7% (6/222) in the everolimus-eluting stent group vs. 6.5% (5/77) in the paclitaxel-eluting stent group. With these results, this non-inferiority randomized trial not only met its primary endpoint, but also demonstrated the superiority of the everolimus-eluting stent over the paclitaxel-eluting stent in terms of in-stent late loss [63].

The SPIRIT-III trial was designed as the U.S. pivotal randomized study for the XIENCE<sup>®</sup> V everolimus-eluting stent. The study randomized a total of 1002 patients (2:1) to either XIENCE<sup>®</sup> V or TAXUS<sup>®</sup>. The trial demonstrated a significantly lower in-segment late loss (the primary endpoint) with XIENCE V as compared to TAXUS<sup>®</sup> (0.14±0.41 vs. 0.28±0.48; *p*<0.0001). Furthermore, the trial demonstrated non-inferior rates of target vessel failure at 9 months (7.2% vs. 9.0% XIENCE<sup>®</sup> V vs. TAXUS<sup>®</sup> respectively; *P* for non-inferiority <0.0001), with a significant 44% reduction in MACE (4.6% vs. 8.1% XIENCE<sup>®</sup> V vs. TAXUS<sup>®</sup> respectively; *p* for superiority 0.028) [64].

The SPIRIT-IV trial randomized 3687 patients at 66 U.S. sites to the Xience<sup>®</sup> V everolimus –eluting stent or the Taxus Express<sup>®</sup> paclitaxel-eluting stent in a 2:1 fashion. The Xience<sup>®</sup> V stent was demonstrated superior with respect to the primary composite end point cardiac death, target-vessel myocardial infarction and ischemia-driven target-lesion revascularization (4.2% versus 6.8%; RR, 0.62; 95% CI, 0.46 to 0.82; *P*=0.001). Moreover, the rates of stent thrombosis were significantly lower for the Xience<sup>®</sup> V stent (0.17% versus 0.85%; *P*=0.004) [65].

In the COMPARE study, the Xience<sup>®</sup> V stent was compared to the Taxus Express<sup>®</sup> stent in 1'800 real-life patients. The primary end point of all-cause mortality, myocardial infarction, and target-vessel revascularization within 12 months was significantly lower in the Xience<sup>®</sup> V group (6% versus 9%, RR 0.69, 95% CI 0.50 to 0.95; *p* for superiority=0.02) driven by a lower rate of stent thrombosis (0.7% versus 3%, RR 0.26, 95% CI 0.11 to 0.64; *P*=0.002), myocardial infarction (3% versus 5%, RR 0.52, 95% CI 0.33 to 0.84; *P*=0.007) and target vessel revascularization (2% versus 6%, RR 0.39, 95% CI 0.24 to 0.64, *P*=0.0001) [66].

The EXCELLENT trial randomizing 1'372 patients in a 3:1 fashion an everolimus-eluting stent or a SES met its primary angiographic endpoint of in-segment late lumen loss at 9 months (everolimus-eluting stent 0.10mm vs. sirolimus-eluting stent 0.05mm, *p*<sub>non-inferiority</sub>=0.023) and revealed no differences in rates of myocardial infarction, target-lesion revascularization and major adverse cardiac events at 12 months clinical follow-up [31]. In the SORT OUT IV trial including 2'774 patients, everolimus-eluting stents were found non-inferior as compared to SESs with regard to major adverse cardiac events (4.9% vs. 5.2%, HR 0.94, 0.67-1.31) and TLR (1.4% vs. 1.7%, HR 0.87, 0.48-1.58) at 9 months, whereas a trend towards a lower rate of definite stent thrombosis with EES was noted (0.1% vs. 0.7%, HR=0.22, 0.05-1.02, *p*=0.05) [67]. Comparable clinical event rates between EESs and SESs have also been reported in the BASKET PROVE trial at a median follow-up duration of two years (3.7%

versus 4.3%,  $p=0.85$ ) - a trial that randomized 2'314 patients undergoing stent implantation of large vessels (stent diameter  $\geq 3.0$  mm) to everolimus-eluting stents, sirolimus-eluting stents or bare metal stents [68]. A propensity-score matched comparison of 1'342 pairs treated with either everolimus-eluting or sirolimus-eluting stents observed a trend towards a lower rate of the primary endpoint, a composite of death, myocardial infarction and target vessel revascularization at three years in favor of the everolimus-eluting stent (14.9% versus 18.0%, HR 0.83, 95% CI 0.68-1.00,  $P=0.056$ ) [69].

The Xience® PRIME, subsequently the Xience® Xpedition and more recently the Xience® Alpine are successive modified versions of the Xience® V coronary stent system, with improved flexibility and deliverability due to enhanced stent delivery systems. Moreover, the more recent stent balloons are supposed to cause less edge dissections due to shorter balloon tapers compared to the Xience® V stent system, and have higher burst pressures. However, the stent coatings including polymer and drug concentrations are similar for the Xience® V, Xience® PRIME, Xience® Xpedition and Xience® Alpine coronary stent platforms.

### 3.5 Risks / Benefits

#### 3.5.1 Introduction

Subjects presenting with acute STEMI and enrolled in either treatment (Orsiro® Hybrid DES) or control (Xience® DES) arms of this study are required to have an indication for primary PCI with coronary stenting due to underlying CAD. It is not anticipated that the treatment group (Orsiro® Hybrid DES) will be at higher risk of experiencing one or more of the listed complications versus the control group (Xience® DES). Both devices used for the purpose of this trial received CE mark. All adverse events will be tracked during the term of follow-up.

#### 3.5.2 Benefits

There are no guaranteed benefits from participation in this study; however, it may be possible that the treatment with the Orsiro® Hybrid DES may improve clinical outcomes. Moreover, in this clinical investigation all subjects will have a more intense medical follow-up compared with standard practice, which can be beneficial to the long-term clinical outcome of study participants. Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. Efficacy and safety data collected on the Orsiro® Hybrid DES will contribute to expand the knowledge of use of drug eluting stents with biodegradable polymer in patients with STEMI undergoing primary PCI.

#### 3.5.3 Potential Risks

Both devices received CE mark. As with any subject undergoing PCI, subjects in this study may experience adverse events and/or outcomes that may include, but are not necessarily limited to the following:

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

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

- Abnormal liver function tests;

- Anemia;
- Arthralgia;
- Diarrhea;
- Hypercholesterolemia;
- Hypersensitivity, including anaphylactic/anaphylactoid type reactions;
- Hypertriglyceridemia;
- Hypokalemia;
- Infections;
- Interstitial lung disease;
- Leukopenia;
- Lymphoma and other malignancies;
- Thrombocytopenia;
- Renal events: renal insufficiency/renal failure.

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

Appropriate contraindications and warnings are included in the Instructions for Use provided with the Investigational Device. Interventional cardiologists selected to participate as investigators in this study will be qualified and board certified. All clinicians will have experience with the treatment and control procedures and have been trained on the use of the Orsiro® Hybrid coronary stent system. Study specific device training will be provided and documented for each study investigator and staff prior to use of the investigational product in human subjects. Patients will undergo thorough pre-procedure assessment and angiographic assessment prior to selection and inclusion into the study. Following the selected intervention, patients will be closely monitored by their physicians. Careful medical follow-up is required so that any complications can be diagnosed and properly managed to minimize harm to the patient. All efforts will be made to minimize risks by selecting investigators who are experienced and skilled in the use of the device and who will comply with the protocol and Instruction For Use.

### **3.6 Justification of choice of study population**

Patients with acute STEMI within 24 hours of the symptom's onset and eligible for primary PCI according to the current guidelines of the European Society of Cardiology [1] will be enrolled. Patients with coronary artery lesions suitable for DES implantation will be included according to the inclusion and exclusion criteria specified below. Inclusion criteria will be kept comprehensive to reflect the routine clinical practice of patients undergoing primary PCI for STEMI. Due to the broad inclusion criteria ('real world, all-comer' patients) enrollment of 80-90% of all patients undergoing primary PCI at each site is expected. A screening log will be kept at each site to assess how many eligible patients were actually included in the trial, and the monitor will be allowed to check the catheterization laboratory diary. Importantly, signs and symptoms showing that the participant is unwilling to participate in the study will result in the participant being excluded from participation. The physician not participating in the study will safeguard participant interest and insure proper medical care.

## **4. STUDY OBJECTIVES AND ENDPOINTS**

### **4.1 Study Objective**

The objective of this study is to assess the safety and efficacy of the ultrathin-strut Orsiro® Hybrid sirolimus-eluting stent with biodegradable-polymer compared with the state-of-the-art thin-strut Xience® (Xience Xpedition® or Xience Alpine®) everolimus-eluting stent with biocompatible permanent polymer in a prospective, multi-center, randomized, controlled superiority trial including patients with acute STEMI undergoing primary PCI.

### **4.2 Primary Endpoint**

The primary endpoint is *Target Lesion Failure* (TLF), a binary composite endpoint. It is defined on a per-patient basis as the occurrence within 365 days post index procedure of any of the following clinical events: cardiac death, target vessel Q-wave or non-Q-wave myocardial infarction (MI) (i.e., Q-wave MI that cannot be attributed to a non-target vessel), or clinically driven target lesion revascularization (TLR). In case multiple events occurred in a given patient, the date of the first event is used for analysis. This is the same primary endpoint as in the BIOSCIENCE study.

### 4.3 Secondary Endpoints

The secondary endpoints of the study include:

- Clinically indicated and not clinically indicated target lesion revascularization (TLR) at 30 days, 1, and 2 years;
- Clinically indicated and not clinically indicated target vessel revascularization (TVR) at 30 days, 1, and 2 years;
- Target vessel failure (TVF) at 30 days, 1, and 2 years;
- Cardiac death at 30 days, 1, and 2 years;
- All-cause death (cardiac and non-cardiac) at 30 days, 1, and 2 years;
- Myocardial infarction (Q-wave and non-Q-wave) at 30 days, 1, and 2 years;
- Definite stent thrombosis at 30 days, 1, and 2 years;
- Definite and probable stent thrombosis at 30 days, 1, and 2 years;
- Device success, defined as achievement of a final residual diameter stenosis of < 30% (by visual estimation) using the assigned device only;
- Lesion success, defined as achievement of < 30% residual stenosis (by visual estimation) using any PCI method;
- Procedural success, defined as achievement of a final diameter stenosis of < 30% (by visual estimation) using any PCI method, without the occurrence of death, MI, or repeat target vessel revascularization during hospital stay.

## 5. STUDY DESIGN

### 5.1 General study design

BIOSTEMI is a prospective, randomized, multi-center, investigator-initiated, assessor-blind, superiority trial to be conducted at interventional cardiology centers in Switzerland and Europe. Patients with acute STEMI will be randomized in a 1:1 randomization fashion to undergo primary PCI with, either an ultrathin strut sirolimus-eluting stent with biodegradable polymer (Orsiro® Hybrid DES), or a thin-strut everolimus-eluting stent with durable polymer (Xience® DES). All patients will be followed at 30 days, 1, and 2 years after stent implantation for clinical endpoints (Figure 1). Patients will be questioned about the occurrence of angina, any adverse cardiac events, recurrent hospitalizations, and cardiovascular medication intake. A total of 1'250 patients (625 per treatment arm) will be enrolled during a one-year period. Patients included in the STEMI subgroup of the BIOSCIENCE trial (n=407, abbreviated BIOSCIENCE STEMI) will be included in the primary analysis of the BIOSTEMI trial using a robust Bayesian approach based on individual patient data. Therefore, a total of 1'657 patients will be finally analyzed in the combined BIOSCIENCE STEMI (n=407) and BIOSTEMI trials (n=1250). Using historical information from the BIOSTEMI trial at the design stage allows a reduction in the number of participants and trial duration.

Enrolling an excessive number of patients in a clinical trial is unethical because patients will be allocated to a treatment that might be shown to be inferior already in the mid-course of the trial (Sutton et al. 2007, Stat. Med. Vol 26). An excessive sample size would prolong trial duration and possibly delay approval of a new superior treatment by regulatory authorities and thereby delay access to patients for whom it is indicated. Additionally, since trials are costly, there could be considerable wastage in economic terms. The U.S. Food and Drug Administration has recognized that Bayesian analyses can lead to smaller trials while still retaining full validity of the results; this is achieved by making better usage of pre-existing high quality evidence (*Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials*; Issued on February 5, 2010 by the U.S. Food and Drug Administration). Accordingly, evidence from a previous trial (BIOSCIENCE) was used in designing the current BIOSTEMI trial, and results from the previous trial (BIOSCIENCE) will be combined with the results of the current trial (BIOSTEMI) using a Bayesian approach.

### 5.2 Randomization

After urgent diagnostic coronary angiography, subjects who have satisfied all general and angiographic inclusion and exclusion criteria, after successful crossing of the first target lesion with a coronary guidewire, will be randomized in a 1:1 ratio to receive either the Orsiro® Hybrid DES (n=625) or the Xience® (Xience Xpedition® or Xience Alpine®) DES (n=625). Each subject will receive one unique randomization number associated with a randomization assignment allocated via the study electronic data capture (EDC) electronic

Case Report Form (eCRF) website. Randomization will be stratified by study center, diabetes and presence or absence of multivessel disease. Once randomization is completed and a treatment is assigned, crossover is not permitted. Once randomized, the subject is considered enrolled in the trial and included in the intent-to-treat (ITT) population.

### **5.3 Methods of minimizing bias and blinding procedures**

The study is a randomized-controlled, assessor-blind trial. Randomization will be concealed using a web-based central randomization. To prevent bias, the randomization lists will be defined prior to the first study enrollment and concealed until a given patient has fulfilled all inclusion/exclusion criteria. To ensure a balanced allocation of stents over time, randomization lists will be generated in blocks of 2, 4, or 6 patients. To enforce concealment, block size will be generated at random. Major adverse cardiac events will be reviewed and classified by a Clinical Event Committee, consisting of cardiologists not participating in the trial. The members of the Clinical Event Committee will be blinded, i.e. unaware of the patient's treatment allocation and trial results. The statistician will be blinded for treatment allocation for the primary analysis of clinical outcomes.

## **6. STUDY POPULATION**

### **6.1 Eligibility criteria**

#### **6.1.1 Inclusion criteria**

Participants fulfilling all of the following inclusion criteria will be eligible for the study:

1. Age  $\geq 18$  years;
2. Chest pain for  $\geq 10$  minutes;
3. ST-segment elevation acute myocardial infarction, defined as:
  - ST-segment elevation  $\geq 1$  mm in  $\geq 2$  contiguous leads, or
  - New (or presumably new) left bundle branch block, or
  - Posterior myocardial infarction with ST depression  $>1$  mm in  $>2$  contiguous anterior leads).
4. Primary PCI occurring within 24 hours of symptom onset;
5.  $\geq 1$  acute infarct artery target vessel with one or more coronary artery stenoses in a native coronary artery from 2.25 to 4.0 mm in diameter that can be covered with one or multiple coronary stents. There is no limit about the number of treated lesions, vessels, or complexity.

#### **6.1.2 Exclusion criteria**

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

1. Known allergy to aspirin, Ticagrelor, Prasugrel, Clopidogrel, Sirolimus, Everolimus or contrast media;
2. Planned surgery within 6 months of primary PCI, unless dual antiplatelet therapy could be maintained throughout the peri-surgical period;
3. Currently participating in another trial before reaching the primary endpoint;
4. Missing informed consent or missing consent from an independent physician;
5. Non-cardiac comorbid conditions with life expectancy of less than 1 year;
6. Mechanical complication of acute myocardial infarction;
7. Acute myocardial infarction due to stent thrombosis.

### **6.2 Recruitment and screening**

Patients presenting with acute STEMI within 24 hours of symptom onset and who qualify for a reperfusion strategy with primary PCI will be screened for the study by the authorized site personnel by reviewing available medical records. Screening will be carried out according to each investigative site's standard of care. Prior to possible entry into the trial, site personnel will review and compare the subject's medical history with the clinical inclusion and exclusion criteria to determine if they are an eligible candidate for the study. Screening logs will be kept at each investigational site of all subjects identified through screening who meet the clinical eligibility criteria. For subjects who are not subsequently enrolled (consented), the reason for non-enrollment will be recorded. Potential study subjects will proceed with the following standard of care procedures to further assess eligibility.

The patient's participation in this study is voluntary. Study participants will not receive any payment for their participation to the study.

### **6.3 Assignment to study groups**

Subjects who have satisfied all inclusion and exclusion criteria, after successful crossing of the first target lesion with a guidewire, will then be randomized in a 1:1 ratio to receive either the Orsiro® Hybrid DES (treatment group, n=625) or the Xience® DES (control group, n=625). Using the pseudonym generated in Cardiabase Webspirit (2mt Ulm, Germany) (9 digit number e.g. 123-456-789) each subject will be randomized to one of the stent via the electronic data capture system website. Randomization will be stratified by site, diabetes and the presence of multivessel disease. Multivessel disease is defined as multiple lesions needing treatment in two or more vessels and/or lesion in the left main. Once randomization is completed and a treatment is assigned, crossover is not permitted. Once randomized the subject is considered enrolled in the trial and included in the intent-to-treat (ITT) population.

### **6.4 Criteria for withdrawal / discontinuation of participants**

All patients who undergo randomization will be included in the primary analysis of clinical outcome in the groups to which they were originally allocated to (intention-to-treat principle). Investigators should make every effort to ensure subjects complete all protocol-required procedures, including study follow-up visits. Patients will be encouraged to remain in the trial until completion of the 2 years follow-up. Follow-up procedures are described in section 8. If a patient refuses further follow-up examinations (drop-out) or is lost-to follow-up, the reason for dropping out or loss will be recorded. If the consent is revoked, the health-related personal data of the patient will be anonymized after data evaluation has been completed (see also paragraph 2.6). If a serious adverse occurs, a patient will be followed until the adverse event resolves or until a stable clinical endpoint is reached.

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

- 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;

The Principal Investigators may also terminate the study prematurely according to certain circumstances, for example:

- ethical concerns;
- insufficient participant recruitment;
- when the safety of the participants is doubtful or at risk, respectively;
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise;
- early evidence of benefit or harm of the experimental intervention.

In the event of major protocol non-compliance, each case will be evaluated individually to determine the appropriate course of action regarding subject study participation. In any of the situations noted above, data collected up to and including the exit of the subject will be used in data analysis. No data will be collected after the exit of the subject from the study. Study exits are expected and will be taken into consideration during data analysis. Additionally, subject attrition has been calculated into the study sample size; therefore, all subjects exited from the study will be counted toward the randomization goal and will not be replaced. Investigators must document, in subject medical records, the reasons and circumstances for all subject exits. Generally, subjects should not be removed from the study due to late identification of eligibility criteria violations, unless increased subject risk is indicated. In cases where further participation in the study poses potential risk to the subject, study exit should be considered. In addition to subject safety, consideration should be given to the scientific validity of the primary endpoints when making decisions concerning subject exit. Study follow-up options and requirements for subjects exited from the study should be determined and applied to all subjects exited for similar reasons. Deviations in subject eligibility, as defined in the protocol, should be considered protocol violations and reported to the CEC 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. For example, a subject may change geographic location or move into a nursing home, but may still remain in contact with the investigator. Identification of vital status will be handled at the investigational site level. Subjects have the right to discontinue from the study at any time or be discontinued at the investigator's discretion.

## 7. STUDY INTERVENTION

### 7.1 Study stent

The Orsiro® Hybrid DES (Biotronik AG, Bülach, Switzerland), eluting sirolimus from a biodegradable polymer, received CE marking approval in February 2011 and is currently available in most countries of Europe and Asia-Pacific. The Orsiro® DES has been developed on the design of the approved and commercially available PRO-Kinetic ENERGY™ (BIOTRONIK AG, Bülach, Switzerland) BMS which received CE mark in September 2008. The Orsiro® Hybrid DES system comprises five main components (Figure 2):

- Stent metallic platform: the platform is made of a ultrathin strut (60 µm) cobalt chromium alloy (Cobalt-Chromium L605), similar to the PRO-Kinetic Energy BMS, with a double helix design.
- Passive component: PROBIO® coating. The PROBIO® coating is a thin layer of amorphous silicon carbide used on all BIOTRONIK coronary stents. This material has semiconducting properties that efficiently prevent the electron transfer from fibrinogen to the metal surface in vitro. Thereby the conversion from fibrinogen to fibrin and its deposition at the stent surface is reduced. Additionally, aSiC:H-coated stents exhibit a lower adhesion and activation of blood platelets and leucocytes. The release of potentially allergenic ions from a silicon carbide coated stent is substantially reduced in comparison to an uncoated metal stent.
- Active component: BIOLute® (poly-L-lactic acid) bioresorbable polymer matrix: The polymer compound used as a carrier material for supply and release of sirolimus is a high molecular Poly-L-Lactic Acid (PLLA). The stent body surface is completely coated by a matrix consisting of the carrier PLLA and the active substance sirolimus (BIOLute®). The matrix has a maximal thickness on the abluminal surface of 25 µm. The largest stent design has a maximal coating mass of 42.3 µg per millimetre 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.
- Immunosuppressive drug: Sirolimus at a concentration of 1.4 µg/mm<sup>2</sup>.
- Stent Delivery System: the delivery system of Orsiro and PRO-Kinetic ENERGY are nearly identical, based on a rapid-exchange 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.

Device description details of the Orsiro® Hybrid DES system can be found in the Instructions for Use (IFU), which are provided with the product. The currently available stent diameters and lengths are summarized in Table 2.

### 7.2 Control stent

The Xience® DES system (Abbott Vascular, Santa Clara, USA), eluting everolimus from a permanent polymer, is currently available in most countries of Europe and Asia-Pacific, and in the USA. The safety and efficacy of the Xience® DES system has been extensively investigated in several clinical trials. Xience Xpedition® and Xience Alpine® received CE marking approval in 2012 and 2014, respectively.

The Xience® DES system comprises four main components (Figure 2):

- Stent metallic platform: the platform is made of a thin strut (81 µm) cobalt chromium alloy (Cobalt-Chromium L605), similar to the MULTI-LINK BMS.
- Active component: permanent biocompatible polymer containing inactive ingredients, including poly-n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer. PBMA is a homopolymer with a molecular weight (Mw) of 264'000 to 376'000 Dalton. PVDF-HFP is a non-erodible semicrystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 Dalton. The drug matrix copolymer is mixed with the immunosuppressive agent and applied to the entire PBMA coated stent surface.
- Immunosuppressive drug: low-dose Everolimus (a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of sirolimus) immunosuppressive drug at a concentration of 100 µg/cm<sup>2</sup>.
- Stent Delivery System: the delivery system of the Xience Xpedition® and Xience Alpine® are nearly identical, based on a rapid-exchange catheter and are designed to improve the acute performance, resulting in less force needed to deliver the stent system.

Device description details of the Xience® (Xience® Xpedition or Alpine) DES systems can be found in the Instructions for Use (IFU), which are provided with the products. The currently available stent diameters and lengths are summarized in Table 3.

### **7.3 Use of study and control stents**

Both the study stent (Orsiro<sup>®</sup> Hybrid DES) and the control stent (Xience<sup>®</sup> DES) will be used according to their indications for use. The randomly assigned stent is not expected to have an influence on the conduct of the procedure that will take place according to the routine practice. Eligible patients with acute STEMI with 24 hours of the symptom's onset will undergo primary PCI as per local protocol, according to the current guidelines of the European Society of Cardiology [1]. The technique of PCI (vascular access route, choice of the vascular sheath diameter, choice of the diagnostic and guiding catheters sizes and shapes, choice of the coronary guidewire) will be left to the discretion of the operator as per standard individual and local practice. The use of manual or mechanical thrombus aspiration and pre-dilatation of the culprit lesion is left to the discretion of the operator. The operator will choose the appropriate length and diameter of the stents to be implanted by visual estimate. The Orsiro<sup>®</sup> and Xience<sup>®</sup> DES systems are commercially available and all sizes may be used for the study. A list of the stent diameters and length are available on Table 2 and Table 3. The randomly allocated stent will be implanted in the culprit lesion of the target vessel. Complete revascularization of all non-culprit lesions within the target infarct vessel will be performed with the randomly allocated study stent, at the discretion of the operator. Staged procedures for the treatment of non-culprit vessels are permitted within 3 months with the uniform use of the randomly allocated study stent in all lesions. Non-culprit vessels treated by the randomly allocated study stent at baseline or during follow-up will not contribute to the primary endpoint. Dual antiplatelet therapy will be prescribed in all patients for 12 months, according to the current guidelines of the European Society of Cardiology [1].

### **7.4 Device modifications**

Failure to implant the study stent at the intended target lesion will be recorded as a treatment failure. In the event of a failure to implant the study stent, the target lesion can be treated with another device from the same treatment group (different stent diameter or length). In the event that the assigned study stent cannot be implanted, crossover to another DES or a bare metal stent is allowed to complete the procedure successfully. Importantly, crossover patients may not receive the non-randomized study stent (i.e. a patient randomized to the Xience<sup>®</sup> DES (Xience<sup>®</sup> Xpedition or Xience Alpine) may not receive the Orsiro<sup>®</sup> DES, and vice versa) to avoid a confounding factor. Otherwise, the choice of the DES or bare metal stent is left to the discretion of the operator. However, the Steering Committee recommends to preferably implant another commercially available DES (e.g. Medtronic Resolute Onyx<sup>®</sup>, Biosensors Biomatrix<sup>®</sup>, Boston Scientific Synergy<sup>®</sup>) instead of a bare metal stent to prevent an exaggerated restenosis rate in patients with treatment failure. If more than one lesion is treated in a given patient, all remaining lesions should still be treated with the originally assigned study stent (as determined by the randomization). Patients with treatment protocol violations will be included in the analysis in the group to which they were originally allocated by the intention-to-treat principle.

### **7.5 Compliance with study intervention, data collection and follow-up for withdrawn participants**

All patients who undergo randomization will be included in the primary analysis of clinical outcome in the groups to which they were originally allocated to (intention-to-treat principle). Patients will be encouraged to remain in the trial until completion of the 2 years follow-up. Follow-up procedures are described in Section 9. If a patient refuses further follow-up examinations (drop-out) or is lost-to follow-up, the reason for dropping out or loss will be recorded and the patient will be censored at the time when the last follow-up examination took place. If a serious adverse occurs, a patient will be followed until the adverse event resolves or until a stable clinical endpoint is reached.

### **7.6 Concomitant treatments**

#### **7.6.1 Introduction**

In order to avoid confounding factors by differential use of evidence-based antithrombotic medications in patients with STEMI, it is important to ensure a similar treatment in both groups. It is recommended that all patients are treated with aspirin and a new potent oral P2Y12 inhibitor (Prasugrel or Ticagrelor, according to local guidelines), prior to the procedure. Prasugrel and Ticagrelor have been shown to significantly reduce ischemic adverse events following PCI in STEMI patients without an excess in bleeding at 1 year [70,71]. Following completion of successful primary PCI, it is recommended to provide antithrombotic treatment according to local practice. The use of manual or mechanical thrombus aspiration is left to the operator discretion according to local practice but is recommended according to the guidelines of the European Society of Cardiology (ESC) in selected patients with large thrombus burden.

## 7.6.2 Antithrombotic regimen

### 7.6.2.1 Before the procedure

All patients included in the study will receive the following antithrombotic treatment before PCI (Table 4):

- Dual antiplatelet therapy, including:
  - Acetylsalicylic acid: 150-300 mg per os or 80-150 mg intravenous loading dose before the procedure; and
  - Prasugrel: 60 mg per os loading dose before the procedure; patients on prasugrel therapy (at least 4 days): no loading dose required; or
  - Ticagrelor: 180 mg per os loading dose before the procedure; patients on Ticagrelor therapy (at least 4 days): no loading dose required.
- Anticoagulant therapy: unfractionated heparin  $\geq 5'000$  International Units (IU) bolus or 70-100 IU/Kg (50-70 IU/Kg when the use of GP IIb/IIIa inhibitor is planned) bolus.
- The use of Bivalirudin or low-molecular-weight heparins BEFORE primary PCI is not allowed to avoid confounding factors.

### 7.6.2.2 During the procedure

All patients included in the study may receive the following antithrombotic treatment (if required) during PCI (Table 4):

- Additional boluses of unfractionated heparin, if required, to maintain an ACT > 250 seconds during the procedure.
- The use of Bivalirudin or low-molecular-weight heparins DURING primary PCI is not allowed to avoid confounding factors.
- The use of GP IIB/IIIA inhibitors is left to the discretion of the operator. The choice of glycoprotein IIb/IIIa antagonist (Tirofiban, Abciximab, Eptifibatide) is left to the discretion of the operator and local practice, but the use of Abciximab is recommended.

### 7.6.2.3 After the procedure

All patients included in the study will receive the following dual antiplatelet therapy regimen after PCI (Table 4), including:

- Acetylsalicylic acid: 75-100 mg per os od maintenance dose; and
- Prasugrel: 10 mg per os od (5 mg per os one daily, if age >75 year-old, or weight <60 kg) maintenance dose; or
- Ticagrelor: 90 mg per os bid maintenance dose; or
- Clopidogrel: 75 mg per os od maintenance dose (patients on chronic oral anticoagulation, according to the 2014 ESC guidelines [1]).

## 7.6.3 Other treatments

A  $\beta$ -blocker should be administered in the absence of contraindications according to the ESC guidelines [1]. The initial dose of  $\beta$  blocker should be low and then titrated up within a few days to the maximum tolerated dose. An angiotensin-converting enzyme inhibitor should be initiated within 24 hours in patients with hypertension, congestive heart failure, or with a left ventricular ejection fraction of <40%. The initial dose of angiotensin-converting enzyme inhibitor should be low, then titrated up within a few days to the maximum tolerated dose. Alternatively, an angiotensin receptor II blocker may be used. All patients should undergo treatment with a potent statin (Atorvastatin or Rosuvastatin, according to local practice), irrespective of cholesterol and LDL levels.

## 7.7 Return or Destruction of study and control stent

Return or destruction of both study (Orsiro® Hybrid DES) and control (Xience® DES) stents will take place according to standard local procedures for coronary stent systems.

## 8. STUDY ASSESSMENTS

### 8.1 Study table of study procedures and assessments

The following evaluations will be performed at baseline:

1. Demographics;

2. Relevant medical history including:
  - General medical, cardiac, neurologic and renal history;
  - Cardiovascular history;
  - Risk factors (e.g. dyslipidemia, hypertension, diabetes mellitus, tobacco use);
  - History of peripheral vascular disease, stroke, transient ischemic attack.
3. Ischemic/anginal status assessment (according to the Canadian Cardiovascular Society (CCS) or Braunwald classifications);
4. Current cardiovascular and diabetic medications, including anti-platelet/anticoagulant medications;
5. Physical examination, including weight, height, arterial blood pressure and heart rate;
6. 12-lead electrocardiogram (ECG) prior to the index procedure and repeated 24 hours after the procedure and at discharge;
7. Routine laboratory tests, including complete blood count, blood chemistry (Na, K, creatinine, urea), glucose (HbA1c if patient with known diabetes), lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), CK, CK-MB and troponin (T/I, or high sensitive, according to local practice): within 24 hours prior to or immediately after the index procedure. CK and CK-MB will be repeated every 6-8 hours after the procedure until the maximum CK level has been reached.
8. For women of child-bearing potential (age < 50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy, a pregnancy test will be performed prior to angiography.

Subjects are considered provisionally enrolled with the signature on the written informed consent form, however a subject will only proceed to the baseline evaluations and index procedure if all initial and applicable procedure-related eligibility criteria are met. Written informed consent may be obtained on the day of the index procedure or prior to the index procedure. The consenting process, including discussion of the study, with its possible benefits and risks, will be documented in the subject's medical record. A copy of the completed informed consent document must be given to the subject; the original must be placed in the medical record. Failure to obtain a signed and hand-dated informed consent on the day of the index procedure or prior to the procedure constitutes a protocol violation, which must be reported in accordance with all applicable regulations. Patients who have signed the informed consent form and meeting all inclusion and exclusion criteria will be included in the study and randomized before primary PCI. Patients will be followed-up annually up to 2 years for clinical outcomes (study visit at 12 months, phone call at 30 days and 2 years ). A detailed summary of the study time schedule is provided in Table 5.

## **8.2 Assessments of outcomes**

### **8.2.1 Assessment of primary outcome**

The primary endpoint of target lesion failure, a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularization, will be assessed at 12 months during on site office visit. Patients will be questioned about the occurrence of angina, any adverse cardiac events, recurrent hospitalizations, and cardiovascular medication intake.

### **8.2.2 Assessment of secondary outcomes**

The secondary endpoints will be assessed at 12 months during on site office visit, as described for the primary endpoint, and at 30 months, and 2 years during a telephone interview. Patients will be questioned about the occurrence of angina, any adverse cardiac events, recurrent hospitalizations, and cardiovascular medication intake.

### **8.2.3 Assessment of safety outcomes**

#### **8.2.3.1 Adverse events**

The safety of the device will be monitored throughout the trial by assessment of adverse device effects (ADE), serious adverse device effects (SADE) and serious adverse events (SAE). Other adverse events will not be considered in this trial (Definitions according to ISO 14155:2011(E)). The following information will be recorded in the source document and appropriate case report form (CRF) during the entire study period: time of onset, duration, resolution, action to be taken, assessment of intensity, and relationship with study treatment (see Section 9 for Adverse Events definition and procedures). In this study, subjects should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning (e.g., "How has your health been since the last visit?"). Any time during the study, the subject may volunteer information that

resembles an adverse event. If it is determined that an AE has occurred, the investigator should obtain all information required to complete the AE eCRF.

### **8.2.3.2 Laboratory parameters**

Routine laboratory tests, including complete blood count, blood chemistry (Na, K, creatinine, urea), glucose (HbA1c if patient with known diabetes), lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), CK, CK-MB and troponin (T/I, or high sensitive, according to local practice): within 24 hours prior to or immediately after the index procedure. CK and CK-MB will be repeated every 6-8 hours after the procedure until the maximum CK level has been reached.

### **8.2.3.3 Vital signs**

Vital signs (including weight, height, arterial blood pressure, heart rate) and 12-lead ECG will be obtained in supine position at the time of the first medical contact.

## **8.3 Assessments in participants who prematurely stop the study**

All participants who undergo randomization will be included in the primary analysis of clinical outcome in the groups to which they were originally allocated to (intention-to-treat principle). If a patient stops prematurely the study, the reason will be recorded and the patient will be censored at the time when the last follow-up examination took place. If a serious adverse occurs, a patient will be followed until the adverse event resolves or until a stable clinical endpoint is reached (see Section 9 for procedures for participants who prematurely stop the study).

## **8.4 Procedures at each visit**

### **8.4.1 Post- index procedure to hospital discharge**

The following routine evaluations will be obtained after the index procedure (primary PCI) to the hospital discharge (defined as time point when the patient is leaving the tertiary care facility):

- Ischemic/anginal status assessment (according to the Canadian Cardiovascular Society (CCS) or Braunwald classifications) at discharge;
- AE and SAE assessment at discharge;
- Anti-platelet/anti-coagulant medical therapy at discharge;
- Other cardiovascular and diabetic medications at discharge;
- Routine laboratory tests: complete blood count (if any bleeding event), CK and CK-MB will be repeated every 6-8 hours after the procedure until the maximum CK level has been reached. In case of any recurrent angina symptoms, CK, CK-MB and troponin (T/I, or high sensitive, according to local practice) will be performed and repeated every 6-8 hours until the maximum CK level has been reached;
- 12-lead electrocardiogram (ECG) 24 hours after the index procedure, or in case of any recurrent anginal symptoms.

### **8.4.2 30 days follow-up**

Subjects will be evaluated at 1 month post-procedure ( $\pm 7$  days) by a telephone interview.

The following assessments must be completed:

- Ischemic/anginal status assessment (according to CCS or Braunwald classifications) since discharge;
- AEs and SAEs since discharge;
- Anti-platelet/anti-coagulant medical therapy since discharge;
- Other cardiovascular and diabetic medications since discharge;
- Any coronary intervention (e.g., repeat revascularization) that occurred since discharge.

### **8.4.3 1-year follow-up**

Subjects will be evaluated at 12 months post-procedure ( $\pm 30$  days) by an on-site office visit. This visit can also be done by the treating cardiologist or general physician. The data will then be transferred to the responsible centre.

The following assessments must be completed:

- Vital signs, including weight, height, arterial blood pressure, heart rate;
- Ischemic/anginal status assessment (according to CCS or Braunwald classification) since previous contact;

- AEs and SAEs since previous contact;
- Anti-platelet/anti-coagulant medical therapy since previous contact;
- Other cardiovascular and diabetic medications since previous contact;
- Any coronary intervention (e.g., repeat revascularization) that occurred since previous contact;
- 12-lead ECG will be performed during the visit.

#### **8.4.4 2-years follow-up**

Subjects will be evaluated at 24 months post-procedure ( $\pm$  30 days) by a telephone interview.

The following assessments must be completed:

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

#### **8.4.6 Unscheduled Study Visit**

Subjects may present to the clinic outside of the scheduled follow-up windows. Such unscheduled study visits will be reported if the subject has experienced an AE. For an unscheduled study visit, concomitant cardiac medications and data regarding adverse events will be collected. Subjects assessed at an unscheduled study visit may require diagnostic testing (e.g. ECG, angiogram, CK/CK-MB levels) and/or a revascularization procedure to further evaluate and treat ischemic symptoms. Any repeat procedure must be reported on the relevant case report forms, including any unscheduled visits prior to the repeat procedure and/or adverse events associated with the procedure. Only commercially available stents are allowed during repeat procedures. Use of investigational stents is not permitted. Any repeat or unscheduled diagnostic or interventional coronary revascularization procedure performed should include a diagnostic assessment of the target lesion(s) and investigational stent(s). Angiographic data collected during any repeat procedure on the target vessel(s) must be made available to the Clinical Event Committee for an independent review and assessment. Angiographic images should be submitted to the Clinical Event Committee for an independent review and assessment of the target lesion and investigational stent.

## **9. SAFETY**

### **9.1 Adverse events**

All serious adverse events (SAE) and major adverse cardiac event will be collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure. The information on SAEs will be systematically recorded by clinical safety assessment during study visits or telephone contact. Patients will continue to be followed-up up to 2 years after the index procedure for adverse events. Patients experiencing a SAE will be followed until the adverse event resolves or until a stable clinical endpoint is reached.

### **9.2 Definition and Assessment of (Serious) Adverse Events and other safety related events**

#### **9.2.1 Adverse Event (AE)**

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2]. This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the investigational medical device.

#### **9.2.2 Adverse Device Effect (ADE)**

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1]. This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This includes any event that is

a result of a use error or intentional misuse.

### 9.2.3 Serious Adverse Event (SAE)

Adverse event that:

- results in death, or
- led to a serious deterioration in health that either:
  - results in a life-threatening illness or injury, or
  - results in a permanent impairment of a body structure or a body function, or
  - required in-patient or prolonged hospitalisation, or
  - results in medical or surgical intervention to prevent life threatening illness

This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system. A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

### 9.2.4 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

### 9.2.5 Health hazards that require measures

Findings in the trial that may affect the safety of study participants and which require preventive or corrective measures intended to protect the health and safety of study participants.

### 9.2.6 Causal Relationship of Adverse Events

A causal relationship towards the medical device or study procedure should be rated by the investigator as:

- **Not related:** The event is definitely not associated with device application or with study procedures; a relationship can be ruled out.
- **Possibly related:** The relationship between device application or study procedures and the event is possible, but other causes cannot definitely be ruled out.
- **Related:** The event is definitely associated with device application or study procedures.

Device deficiencies that might have led to an SAE are always related to the medical device.

### 9.2.7 Reporting of (Serious) Adverse Events and other safety related events

#### 9.2.7.1 Reporting to the Principal Investigators:

The following events are to be reported to the Coordinating Investigator within 24 hours upon becoming aware of the event:

- All SAEs
- Health hazards that require measures
- Device deficiencies

The Coordinating Investigator will evaluate SAEs with regard to causality and seriousness. Device deficiencies are assessed regarding their potential to lead to an SAE.

#### 9.2.7.2 Reporting to Authorities

The Local Investigator has also the responsibility to report **health hazards** that require immediate safety and protective measures within 2 days to the local Ethics Committee as well as to the Coordinating Investigator. All other in the trial involved Ethics Committees receive health hazards having occurred in Switzerland via the Coordinating Investigators within the same timeline. All participating investigators will be informed regarding the occurrence of a health hazard. The Coordinating Investigator will notify Swissmedic of reportable events, based on the national regulations for materiovigilance procedures.

#### 9.2.7.3 Periodic safety reporting

A yearly safety report will be submitted by the Principal Investigators to the Ethics Committee.

#### 9.2.7.4 Follow up of (Serious) Adverse Events

Participants terminating the study, either regularly or prematurely, with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert will be followed until the SAE or AE resolves or until a stable clinical endpoint is reached. In case of loss to follow-up of a participant with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert, efforts will be actively undertaken by the Principal Investigators and local investigators to ensure that the patient will be adequately followed-up locally and medically supported.

## 10. STATISTICAL METHODS

### 10.1 Introduction

The BIOSTEMI clinical trial is a prospective, multicenter, randomized, controlled study. A total of 1'250 subjects will be randomized, stratified by study center and diabetes status, in a 1:1 ratio with 625 subjects randomized to receive the Orsiro® Hybrid sirolimus-eluting stent (BP-SES) and 625 subjects randomized to receive the Xience® everolimus-eluting stent (DP-EES). The trial is designed to assess the superiority of the Orsiro® BP-SES compared to the Xience® DP-EES with respect to occurrence the primary endpoint target lesion failure until and including 365 days post index procedure. For this purpose, new data from BIOSTEMI subjects will be combined with historical data from the subgroup of STEMI subjects from the BIOSCIENCE trial (n=407, called BIOSCIENCE STEMI hereafter) employing robust Bayesian priors. Only subjects who meet all clinical and angiographic eligibility criteria of the BIOSTEMI trial, and who provided written informed consent, will be included in the analysis. All patients who undergo randomization will be included in the primary and secondary analyses of clinical outcomes in the study arm to which they were originally allocated according to the *intention-to-treat* principle. The primary and secondary endpoints will be analyzed using a robust Bayesian approach. No adjustments will be made for multiple comparisons; p-values, 95% confidence intervals and 95% credibility intervals will be two-sided.

### 10.2 Analysis of primary endpoint

The primary endpoint is a binary variable that indicates whether TLF occurred in a given patient during the time it was observed. For the primary analyses, observation time was censored at 365 days or at the time the patient was lost to follow-up, last valid contact before the patient withdrew consent, or died. The TLF incidence rate is the average number of TLF events per patient per year; it will be compared between the two trial arms. The primary endpoint from BIOSTEMI subjects (N=1'250) will be combined using a robust Bayesian approach with individual subject data from the BIOSCIENCE STEMI trial (N=407, Pilgrim T. et al. EuroIntervention 2015, in press). The primary endpoint, incidence rate of target lesion failure within 365 days post index procedure, will be analysed with log-Poisson models (Generalized Linear Models with log link function and Poisson distributed response) applied to the new data from BIOSTEMI with Robustified Historical Priors (RHPs) that incorporate historical information from BIOSCIENCE STEMI. Compared to conventional Meta-analytic approaches, RHPs will down-weight historical information if it turns out to be inconsistent with the new data. The parameter of interest is the Rate Ratio (RR) defined as Rate(BP-SES) / Rate(DP-EES). We will report the median of the posterior distribution of the RR and two-sided 95% Credibility Intervals (CrI). Superiority of BP-SES will be declared if the upper limit of this 95% CrI is  $\leq 1$ .

The RHPsmethod used here is based on Schmidli et al. [72] adapted to the setting of a single historical trial. Our method is specific for Poisson models that use a log link function. The log of the estimated rates are noted  $\beta$  hereafter. We derived the historical priors for rates from BIOSCIENCE STEMI subgroup individual data with a Poisson model using a vague prior defined in the log domain as a Gaussian centred at  $\mu=0$  with standard deviation  $\sigma=3$  (which translates to a precision parameter  $\tau=0.11$ ). This yields a vague prior distribution for the event rates with a 95% credibility interval ranging from 0.003 to 358 clinical events per patient per year. The prior is defined in the log domain as

$$P_V(\beta) \sim \text{Normal}(\mu = 0.000, \tau = 0.111) \quad (\text{eq.1})$$

The historical informative priors are of the same form where parameter values for the primary endpoint were estimated from the 407 BIOSTEMI subjects as reported in Table 6.

We derive Robustified Historical Priors by mixing historical informative priors and the vague priors with mixing weight  $W_R = 0.5$ .

$$P_{\text{ROB\_SES}}(\beta) = (1-W_R) P_{\text{SES}}(\beta) + W_R P_V(\beta) \quad (\text{eq.2})$$

$$P_{\text{ROB\_EES}}(\beta) = (1-W_R) P_{\text{EES}}(\beta) + W_R P_V(\beta) \quad (\text{eq.3})$$

The rate ratio for the primary endpoint TLF will be obtained from a log-Poisson models applied to the new data from BIOSTEMI with the RHPs given in eq. 2 and eq. 3. For descriptive purposes, incidence curves will be constructed for time-to-event variables using the Kaplan-Meier method using individually pooled data, combining the BIOSCIENCE STEMI and BIOSTEMI patients.

### **10.3 Determination of Sample Size**

The BIOSTEMI trial is powered for superiority on the primary endpoint at 1 year using the robust Bayesian approach that incorporates historical information as described above. Power calculation was based on a Monte Carlo simulation where data of the 407 BIOSCIENCE STEMI patients were included via RHPs and data for the BIOSTEMI patients were simulated from a binomial distribution according to the assumptions described hereafter. In the STEMI subgroup of the BIOSCIENCE trial, a rate ratio of 0.38 was associated to the experimental arm BP-SES (Pilgrim T. et al. EuroIntervention 2015, in press). To be conservative, a less pronounced rate ratio of 0.60 was expected in the BIOSTEMI trial and used for the present sample size calculation. This assumption yields an incidence rate for the primary endpoint of 4.2% in the BP-SES and of 7.0 % in the DP-EES for the BIOSTEMI trial. Drop-out rate was assumed to be 5% at 1 year. A 1:1 allocation ratio will be used and a two-sided  $\alpha=0.05$ . Finally, enrolment of a total of 1'250 patients (625 per arm) in the BIOSTEMI trial would provide over 80% power to detect a rate ratio of 0.60.

### **10.4 Analyses of secondary endpoints and analyses at 2 years of follow-up**

Secondary clinical endpoints at 1 year of follow-up will be analysed using the same approach as for the primary endpoint, a robust Bayesian analysis with a log-Poisson model incorporating historical information via a RHPs estimated from the respective secondary clinical endpoint from BIOSCIENCE STEMI subjects. Both the primary endpoint and all secondary clinical endpoints will be evaluated again at 2 years of follow-up, similarly using robust Bayesian analysis with a log-Poisson model incorporating historical information via a RHP estimated from the respective secondary clinical endpoint from BIOSCIENCE STEMI subjects. For descriptive purposes, incidence curves will be constructed for time-to-event variables using the Kaplan-Meier method using individually pooled data, combining the BIOSCIENCE STEMI and BIOSTEMI patients.

### **10.5 Secondary Analyses**

Secondary analyses will be based solely on the BIOSTEMI subjects. Description of study participants and medication will be presented according to clinical baseline and procedural characteristics analysed with conventional statistical methods. Mantel-Cox log-rank tests will be used to compare clinical outcomes between arms, and will be reported with rate ratios and 95% confidence intervals. Poisson models using a vague prior (eq.1) will be used in a secondary analysis to compare clinical outcomes between arms. Pre-specified stratified analyses of the primary endpoint will be carried out according to the following patient characteristics recorded at baseline: presence or absence of diabetes, gender, age  $\geq 65$  years, BMI  $\geq 30$  kg/m<sup>2</sup>, and renal failure. For descriptive purposes, incidence curves will be constructed for time-to-event variables using the Kaplan-Meier method.

### **10.6 Interim analyses and statistical criteria of termination of trial**

No interim analyses are planned and no such analyses will be conducted to terminate the trial before all patients have been enrolled.

### **10.7 Detailed description of planned analyses**

A detailed statistical analysis plan will be written as a separate document.

### **10.8 Handling of missing data and drop-outs**

Patients that are lost to follow-up, but eligible for primary analyses will be included in the analyses and censored at the time of loss to follow-up. Stratified analyses will be based on patients where the baseline stratification variable is available.

## **11. QUALITY ASSURANCE AND CONTROL**

### **11.1 Data handling and record keeping / archiving**

The Local Investigator is required to prepare and maintain adequate and accurate case histories designed to

record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

### **11.2 Case Report Forms**

An electronic data capture (EDC) system will be built for the study. The EDC system will include electronic case report forms (eCRFs) designed to capture study information, which are completed by trained site staff. eCRFs documenting SAEs, U(S)ADEs, device failures and device malfunctions, should be submitted via the EDC system as soon as possible, preferably within 24 hours after the investigator becomes aware of the event. All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrollment or follow-up visit. All data collected will not be identifiable reference to the subjects. The subject's anonymity will be maintained and the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects will be identified only by their assigned study number and initial on all CRFs and other records and documents submitted to the investigators, the monitor, and other authorised parties.
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.
- The investigator will maintain all study documents in strict confidence.
- CRF entries will be performed by authorized persons and it will be assured that any authorized person can be identified.

### **11.3 Specification of source documents**

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Source documents include demographic data, visit dates, participation in study and Informed Consent Forms, randomisation number, SAEs, AEs and concomitant medication, and results of relevant examinations. The investigator assures that source documents are appropriately stored and completed. The patient's file will reveal that this patient is a study participant by entering the following details: study name, protocol number, date of enrollment, informed consent obtained prior to any study specific procedure. Each follow up visit will be reported in the source data and should at least contain the information required according the protocol. The investigator assures that medical files and Case Record Forms are accessible for inspection by authorities and monitoring visits.

### **11.4 Investigator Records**

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

- all correspondence relating to the study with another investigator, the CEC, a monitor, the sponsor, or any other regulatory agency.
- all clinical forms and documentation, including:
  - copy of the signed subject consent form;
  - date and time of exposure to investigational stent;
  - all procedure and follow-up report forms, including supporting documents;
  - records of any adverse event, including supporting documentation;
  - records pertaining to subject deaths during the study;
  - documentation and rationale for any deviations from.

### **11.5 Record keeping / archiving**

According to current laws for clinical trials on medical implantable devices, recorded data will be kept and archived for 15 years after regular termination or premature termination of the clinical trial.

### **11.6 Data management, security, validation, analysis and archiving**

An electronic data capture (EDC) system (Cardibase web-based clinical database system) will be developed for the purpose of the study. The EDC system will include electronic case report forms (eCRFs) designed to capture study information, which are completed by trained site staff. The EDC system will be the conduit for the eCRF data entry, data validation, and access to realtime configured functions, tools, and reports for the Steering Committee. Data management and analysis will be performed by the Clinical Trials Unit (CTU), Bern, Switzerland, who will be in charge of the data management procedures, including coding, verification, validation, security and storage of the database. Study data will be archived on the EDC system for 15 years

after regular termination or premature termination of the clinical trial.

### **11.7 Monitoring**

Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and ISO14155, and that the protocol is followed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

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

### **11.8 Audits and Inspections**

The study site may be subject to audits and inspections to verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and ISO14155, and that the protocol is followed. The study documentation and the source data/documents should be accessible to auditors/inspectors (also CEC) and questions should be answered during inspections. All involved parties must keep the participant data strictly confidential.

### **11.9 Confidentiality, Data Protection**

Direct access to the source documents will be permitted for purposes of monitoring, audits and inspections (ICHE6, 6.10). The Steering Committee will have access to the protocol, dataset, and statistical code, during and after the study for publication and dissemination.

## **12. PUBLICATION AND DISSEMINATION POLICY**

The Principal Investigators of the study intend to publish the multicentre results of this clinical trial. The publication of the principal results from any single center within the trial is not allowed until publication of the multicenter results. Exceptions to this rule require the prior approval of the Steering Committee. Anticipated manuscripts from secondary analyses with principal authorship from the Steering Committee are anticipated. All publications will follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

## **13. FUNDING AND SUPPORT**

BIOSTEMI is an investigator-initiated study supported by Biotronik AG, Bülach, Switzerland.

## **14. INSURANCE**

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

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## 16. TABLES

**TABLE 1: ORSIRO® HYBRID DES CLINICAL TRIALS SUMMARY**

	<b>BIOFLOW-I</b>	<b>BIOFLOW-II</b>	<b>BIOFLOW-III</b>	<b>BIOFLOW-IV</b>	<b>BIOSCIENCE</b>
<b>Location</b>	Romania	Europe	Europe, Chile	Europe, Japan	Switzerland
<b>Design</b>	<ul style="list-style-type: none"> <li>• Prospective</li> <li>• Multi-center</li> <li>• Non-randomized</li> <li>• Single-arm</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective</li> <li>• Multi-center</li> <li>• <b>Randomized</b> (2:1 vs. Xience Prime™)</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective</li> <li>• Multi-center</li> <li>• Non-randomized</li> <li>• Single arm</li> <li>• Open label</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective</li> <li>• Multi-center</li> <li>• <b>Randomized</b> (2 :1 vs. Xience Prime™/Xpedition™)</li> </ul>	<ul style="list-style-type: none"> <li>• Prospective</li> <li>• Multi-center</li> <li>• <b>Randomized</b> (1 :1 vs. Xience Prime™)</li> </ul>
<b>Primary endpoint</b>	Late lumen loss at 9 months	Late lumen loss at 9 months	<b>Target lesion failure at 12 months</b>	<b>Target lesion failure at 12 months</b>	<b>Target lesion failure at 12 months</b>
<b>Number of subjects enrolled</b>	30	452	1'356	555 planned	2'119
<b>Lesion criteria</b>	<ul style="list-style-type: none"> <li>• Single, de novo lesion</li> <li>• Native artery</li> <li>• ≥50% and ≤100%</li> </ul>	<ul style="list-style-type: none"> <li>• 1 or 2 de novo lesions</li> <li>• Separate arteries</li> <li>• ≥50% and ≤100%</li> <li>• ≤26 mm</li> <li>• RVD ≥2.25 mm and ≤4.0 mm</li> </ul>	All-comers	<ul style="list-style-type: none"> <li>• 1 or 2 de novo lesions</li> <li>• Separate arteries</li> <li>• ≥50% and ≤100%</li> <li>• ≤26 mm</li> <li>• RVD ≥2.25 mm and ≤3.75 mm</li> </ul>	All-comers
<b>Follow-up</b>	<ul style="list-style-type: none"> <li>• 1 month and 1, 2, 3 years: clinical</li> <li>• 4 and 9 months: clinical and angiography</li> <li>• 4 and 9 months: IVUS (15 patients)</li> </ul>	<ul style="list-style-type: none"> <li>• 1, 6, 12 months and 2, 5 years: clinical</li> <li>• 9 months: clinical and angiography</li> <li>• 9 months: OCT and IVUS (60 patients)</li> </ul>	<ul style="list-style-type: none"> <li>• 6, 12 months and 3, 5 years: clinical</li> </ul>	<ul style="list-style-type: none"> <li>• 1, 6, 12 months and 2, 5 years: clinical</li> </ul>	<ul style="list-style-type: none"> <li>• 1, 6, 12 months and 2, 5 years: clinical</li> </ul>
<b>Status (enrollment period)</b>	Primary endpoint completed (enrollment July 2009)	Primary endpoint completed (enrollment July 2011-March 2012)	Primary endpoint completed (enrollment August 2011-March 2012)	Start enrollment September 2013	Primary endpoint completed (enrollment February 2012-June 2013)

**TABLE 2: THE ORSIRO® HYBRID DES SYSTEM**

STENT LENGTH (mm)	STENT DIAMETER (mm)					
	2.25	2.5	2.75	3.0	3.5	4.0
9	2.25	2.5	2.75	3.0	3.5	4.0
13	2.25	2.5	2.75	3.0	3.5	4.0
15	2.25	2.5	2.75	3.0	3.5	4.0
18	2.25	2.5	2.75	3.0	3.5	4.0
22	2.25	2.5	2.75	3.0	3.5	4.0
26	2.25	2.5	2.75	3.0	3.5	4.0
30	2.25	2.5	2.75	3.0	3.5	4.0
35	2.25	2.5	2.75	3.0	3.5	4.0
40	2.25	2.5	2.75	3.0	3.5	4.0

**TABLE 3: THE XIENCE XPEDITION® AND XIENCE ALPINE® DES SYSTEM**

STENT LENGTH (mm)	STENT DIAMETER (mm)						
	2.25	2.5	2.75	3.0	3.25	3.5	4.0
8	2.25	2.5	2.75	3.0	3.25	3.5	4.0
12	2.25	2.5	2.75	3.0	3.25	3.5	4.0
15	2.25	2.5	2.75	3.0	3.25	3.5	4.0
18	2.25	2.5	2.75	3.0	3.25	3.5	4.0
23	2.25	2.5	2.75	3.0	3.25	3.5	4.0
28	2.25	2.5	2.75	3.0	3.25	3.5	4.0
33	2.25	2.5	2.75	3.0	3.25	3.5	4.0
38	2.25	2.5	2.75	3.0	3.25	3.5	4.0
48	-	2.5	2.75	3.0	3.25	3.5	4.0

**TABLE 4: ANTITHROMBOTIC THERAPY**

TIMING	MEDICATION	REGIMEN
PRIOR TO PROCEDURE	Acetylsalicylic acid	150-300 mg per os or 80-150 mg intravenous loading dose before the procedure
	Prasugrel, or Ticagrelor	<ul style="list-style-type: none"> <li>- <u>Prasugrel</u>: 60 mg per os loading dose before the procedure; patients on prasugrel therapy (at least 4 days): no loading dose required; or</li> <li>- <u>Ticagrelor</u>: 180 mg per os loading dose before the procedure; patients on Ticagrelor therapy (at least 4 days): no loading dose required.</li> </ul>
DURING THE PROCEDURE	Heparin	<ul style="list-style-type: none"> <li>- <math>\geq 5'000</math> International Units (IU) bolus or 70-100 IU/Kg (50-70 IU/Kg when the use of GP IIb/IIIa inhibitor is planned) bolus.</li> <li>- Additional boluses of unfractionated heparin, if required, to maintain an ACT &gt; 250 seconds during the procedure.</li> </ul>
	GP IIB/IIIA inhibitors	Per investigator's discretion
AFTER THE PROCEDURE	Acetylsalicylic acid	75-100 mg per os od, <u>lifelong</u> .
	Prasugrel, or Ticagrelor	<ul style="list-style-type: none"> <li>- <u>Prasugrel</u>: 10 mg per os od (5 mg per os one daily, if age &gt;75 year-old, or weight &lt;60 kg) maintenance dose <u>for 12 months</u>; or</li> <li>- <u>Ticagrelor</u>: 180 mg per os bid maintenance dose, <u>for 12 months</u>.</li> </ul>
	Clopidogrel (patients on chronic oral anticoagulation)	Antithrombotic therapy according to the 2014 Guidelines of the European Society of Cardiology (1)

**TABLE 5: STUDY SCHEDULE**

STUDY EVENTS	SCREENING	INTERVENTION PERIOD				
		PROCEDURE	POST-PROCEDURE TO HOSPITAL DISCHARGE	30 DAYS ± 7 DAYS	1 YEAR ± 30 DAYS	2 YEARS ± 30 DAYS
Type of contact				Telephone interview	Office visit	Telephone interview
Patient information and Informed consent	X					
Demographics	X					
Medical history	X			X	X	X
Inclusion/exclusion criteria	X					
Physical examination	X				X	
Vital signs: blood pressure, heart rate, weight, height	X	X	X		X	
<sup>1</sup> Laboratory tests: complete blood count, blood chemistry, lipids, glucose	X		X			
<sup>2</sup> Laboratory Tests: CK, CK-MB	X		X			
<sup>3</sup> Laboratory Tests: Troponin	X		X			
<sup>4</sup> 12-lead ECG	X		X		X	
<sup>5</sup> Pregnancy Test	X					
Randomisation		X				
Coronary angiography		X				
Assesment of the primary endpoint					X	
Assesment of the secondary endpoints		X		X	X	X
Assessment for concomitant medical therapy	X	X	X	X	X	X
Adverse Events and severe adverse event monitoring		X	X	X	X	X

<sup>1</sup> Within 24 hours prior to or immediately after the index procedure.

<sup>2</sup> CK, CK-MB are determined prior to PCI and every 6-8 hours until CK maximum level has been reached.

<sup>3</sup> Troponin T/Troponin I/high sensitive troponin, whichever is clinical routine.

<sup>4</sup> ECG prior to primary PCI, 24 hours post-procedure and at discharge.

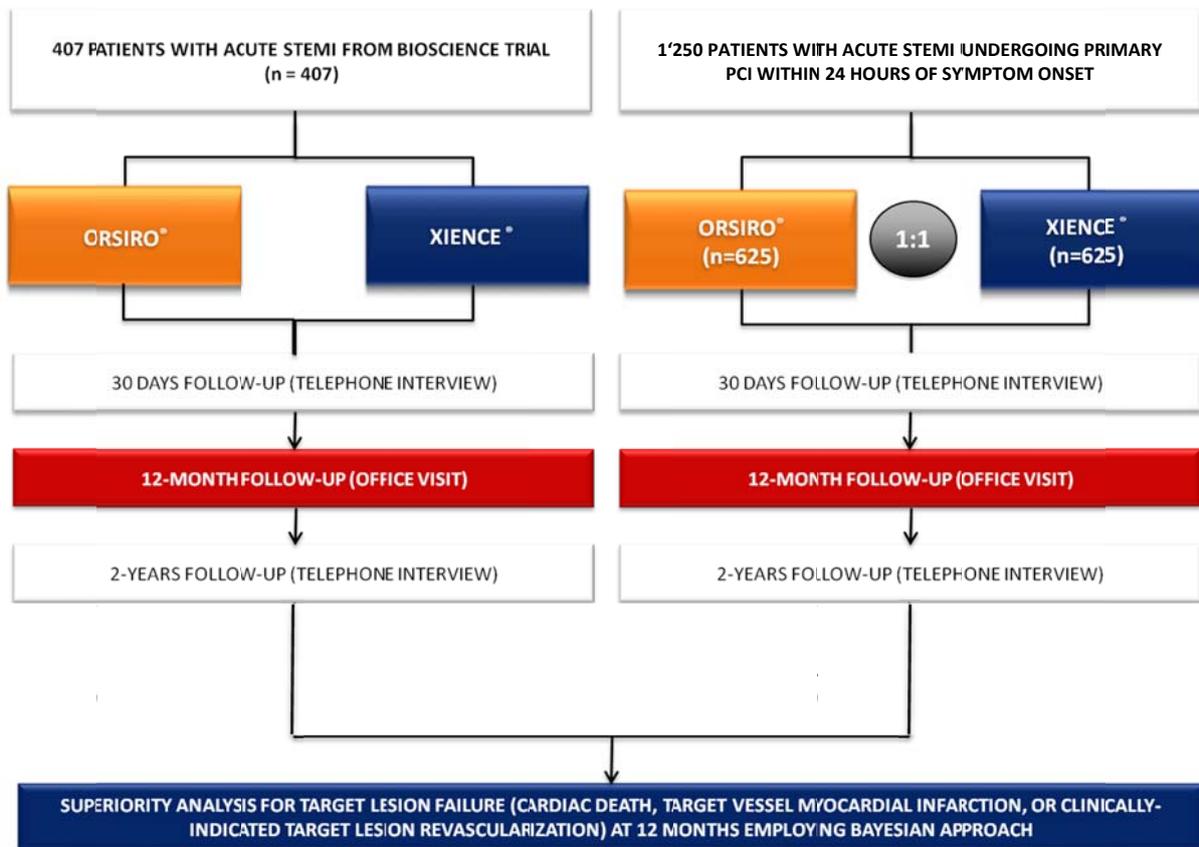
<sup>5</sup> Female of childbearing potential (age < 50 years and last menstruation within the last 12 months), who did not underwent tubal ligation, ovariectomy or hysterectomy.

**TABLE 6: SUMMARIES OF THE POSTERIOR DISTRIBUTION FOR THE LOG INCIDENCE RATE OF TLF OBTAINED FROM 407 STEMI SUBJECTS FROM THE BIOSCIENCE STEMI TRIAL OBTAINED WITH A LOG-POISSON MODEL USING THE VAGUE PRIOR GIVEN IN EQ. 1.**

TRIAL ARM	$\mu$	$\sigma$	$\tau$	HISTORICAL INFORMATIVE PRIORS
BP-SES	-3.422	0.377	7.036	$P_{SES}(\beta) \sim \text{Normal}(\mu = -3.422, \tau = 7.036)$
DP-EES	-2.458	0.244	16.796	$P_{EES}(\beta) \sim \text{Normal}(\mu = -2.458, \tau = 16.796)$

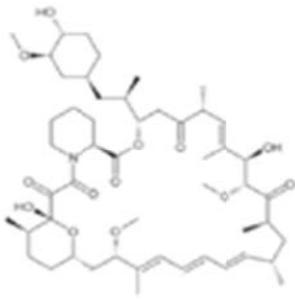
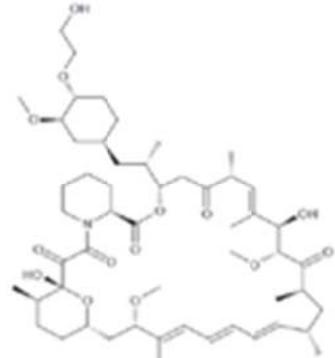
## 17. FIGURES

FIGURE 1: STUDY FLOW CHART



PCI: percutaneous coronary intervention; TLR: target lesion revascularization; TVR: target vessel revascularization; TVF: target vessel failure; Bayesian approach: combined analyses of BIOSCIENCE and BIOSTEMI patients using a robust Bayesian approach

**FIGURE 2: STUDY DES AND CONTROL DES COMPONENTS**

	<b>Orsiro® Hybrid DES</b>	<b>Xience® DES</b>
		
<b>Stent material</b>	Co-Cr, L-605	Co-Cr, L-605
<b>Stent thickness</b>	60 µm	81 µm
<b>Passive coating</b>	Silicon carbide	None
<b>Polymer coating</b>	Biodegradable (PLLA)	Durable (PBMA/PVDF-HFP)
<b>Immunosuppressive drug</b>	Sirolimus	Everolimus
		

PBMA, poly n-butyl methacrylate; PLLA, poly-l lactic acid; PVDF-HFP, poly vinylidene fluoride co-hexafluoropropylene.

## 18. APPENDICES

### APPENDIX I: DEFINITIONS

#### BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

##### A. Severity

- **Class 1:** New onset of severe or accelerated angina. Patients with new onset (<2 months in duration) exertional angina pectoris that is severe or frequent (>3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.
- **Class 2:** Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.
- **Class 3:** Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours

##### B. Clinical circumstances in which unstable angina occurs

- **Class A:** Secondary unstable angina. Patients in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia. Such conditions reduce myocardial oxygen supply or increase myocardial oxygen demand and include anaemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrhythmia, unusual emotional stress, thyrotoxicosis, and hypoxemia secondary to respiratory failure.
- **Class B:** Primary unstable angina. Patients who develop unstable angina pectoris in the absence of an extracardiac condition that have intensified ischemia, as in class A.
- **Class C:** Postinfarction unstable angina. Patients who develop unstable angina within the first 2 weeks after a documented acute myocardial infarction.

#### BLEEDING

##### BARC (Definition for bleeding)

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###### Type 0 No Bleeding

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**Type 1** Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional.

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**Type 2** Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that **does not** fit the criteria for Types 3, 4, or 5, but **does** meet at least one of the following criteria:

- 1) Requiring non-surgical, medical intervention by a health care professional
  - 2) Leading to hospitalization or increased level of care
  - 3) Prompting evaluation
- 

###### Type 3

###### Type 3a

- Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

###### Type 3b

- Overt bleeding plus hemoglobin drop  $\geq 5$  g/dL (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous inotropes

###### Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal).
  - Subcategories; Confirmed by autopsy or imaging or LP

- 
- Intra-ocular bleed compromising vision
- 

#### **Type 4 - CABG-related bleeding**

- Perioperative intracranial bleeding within 48 hrs
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of  $\geq 5$  units of whole blood or packed red blood cells within a 48 period\*.
- Chest tube output  $\geq 2L$  within a 24 hour period

If a CABG - related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'

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#### **Type 5 - Fatal Bleeding**

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Type 5a: Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Type 5b: Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious

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Comment: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes.

\* Cell saver products will not be counted

### **CABG**

Coronary Artery Bypass Grafting

#### ***Urgent versus elective:***

An urgent CABG is defined as one that takes place within 24 hours of the index procedure.

### **CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION (CCS)**

- Class 1: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous, rapid, or prolonged exertion at work or during recreation.
- Class 2: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or any only during the first hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
- Class 3: Marked limitations of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.
- Class 4: Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.

### **COMPLETE BLOOD COUNT (CBC)**

Measure of the concentration of white blood cells, red blood cells, and platelets in the blood.

### **DEATH**

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

**Cardiac death:** Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death.

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

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

### **DE NOVO LESION**

A coronary artery lesion not previously treated.

#### **DEVICE SUCCESS**

The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) **AND** either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using the assigned device only. These measurements will be made by the independent angiographic core laboratory. If the core laboratory is unable to assess the % residual stenosis, the investigator's assessment as recorded in the CRF will be used for the statistical analysis.

#### **DIAMETER STENOSIS (%)**

Diameter of the reference vessel minus the minimal luminal diameter; divided by the reference diameter and multiplied by 100.

#### **DISSECTION, NHLBI CLASSIFICATION (National Heart Lung and Blood Institute)**

- Type A Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material
  - Type B Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles
  - Type C Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material
  - Type D Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow
  - Type E Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen
- Type Filling defect accompanied by total coronary occlusion

#### **HEMORRHAGIC VASCULAR COMPLICATION**

Vascular complications include the following:

- Hematoma at access site > 5 cm
- False aneurysm
- AV fistula
- Retroperitoneal bleed
- Peripheral ischemia/nerve injury
- Any transfusion required will be reported as a vascular complication unless a clinical indication clearly other than catheterization complication is present
- Vascular surgical repair

#### **IN-SEGMENT MEASUREMENT**

In-segment measurement is defined as the measurement within the treated lesion. The treated lesion is considered to start 5 mm proximal of the stented lesion and to end 5 mm distal of the stented lesion.

#### **IN-STENT MEASUREMENT**

In-stent measurement is defined as the measurement within the stented segment.

#### **INTRACORONARY THROMBUS [25, 26, 27]**

##### ***Non-occlusive thrombus:***

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

**Occlusive thrombus:**

A TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

**LATE LUMEN LOSS**

Late lumen loss is defined as the difference in minimal luminal diameter (MLD) between post-procedural and follow up MLD in mm.

**LESION CLASS (AMERICAN COLLEGE OF CARDIOLOGY / AMERICAN HEART ASSOCIATION CLASS)**Type A Lesions

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

Type B Lesions

Moderately complex, tubular (length 10 to 20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (> 45°, < 90°), irregular contour, moderate or heavy calcification, total occlusion < 3 months old, ostial in location, bifurcation lesions requiring double guidewires, and some thrombus present.

*Type B1:* One adverse characteristic.

*Type B2:* Two or more adverse characteristics.

Type C Lesions

Severely complex, diffuse (length > 2 cm), excessive tortuosity of proximal segment, extremely angulated segment > 90°, total occlusions > 3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

**LESION SUCCESS**

The attainment of < 30% residual stenosis by QCA (**AND** either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method. These measurements will be made by the independent angiographic core laboratory. If the core laboratory is unable to assess the % residual stenosis, the investigator's assessment as recorded in the CRF will be used for the statistical analysis.

**MAJOR ADVERSE CARDIAC EVENTS (MACE)**

Defined as a composite of cardiac death, myocardial infarction (Q-wave and Non-Q wave), or clinically-indicated target lesion revascularization.

**MINIMAL LUMINAL DIAMETER (MLD)**

MLD is defined as the mean minimum lumen diameter derived from two orthogonal views (by the quantitative coronary angiography laboratory).

**MYOCARDIAL INFARCTION**

In percutaneous coronary intervention trials, initial blood sampling of CK (and CK-MB or Troponin, if CK is elevated) must be performed prior to the index procedure. Repeat samples should be performed at least twice between 8 and 24 hours following the procedure and at least 4 hours apart. Three categories can be distinguished being:

- Peri – Procedural MI
- Post – Intervention MI
- Electrocardiographic Classification

## Peri – Procedural MI

is defined as within 48 hours after PCI and within 7 days after CABG. Within this category we distinguish:

### Peri-procedural

Total CK >2 times upper limit of normal (ULN) in the presence of a confirming cardiac

specific biomarker (a positive value of CK-MB, Troponin I/T) on any one sample obtained after the procedure. If total CK is not available then CKMB >3 times ULN is considered evidence of periprocedural MI. If neither CK nor CKMB are available then a Troponin elevation that is >5 times the 99th percentile or diagnostic value for the specific institution is considered evidence of peri-procedural MI.

### Peri-procedural MI in the setting of evolving MI

1. If the peak total CK (or CK-MB) from the index infarction has not yet been reached: recurrent chest pain lasting >20 minutes (or new ECG changes consistent with MI) AND the peak CK (or CK-MB in absence of CK) level measured within 24 hours after the event is elevated by at least 50% above the previous level.
2. If the elevated CK (or CK-MB) levels from the index infarction are falling or have returned to normal within 24 hours post index PCI: EITHER a new elevation of CK >2 x ULN within 24 hours post index PCI if the CK level has returned to <ULN OR a rise by >50% above the previous nadir level if the CK level has not returned to <ULN.

## Post – Intervention MI

Within this category we distinguish:

**Non-procedural related MI (spontaneous MI)** (adapted from ESC/ACC guidelines JACC 2000): either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (Troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  - a. ischemic symptoms;
  - b. development of new pathologic (defined by Minnesota Code) Q-waves on the ECG;
  - c. ECG changes indicative of ischemia (ST segment elevation or depression);
2. Pathologic findings of an acute MI.
3. Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.

**MI after CABG.** A definite diagnosis of myocardial infarction is made:

1. Within the first 7 days post-intervention (CABG or Stent) when the two following criteria both are positive:
  - A. Development of new abnormal Q-waves not present on the patient's baseline (i.e. before allocation) ECG. The Minnesota Code for pathologic Q-waves will be used.
  - B. Enzyme changes defined as more than 10% of the ratio of [peak CK-MB/peak total CK] on 3 consecutive samples OR enzyme changes defined as CKMB >5x ULN.
2. Beyond 7 days after any intervention procedure (CABG or Stent) the standard definition for non-procedural related MI applies.

**Comment 1:** MI after CABG refers to both, studies including CABG as investigational treatment (e.g. Freedom and Syntax studies) and patients undergoing CABG as a repeat intervention.

**Comment 2:** This unusual definition of MI, within 7 days post-intervention, is based on published results from the EAST-study. This study showed electrocardiographic peri-operative QMI to be a weak end-point without prognostic importance in patients treated with bypass surgery.

## Electrocardiographic Classification

Within this category we distinguish:

#### **Q-wave MI**

Development of new pathological s in 2 or more contiguous leads (according to the Minnesota code as assessed by the ECG core laboratory) with or without post-procedure CK or CK-MB levels elevated above normal.

#### **Non Q-wave MI**

All MIs not classified as Q-wave.

#### **PROCEDURE SUCCESS**

The attainment of < 20% residual stenosis by QCA (**AND** either a TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, using any percutaneous method without the occurrence of death, MI, or repeat revascularization of the target vessel during the hospital stay. These measurements will be made by the independent angiographic core laboratory. If the core laboratory is unable to assess the % residual stenosis, the investigator's assessment as recorded in the CRF will be used for the statistical analysis.

#### **STENT THROMBOSIS**

##### **Timing:**

Acute stent thrombosis: 0 – 24 hours post stent implantation

Subacute stent thrombosis: > 24 hours – 30 days post stent implantation

Late stent thrombosis: > 30 days – 1 year post stent implantation

Very late stent thrombosis: > 1 year – 5 years post stent implantation

##### **Angiographic definition of stent thrombosis:**

Stent thrombosis is considered to have occurred if:

Thrombolysis In Myocardial Infarction (TIMI) flow is:

- TIMI flow grade 0 with occlusion originating in the in-segment (peri-stent) region
- TIMI flow grade 1, 2 or 3 originating in the in-segment (peri-stent) region in the presence of a thrombus (see definition of "Intracoronary thrombus" above)

**AND** at least one of the following criteria have been fulfilled:

1. acute ischemic symptoms (typical chest pain with duration >20 minutes)
2. ischemic ECG changes:
  - A. ST-segment elevation in territory of implanted stent
  - B. ST-segment depression or T-wave inversion in territory of implanted stent
3. typical rise and fall in cardiac biomarkers (3xULN of CK-MB).

##### **Clinical definition of suspected stent thrombosis:**

Irrespective of the time after the index procedure, clinical stent thrombosis is considered to have occurred in the following cases:

1. Any cardiac or sudden death, which is possibly related to acute ischemia in the territory of the implanted stent as evidenced by either electrocardiographic changes (ST elevation or ST depression in the territory of the stented segment) or autopsy finding (thrombotic occlusion of the stent).
2. Any myocardial infarction (MI) which is possibly related to acute ischemia in the territory of the implanted stent as evidenced by electrocardiographic changes in patients who do not undergo angiography.

#### **TARGET LESION (TL)**

The target lesion is the treated lesion starting 5 mm proximal of the stented lesion and to end 5 mm distal of

the stented lesion.

### **TARGET LESION FAILURE (TLF)**

TLF is defined as the composite of Cardiac death, Target vessel Q-wave or non-Q wave Myocardial Infarction (MI) (i.e., Q-wave MI that cannot be attributed to a non-target vessel), clinically driven Target Lesion Revascularization (TLR) and Emergent Coronary Artery Bypass Grafting (CABG).

### **TARGET LESION REVASCULARIZATION (TLR)**

TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel. All TLRs will be recorded in the CRF (Reintervention Justification Form) and be classified prospectively as justified or non-justified by the investigator prior to the reintervention as well as retrospectively by the independent angiographic core laboratory (in the case of % diameter stenosis).

#### **Clinically-indicated**

Angiography at follow-up shows a percent diameter stenosis  $\geq 50\%$  (QCA) **and** if one of the following occurs:

1. A positive history of recurrent angina pectoris presumably related to the target vessel.
2. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the target vessel.
3. Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve). The results of the test must be documented in the Case Report Form.

A TLR with a diameter stenosis  $\geq 70\%$  (QCA) in the absence of the above mentioned ischemic signs or symptoms is also considered justified.

**Non-clinically indicated** TLRs are interventions for:

1. All stenoses  $< 50\%$  in the presence or absence of ischemic signs or symptoms;
2. All stenoses  $\geq 50\%$  but  $< 70\%$  without ischemic signs or symptoms.

### **TARGET VESSEL (TV)**

The TV is defined as the index coronary artery which was in physical contact with any component (guiding catheter, guide wire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

### **TARGET VESSEL FAILURE (TVF)**

TVF is defined as target vessel revascularization, Q-wave or non-Q wave MI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel

### **TARGET VESSEL REVASCULARIZATION (TVR)**

A TVR is defined as a revascularization of any segment of the index coronary artery which was in physical contact with any component (guiding catheter, guide wire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

#### **TIMI CLASSIFICATION**

TIMI 0	No perfusion
TIMI 1	Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run
TIMI 2	Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel
TIMI 3	Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds

**URGENT REVASCULARIZATION**

An urgent (as opposed to “elective”) revascularization is one that takes place within 24 hours of the index procedure.

**APPENDIX II: PATIENT INFORMATION AND INFORMED CONSENT FORM**