ECRI-005

Clinical Investigational Plan

Multicenter Randomized Study of the MiStent Sirolimus Eluting Absorbable Polymer Stent System (MiStent SES) for Revascularization of Coronary Arteries (DESSOLVE III)

Version 2.0, March 7th, 2018

Sponsor:

European Cardiovascular Research Institute (ECRI)

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Protocol approval page

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Protocol version: 2.0, dated 07 March 2018

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

_____ _____

P.W. Serruys, International Center for Circulatory Health — Date
NHLI, Imperial College, London, United Kingdom
Steering Committee Member,
Principal Investigator

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W. Wijns, The Lambe Institute for Translational Medicine and Curam — Date
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Principal Investigator

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Gerrit-Anne van Es — Date
Managing Director, ECRI-Trials B.V.

Protocol Signature page Site Principal Investigator

I have read this protocol and/or amendment and appendices and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the study.

I will conduct the study in accordance with the protocol and ISO 14155 guidelines, as well as local regulations, and I accept respective revisions to the protocol approved by authorized personnel of the Sponsor and by regulatory authorities.

Protocol version: 2.0, dated 07 March 2018

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

_____
Principal Investigator

_____ _____
Principal Investigator (signature) Date

_____
Institution Name/Location

Protocol Amendment

Overview of changes

Sections and numbering are references to the track changes in the protocol amendment version 2.0 dated March 7, 2018. Changes to the text are indicated in **bold**.

Section	DESSOLVE III protocol version 1.0	DESSOLVE III protocol version 2.0	Rationale
Synopsis (Follow-up)	All patients will have annual contact through *3* years follow-up to assess clinical status and adverse events.	All patients will have annual contact through **5** years follow-up to assess clinical status and adverse events.	Since early results show a potential benefit of the MiStent SES, we want to collect additional data to assess the long-term results of the MiStent
Chapter 4 (Objective)	The patients will be followed through *3* years for major clinical events.	The patients will be followed through **5** years for major clinical events.	Since early results show a potential benefit of the MiStent SES, we want to collect additional data to assess the long-term results of the MiStent
Par. 8.5.1 (Blinding)	Subjects will be blinded through the completion of *3*-year follow-up.	Subjects will be blinded through the completion of **5**-year follow-up.	Since early results show a potential benefit of the MiStent SES, we want to collect additional data to assess the long-term results of the MiStent
Par. 8.11 (Follow-up Period)	Phone contacts are scheduled at 6 months (+14 days), 2 years (+30 days) and 3 years (+30 days).	Phone contacts are scheduled at 6 months (+14 days), 2 years (+30 days), 3 years (+30 days)**, 4 years (+30 days) and 5 years (+30 days)**.	Since early results show a potential benefit of the MiStent SES, we want to collect additional data to assess the long-term results of the MiStent

	All one-year follow-up visits must be scheduled at least at one year after randomization (and henceforth not earlier). This also applies to the scheduling of the 2 and 3 year visits.	All one-year follow-up visits must be scheduled at least at one year after randomization (and henceforth not earlier). This also applies to the scheduling of the 2, 3, **4 and 5 year** visits.	Since early results show a potential benefit of the MiStent SES, we want to collect additional data to assess the long-term results of the MiStent
Par. 8.13 (Subjects Lost of Follow-Up)	Vital status will be searched in public sources at the end of the 3 year follow-up period.	Vital status will be searched in public sources at the end of the **5** year follow-up period.	Since early results show a potential benefit of the MiStent SES, we want to collect additional data to assess the long-term results of the MiStent

DESSOLVE III protocol version 1.0:

Schedule of Events	**Baseline (prePCI)**	**Procedure**	**Post-procedure\ Discharge**	**30 days (+7 days)**	**6 months (+14 days)**	**1 year (+30 days)**	**2 year (+30 days)**	**3 years (+30 days)**
				Visit	**TC Contact**	**Visit**	**TC Contact**	**TC Contact**
Inclusion/Exclusion Criteria	•							
Informed Consent	•							
History & Risk Factors	•							
Anginal status	•		•	•	•	•	•	•
Recording of Medications	•		•	•	•	•	•	•
12-Lead ECG	•[1]		•[2]	•		•		
Creatinine	•							
Cardiac enzymes (CK, CKMB, Troponin)	•[3]		•[4]					
Serious Adverse Events[5]		•	•	•	•	•	•	•

DESSOLVE III protocol version 2.0:

Schedule of Events	Baseline (prePCI)	Procedure	Post-procedure\ Discharge	30 days (+7 days)	6 months (+14 days)	1 year (+30 days)	2 year (+30 days)	3 years (+30 days)	4 year (+30 days)	5 years (+30 days)
				Visit	TC Contact	Visit	TC Contact	TC Contact	TC Contact	TC Contact
Inclusion/Exclusion Criteria	•									
Informed Consent	•									
History & Risk Factors	•									
Anginal status	•		•	•	•	•	•	•	•	•
Recording of Medications	•		•	•	•	•	•	•	•	•
12-Lead ECG	•[1]		•[2]	•		•				
Creatinine	•									
Cardiac enzymes (CK, CKMB, Troponin)	•[3]		•[4]							
Serious Adverse Events[5]		•	•	•	•	•	•	•	•	•

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1 PROTOCOL SYNOPSIS

Protocol Number	ECRI-005
Title	DESSOLVE III: Multicenter Randomized Study of the MiStent Sirolimus Eluting Absorbable Polymer Stent System (MiStent SES) for Revascularization of Coronary Arteries III
Investigational (Study) Device	MiStent SES (MISTENT) The MiStent® Sirolimus Eluting Absorbable Polymer Coronary Stent System. Description: The MiStent SES system is a balloon expandable sirolimus eluting stent with an absorbable polymer coating.
Comparator (Control) Device	XIENCE EES (XIENCE) XIENCE V® or XIENCE PRIME™ or XIENCE Xpedition™ Everolimus Eluting Coronary Stent System. Description: The XIENCE systems are balloon expandable drug eluting stents using everolimus with a non-erodible or durable polymer coating. *NOTE: For this study, only XIENCE stents with "comparable" stent sizes to MISTENT will be used. XIENCE stents up to 30mm length with diameters between 2.5 mm and 3.5 mm will be allowed for implantation.
Objective	To compare the MISTENT with the XIENCE with respect to target lesion failure (TLF) at 12 months in a non-inferiority trial in a "real world" patient population.
Design	This is a prospective, randomized, 1:1 balanced, controlled, single-blind, multi-center study comparing clinical outcomes at 12 months between MISTENT and XIENCE in a "Real world, all comers" patient population (patients with symptomatic coronary artery disease including patients with chronic stable angina, silent ischemia, and acute coronary syndromes, who qualify for percutaneous coronary interventions).
Number of Subjects	Enrollment of 1400 patients with 700 MISTENT and 700 XIENCE.
Investigational Sites	Approximately 17 sites in Europe will participate.

Follow-up	All patients will be (at minimum) contacted at 30 days, 6 months, and 12 months post procedure to assess clinical status and adverse events. The 30 day and 12 month will be a clinic visit. All patients will have annual contact through 5 years follow-up to assess clinical status and adverse events.
Primary Endpoint	The primary endpoint for this trial is a non-inferiority comparison of a device-oriented composite endpoint (DOCE) or TLF of the MISTENT group to the XIENCE group at 12 months post-procedure. TLF is a composite of clinical endpoint of cardiac death, myocardial infarction (MI, WHO Extended Definition) not clearly attributable to a nontarget vessel and clinically-indicated target lesion revascularization (TLR).
Secondary Endpoints	**Secondary Endpoints** (evaluated at each follow-up visit/contact) 1. Composite Endpoints • POCE defined as all-cause death, any MI, or any revascularization • MACE defined as all-cause death, any MI, or any TVR • TVF defined as cardiac death, TV MI, or clinically indicated TVR • DOCE/TLF defined as cardiac death, TV MI or clinically-indicated TLR (for all follow-up/visits other than 12 months) 2. Mortality • All death • Cardiac death • Non-cardiac death (vascular and non-cardiovascular) 3. Myocardial Infarction • All MI • TV-MI • Non-TV-MI 4. Revascularization • Target Lesion revascularization (TLR) (any, clinically-indicated TLR, non-clinically indicated TLR) • Target Vessel revascularization (TVR) (any, clinically-indicated TVR, non-clinically indicated TVR) • Non-TV revascularization • Any revascularization 5. Stent thrombosis rates according to ARC classification • ST - Early (Acute, Sub-acute), Late, Very Late. • ST - Definite, Probable, Possible • ST – Definite/Probable

General Inclusion and Exclusion Criteria	**Inclusion Criteria:** 1. Male or female patients ≥18 years; 2. Presence of one or more coronary artery stenoses of ≥50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation. 3. The vessel should have a reference vessel diameter ranging from 2.5 mm to 3.75 mm (no limitation on the number of treated lesions, vessels, or lesion length); ***All*** lesions of the patient must comply with the angiographic inclusion criteria. 4. The patient is judged to be capable of providing voluntary informed consent and has been fully informed of the nature of the study, is willing to comply with all study requirements and will provide written informed consent as approved by the Ethics Committee of the respective clinical site. **Exclusion Criteria:** 1. Known pregnancy or breastfeeding at time of randomization; 2. Known contraindication or hypersensitivity to sirolimus, everolimus, cobalt-chromium, or to medications such as aspirin, heparin, bivalirudin, and all of the following four medications: clopidogrel bisulfate, ticlopidine, prasugrel, ticagrelor; 3. Concurrent medical condition with a life expectancy of less than 12 months. 4. The patient is unwilling/not able to return for outpatient clinic at 1 month and 12 months follow-up. 5. Currently participating in another trial and not yet at its primary endpoint.
Antiplatelet Medication	All patients with stable coronary artery disease pre-index procedure must receive dual anti-platelet therapy, being aspirin (ASA) and platelet aggregation inhibition therapy for at least 6 months after PCI followed by ASA monotherapy indefinitely. All patients with acute coronary syndrome pre-index procedure must receive dual anti-platelet therapy, being aspirin (ASA) and platelet aggregation inhibition therapy for at least 12 months after PCI followed by ASA monotherapy indefinitely.
Statistical Analysis Plan	**Primary Analysis:** The study is powered at 85% to show non-inferiority for the MISTENT

	when compared to XIENCE. The primary analysis will be based on an intent-to-treat (ITT) patient population, that is, those patients who have signed an approved consent form and are randomized to a study stent(s). A secondary per protocol (PP) evaluation will be conducted on patients that received only the assigned study stent(s) at the target lesion(s). **Assumptions:** 1:1 randomization (treatment allocation ratio MISTENT to XIENCE) One-sided alpha = 5% Power = 85% Non-inferiority margin of 4.0% XIENCE TLF – 8.3% at 12M[1] The MISTENT expected TLF assumption is based on an assumed no difference in event rate as compared to the control stent. **Study Sample Size Calculation: 1400 Subjects** A sample size calculation of 1364 patients with 682 in each arm has been calculated using the assumptions above, using PASS software, using the standard normal distribution (Z test). Accounting for loss to follow-up of approximately 2%, these numbers are increased to 700 and 700 respectively, for a total randomized sample of 1400 subjects.

[1] Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. NEJM 2010;363:136-46.

2 INTRODUCTION

2.1 Coronary Artery Disease

Coronary artery disease (CAD) is a progressive, pathological condition that leads to hardening, or atherosclerosis, of the coronary arteries due to the gradual deposition of lipid and cholesterol plaques on the inner layer, or intima of the arteries. The burden of CAD remains high across Europe and the rest of the world. CAD continues to be the main cause of death and a major cause of morbidity and loss of quality of life. The decline in age-standardized mortality rates and in incidence of CAD in many countries illustrates the potential for prevention of premature deaths and for prolonging life expectancy. New therapeutic options for prevention and treatment of CAD have resulted in an increasing number of patients who survive a cardiovascular event; in developed countries the burden has shifted from the middle-aged to the elderly and the prevalence of CAD increases exponentially with aging.

CAD is a leading public health problem accounting for a significant proportion of total societal costs and representing 27% of total cardiovascular disease costs. Together with cerebrovascular diseases, CAD accounts for 64% of all cardiovascular deaths. Treatment of CAD is complex and often involves invasive, minimally invasive or noninvasive coronary interventions and life style modification. In the minimally invasive arena, the most widely utilized and perhaps one of most effective is coronary stenting with drug eluting stents (DES).

2.2 Coronary Revascularization Using Stents

Coronary stenting as a transcatheter procedure to restore coronary arterial patency is a concept that subsequently developed from the limitations of percutaneous transluminal coronary angioplasty (PTCA) procedures. The first of the contemporary balloon-expandable stents was the Palmaz-Schatz stent. Clinical assessments of the Palmaz-Schatz stent and the next generation stents developed by multiple manufacturers over the last 20 years demonstrated several benefits of coronary stenting relative to standalone PTCA. These include prevention of elastic recoil and reduced restenosis.

While all coronary stents are generally intended for the same interventional purpose, stents can differ significantly with respect to their design. Most commonly, stents are characterized by their structural design, materials and methods of expansion. Structural elements and materials are varied in an effort to improve clinical performance. The clinical effectiveness of the use of a bare metal stent (BMS) has been limited by the occurrence of late in-stent restenosis primarily due to vascular smooth muscle cell migration and proliferation of the neointima into the lumen of the stent.

2.3 Drug Eluting Stents

Combining the mechanical support of a stent with an adjunctive treatment to limit neointimal in-growth has been postulated to further improve therapeutic outcomes. This combined approach was initially used successfully in intracoronary brachytherapy. However, this approach was shown to be limited by persistent late thrombosis, edge effects, and by the complexity of delivering radiation therapy in the catheterization laboratory.

Drug-eluting stents (DES) have been introduced globally in the last several years. In most cases, DES manufacturers have modified existing BMS designs (typically stainless steel or CoCr alloys) by applying a permanent polymer coating which elutes a drug intended to reduce the extent of restenosis. Delivery of drugs such as paclitaxel, sirolimus, everolimus, zotarolimus, etc. from such coated stents was developed to address restenosis caused by the growth and proliferation of neointima following stent implantation.

The performance of a DES relies on various factors, with drug dose and release kinetics having the most impact on overall efficacy. The polymer component is critical in controlling the release of the drug, but serves no other purpose after the drug has been released. DES products, such as TAXUS (Boston Scientific, Natick, MA) and CYPHER (Cordis, Warren, NJ) have experienced widespread clinical use and although the permanent polymers are designed to be biocompatible, it's important to note that they also have the potential to produce an immune response within the vessel that can lead to delayed healing and ultimately poor re-endothelialization, positive remodeling of the vessel, uncovered struts and stent strut malapposition. These findings have often been indicated to be an underlying cause for very late stent thrombosis (>1 year post procedure).[2]

Additionally, long-term interventional investigations with these stents indicate that revascularization with stents with durable polymers appear to undergo a process of ongoing erosion of the luminal space, described as late "catch-up" restenosis or "late lumen creep". This suggests that durable polymer DES does not prevent the restenotic process but merely delay the advancement of neointimal tissue growth.

2.4 XIENCE

The XIENCE family of everolimus eluting stents (Abbott Vascular, Santa Clara, CA) is considered to be the current standard for DES given the ease of use and clinical performance. XIENCE, designed to have a more biocompatible polymer, has demonstrated consistent reductions in stent thrombosis compared to the TAXUS and has demonstrated significant reductions in definite stent thrombosis over the CYPHER. In the 1,002 patient SPIRIT III

[2] Stefanini G, Kalesan B, Serruys P, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomized non-inferiority trial. Lancet 2011; 378:1940-1948.

U.S. pivotal clinical trial, XIENCE demonstrated statistical superiority to TAXUS on the study's primary endpoint of in-segment late loss at eight months. XIENCE also demonstrated statistical non-inferiority to TAXUS of target vessel failure (TVF) at nine months (7.2% for XIENCE vs. 9.0% for TAXUS) and low rates of stent thrombosis between one and two years, defined as very late stent thrombosis, per Academic Research Consortium (ARC) definition of definite/probable stent thrombosis (0.3%for XIENCE, 1.0% for TAXUS).

However, animal model data continue to suggest that all DES with permanent polymers, including XIENCE, show evidence of delayed endothelialization at 14 days compared to bare-metal stents using scanning electron microscopy at 14 days. In addition, the rates of stent thrombosis remain too high, especially in high-risk cohorts, which necessitate prolonged dual antiplatelet therapy.

2.5 Bioabsorbable Polymers

In an effort to enhance safety and efficacy, the focus has shifted to developing strategies to eliminate the potential harm associated with permanent polymer-based DES. One of these solutions is the use of bioabsorbable polymers. Stents coated with bioabsorbable polymers could achieve excellent acute and long-term efficacy results, but disappear completely within months, thus potentially reducing the incidence of polymer related latent clinical adverse events. To date, a number of biodegradable polymer-based DES have been tested in humans (and approved) with results indicating that it is a safe and efficacious alternative to permanent polymer DES.[3,4]

2.6 The MiStent® Sirolimus Eluting Absorbable Polymer Coronary Stent System

In order to address these concerns, Micell Technologies (Durham, NC) has developed the MiStent® Sirolimus Eluting Absorbable Polymer Coronary Stent System (MiStent SES) consisting of a cobalt-chromium (CoCr) BMS platform and an absorbable polymer/drug coating containing crystalline sirolimus.

This next-generation SES is intended to combine the long-term safety and stability characteristics of a BMS with the demonstrated clinical advantages of a DES. Micell's proprietary surface modification technology provides a unique drug delivery system through the use of absorbable polymers and an approved drug with a well-known safety and efficacy profile (sirolimus). The rapid-absorbing polymer formulation is intended to control drug

[3] Meredith I, Verheye S, Dubois C, et al. Primary Endpoint Results of the EVOLVE Trial. A Randomized Evaluation of a Novel Bioabsorbable Polymer-Coated, Everolimus Coronary Stent. J Am Coll Cardiol 2012;59:1–9).
[4] Garg S, Sarno G, Serruys P, et al. The twelve-month outcomes of a biolimus eluting stent with a biodegradable polymer compared with a sirolimus eluting stent with a durable polymer. EuroIntervention 2010;6:233-239.

elution and limit the duration of polymer exposure precisely and consistently. As a result, Micell's coating is intended to deliver a precise therapeutic solution for coronary artery disease with the potential to avoid the long-term safety concerns associated with current permanent polymer drug-eluting stents.

The polymer is applied using a proprietary coating process that utilizes Electrostatic Rapid Expansion of Supercritical fluids (e-RESS). This method is used to deposit a coating of polylactide-co-glycolic acid (PLGA) on a BMS with a few simple processing steps. The drug is within the polymer coating which helps regulate the drug's time-release properties by maintaining the drug in crystalline particle morphology.

Following stent implantation, this polymer/drug coating is deposited from the stent struts into the adjacent tissue and is designed to be off the stent and in the tissue within 45 to 60 days and fully absorbed from the tissue in 90 days. The deposited material continues to elute and deliver drug to the surrounding tissue as the polymer is absorbed by the tissue leaving an inert BMS within the coronary artery. The crystalline sirolimus drug continues a controlled elution from within the tissue for up to 9 months for sustained inhibition of neointimal proliferation even after the polymer is absorbed.

This controlled release system provides the benefit of protection from an initial burst release followed by rapid drug degradation and allows for targeted delivery of the active ingredient into the surrounding tissue with continuous and predictable drug elution throughout the affected artery following stent implantation. The drug delivery characteristics inhibit growth of tissue into the artery and results in enhanced vessel patency.

Micell Technologies have conducted two investigational studies with the MiStent SES; DESSOLVE I and DESSOLVE II.

2.6.1 DESSOLVE I Clinical Study

DESSOLVE I was a first-in-human, 30 patient prospective, open-label, non-randomized, single arm, multicenter study to demonstrate whether the MiStent SES could safely and effectively improve coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo lesions of length ≤20 mm, in native coronary arteries with reference vessel diameter between 2.5 mm and 3.5 mm. Patients returned in subgroups of 10 at either 4-, 6- or 8-months post procedure for angiographic, intra-vascular ultrasound (IVUS) and optical coherence tomography (OCT) evaluations. All patients were to undergo angiographic, IVUS and OCT assessments at 18 months post-procedure, with 27/30 (90%) patients returning for invasive imaging studies. Only clinical follow up was obtained at 12 months and will also be obtained at years 2 through 5.

Protocol-mandated angiographic follow-up through 240 days was available for all 30 patients. Angiographic results for the primary endpoint, as assessed by the angiography core laboratory, from the follow-up at 4, 6 and 8 months were as follows: a mean (±SD) in-stent LLL of 0.01±0.12, 0.21±0.36 and 0.09±0.10 mm respectively with an overall mean of 0.10 (±0.23) mm. Angiographic analysis of paired imaging results revealed an in-stent LLL at 4/6/8 month of 0.07±0.12 mm as compared to 0.09±0.15 mm at 18 months. MACE, defined as any death, myocardial infarct (MI) or target vessel revascularization (TVR) was 0.0% (0/30) for both in-hospital and at 30 days, and 3.3% (1/30) at 240 days post index procedure. Between 30 days and 240 days of follow-up one patient experienced a non-target vessel non-Q-wave MI, resulting in a total MI rate of 3.3% (1/30) at 240 days post index procedure. There were no deaths, TLR or TVR. No patients experienced a protocol defined TVF or TLF through 30 days or 240 days post index procedure. There were no ARC-defined stent thrombosis (ST) events reported throughout the entire 8-month follow-up period. All 30 patients had a follow-up contact at 12 months and no additional MACE (death, MI, TVR) or ST were reported in any patient through 360 days. At 2 years, no additional MACE were reported. Prior to the 3 year follow-up, one patient experienced a non-target vessel non-Q-wave MI for a 3 year MACE rate of 6.9% (2/29). No target vessel MACE was reported through 3 years follow-up.

These data compare favorably with the published literature for similar DES and offer a unique observation of minimal progression of late lumen loss through 18 months.

2.6.2 DESSOLVE II Clinical Study

DESSOLVE II was a prospective, single-blind, 2:1 unbalanced randomized, controlled, multicenter study to demonstrate whether the MiStent SES could safely and effectively improve coronary luminal diameter in patients with symptomatic ischemic heart disease due to discrete de novo lesions of length ≤27 mm, in native coronary arteries with reference vessel diameter between 2.5 mm and 3.5 mm. All eligible patients were randomly assigned in a 2:1 ratio to receive the MiStent SES or the control Endeavor DES system. The study is powered at 90% to show superiority for an in-stent late lumen loss at 9-months for the MiStent SES when compared with the control stent, the Endeavor DES.

Follow-up assessments were performed at 30-days, 6-months and 9-months after the index procedure, and continued at 12-months and annually at years 2 through 5. All patients were to return at 9 months post procedure for angiographic assessment. In addition, one subgroup of 38 patients (24 MiStent SES and 14 Endeavor DES controls) underwent Optical Coherence Tomography (OCT) at procedure and at 9 months and

another subgroup of 29 patients (19 MiStent SES and 10 Endeavor DES controls) underwent endothelial function testing (EFT) by rapid atrial pacing at 9 months. The study is powered at 90% to show superiority for an in-stent late lumen loss at 9-months for the MiStent SES when compared with the control stent, the Endeavor DES.

In this study, 184 patients (with 184 lesions) were randomized, 123 MiStent SES and 61 Endeavor DES, which yielded an analysis population of 181 patients (with 181 lesions) with 121 MiStent SES and 60 Endeavor DES. Three patients received non-study stents at the target lesion.

The mean (±SD) in-stent late loss was 0.27 (±0.46) mm for the MiStent SES arm and 0.58 (±0.41) mm for the Endeavor DES arm. The difference between the two arms of -0.31 mm (95% Confidence Interval (CI) -0.45 to -0.16) was statistically significant ($p< 0.001$) and the MiStent SES was superior to the Endeavor DES, satisfying the primary efficacy objective of the trial.

The overall MACE rate from discharge to 9 months was 4.3% (5/116) in the MiStent SES and 6.7% (4/60) in Endeavor DES arm. The difference between the two arms was -2.4% with a two-tailed 95% CI from -11.9% to 4.4%. These results indicate that the safety profiles of the two study devices are comparable, while the usefulness outcomes reflect numerically better performance for the MiStent SES at 9 months follow up.

The MACE and TLF rates out to 3 years for both the MiStent SES and control stent are reported below.

	MiStent SES (n=121)	MiStent SES (n=121)	Endeavor DES (n=60)	Endeavor DES (n=60)
	MACE	TLF	MACE	TLF
9 Months	4.3% (5/117)	3.4% (4/117)	6.7% (4/60)	5.0% (3/60)
12 Months	5.1% (6/118)	4.2% (5/118)	8.3% (5/60)	5.0% (3/60)
2 Years	6.7% (8/120)	5.0% (6/120)	13.3% (8/60)	5.0% (3/60)
3 Years	8.3% (10/120)	5.8% (7/120)	15.3% (9/59)	6.8% (4/59)

The clinical studies confirm safety and equivalence of the MiStent in adverse clinical events to the control stent, Endeavor. The event rate was low, albeit in the low risk patients and lesions usually studied in trials at this stage. In terms of neointimal response as shown by late lumen loss, the MiStent was numerically superior to Endeavor and is in line with other currently available DES.

2.7 Study Objectives

This protocol will provide data to comply with regulatory requirements as well as gain substantial additional information on patients in a real world setting. This protocol will compare clinical outcomes of the MISTENT and XIENCE in a broad patient and lesion population. These data may also be used to support regulatory approvals in other countries and provide data on various lesion types that may be treated in order to expand the indications for MISTENT.

3 DEVICE DESCRIPTION

Micell Technologies has developed a novel coronary drug eluting stent system. The MiStent® Sirolimus Eluting Absorbable Polymer Coronary Stent System (MiStent SES) consists of four components; a bare metal stent (BMS), a delivery system, the absorbable polymer coating and the anti-proliferative drug, sirolimus. The device system received CE Marking in June 2013.

3.1 The Stent Platform and Delivery Catheter

The underlying BMS platform of the MISTENT is a thin, laser-cut and electro-polished L605 cobalt chromium (CoCr) alloy tube. The delivery catheter is a rapid exchange design compatible with guide wires up to 0.014 inch diameter and 6 Fr guide catheters. The delivery balloon is composed of polyamide (Rilsan® nylon). The nominal inflation pressure of the balloon is 8 atm, and the rated burst pressure is 16 atm.

A photo of the stent is shown in Figure1. Available stent diameters for this trial are 2.5, 2.75, 3.0 and 3.5 mm and available stent lengths are 9-30mm.

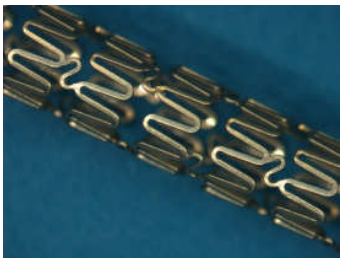

Figure 1. The cobalt chromium alloy stent.

3.2 Drug and Polymer Coating of the MISTENT

The stent coating consists of poly (lactic-*co*-glycolic acid) (PLGA) and crystalline particles of sirolimus. Sirolimus was first discovered as a product of the bacterium Streptomyces hygroscopicus in a soil sample from Easter Island, an island also known as "Rapa Nui", hence the name, rapamycin. Sirolimus possesses immunosuppressive and anti-proliferative activity and hence, the drug has the ability to interrupt cell migration and proliferation. Sirolimus has also used in several other CE-marked DES with extensive experience in both clinical trials and practice – these trials have previously shown the anti-proliferative effect of sirolimus in conjunction with coronary stents and have demonstrated significantly lower restenosis rates in coronary arteries following angioplasty as compared to BMS, resulting in fewer repeat revascularization procedures.

PLGA is a well-known and characterized biodegradable and biocompatible polymer and is used in a host of FDA approved and CE Marked therapeutic devices, such as grafts, sutures, implants, and prosthetic devices. PLGA acts as a carrier material loaded with a

crystalline form of sirolimus that affords controlled release of drug through the healing period following coronary intervention to minimize neointimal thickening and restenosis of the lesion. The coating (drug and polymer) on the MISTENT is deposited onto the stent with a proprietary process developed by Micell Technologies. This coating is approximately 5-15 mm thick (greater on the abluminal surface) and encapsulates the stent struts for drug release throughout the stented region. The MISTENT contains approximately the same amount of sirolimus for the corresponding stent size as another approved DES, the CYPHER stent, and the coating and particle size have been chosen to allow controlled delivery of the drug. It has been shown that the polymer is fully eluted and reabsorbed within 3-months post-implant while drug remains in the tissue surrounding the stent for up to 9 months to continue to control the growth of neointimal tissue.

4 OBJECTIVE

The primary objective of this study is to compare the performance of MISTENT to that of XIENCE in an all-comers patient population with symptomatic ischemic heart disease. The patients will be followed through 5 years for major clinical events.

5 DESIGN OF THE TRIAL

This is a prospective, single-blind (patient), 1:1 balanced randomized, controlled, multicenter study. Approximately 17 sites in Europe will participate. The enrollment required for this study is 1400 patients and as this is a 1:1 randomization, it is anticipated that 700 patients will be treated with the MISTENT and 700 patients will be treated with the control XIENCE V® or XIENCE PRIME™ or XIENCE Xpedition™ Everolimus Eluting Coronary Stent System (XIENCE) (Abbott Vascular, Santa Clara, CA).

Clinical data will be adjudicated by an independent Clinical Event Committee.

An independent Data Safety and Monitoring Board (DSMB) will monitor the individual and collective safety of the patients in the study during enrolment phase.

6 ENDPOINTS

6.1 Primary Endpoint (Non-inferiority)

The primary endpoint for this trial is a non-inferiority comparison of a device-oriented composite endpoint (DOCE) or TLF of the MISTENT group to the XIENCE group at 12 months post-procedure. TLF is a composite of clinical endpoint of cardiac death, myocardial infarction (MI, WHO Extended Definition) not clearly attributable to a nontarget vessel and clinically-indicated target lesion revascularization (TLR).

6.2 Secondary Endpoints at all follow-up visits/contacts

1. Composite Endpoints
    a. POCE defined as all-cause death, any MI, or any revascularization
    b. MACE defined as all-cause death, any MI, or any TVR
    c. TVF defined as cardiac death, TV MI, or clinically indicated TVR
    d. DOCE/TLF defined as cardiac death, TV MI or clinically-indicated TLR (for all follow-up/visits other than 12 months)
2. Mortality
    a. All death
    b. Cardiac death
    c. Non-cardiac death (vascular and non-cardiovascular)
3. Myocardial Infarction
    a. All MI
    b. TV-MI
    c. Non-TV-MI
4. Revascularization
    a. Target Lesion revascularization (TLR) (any, clinically-indicated TLR, non-clinically indicated TLR)
    b. Target Vessel revascularization (TVR) (any, clinically-indicated TVR, non-clinically indicated TVR)
    c. Non-TV revascularization
    d. Any revascularization
5. Stent thrombosis rates according to ARC classification
    a. ST - Early (Acute, Sub-acute), Late, Very Late.
    b. ST - Definite, Probable, Possible
    c. ST- Definite/Probable

7 SUBJECT SELECTION

Subjects participating in the study must meet all the inclusion criteria. Subjects who meet any of the exclusion criteria must not be registered in the study.

7.1 Inclusion Criteria

"All comers" patients:

1. Male or female patients ≥18 years;
2. Presence of one or more coronary artery stenoses of ≥50% in a native coronary artery or in a saphenous venous or arterial bypass conduit suitable for coronary stent implantation.
3. The vessel should have a reference vessel diameter ranging from 2.5 mm to 3.75 mm (no limitation on the number of treated lesions, vessels, or lesion length);

   All lesions of the patient must comply with the angiographic inclusion criteria.
4. The patient is judged to be capable of providing voluntary informed consent and has been fully informed of the nature of the study, is willing to comply with all study requirements and will provide written informed consent as approved by the Ethics Committee of the respective clinical site.

7.2 Exclusion Criteria

1. Known pregnancy or breastfeeding at time of randomization;
2. Known contraindication or hypersensitivity to sirolimus, everolimus, cobalt-chromium, or to medications such as aspirin, heparin, bivalirudin, and all of the following four medications: clopidogrel bisulfate, ticlopidine, prasugrel, ticagrelor;
3. Concurrent medical condition with a life expectancy of less than 12 months.
4. The patient is unwilling/ not able to return for outpatient clinic at 1 month and 12 months follow-up.
5. Currently participating in another trial and not yet at its primary endpoint.

8 STUDY PROCEDURES

8.1 Patient Enrollment

Patients who meet criteria for eligibility will be asked to participate. The minimum number of patients to be enrolled and treated in the trial is 1400. No lead-in training phase is required for this study.

Patients will be considered randomized into the study (ITT) when an Ethical Committee approved consent form has been signed, all inclusion/exclusion criteria have been met and the patient is randomized into either the MISTENT or the XIENCE arm of the study. This will occur when it is confirmed that the patient meets the angiographic criteria to participate in the study. Patients will be considered treated when an attempt to place the randomized device into the patient (inserted into the patient's body) was made.

This is a single-blind trial, such that the patient will not be told which stent they have received. All patients enrolled into the study will be assigned a patient study number via the database system.

8.2 Patient Information and Informed Consent

Patient eligibility should be assessed by a member of the research team and the investigator. Before any protocol driven assessments that are considered beyond standard-of-care for a potential subject are performed, an informed consent must be obtained. Before randomizing the patient, assessment should be completed to assure all inclusion criteria are met and no exclusion criteria are present, short of the angiographic evaluation of the target lesion. Randomization will only occur if the subject meets the angiographic inclusion criteria: 1) target lesion(s) must have ≥50 % diameter stenosis by visual estimate and 2) target lesion(s) must have a reference vessel diameter ranging from 2.5 mm to 3.75 mm.

The background of the proposed trial and the benefits and risks of the procedures and trial should be explained to the patient. The patient must sign the consent form prior to enrollment. Failure to obtain signed, informed consent renders the patient ineligible for the trial. This form or a modification based on local Ethics Committee recommendations must be completed by all enrolled patients. The patient will receive a copy of the signed informed consent for his/her records. Copies of the signed informed consent will be kept in the patient's medical records.

In this all-comers study, there may be occasions where the patient cannot sign the informed consent form prior to undergoing any study-specific procedures (for instance, in the treatment acute myocardial). In the event that the patient is unable to give informed consent (physically or mentally incapacitated), a personal or professional legal representative should sign the informed consent form on behalf of the patient prior to inclusion in the trial. As soon as the patient is capable of doing so, he should go through the full-length informed consent procedure and be given time to either sign the informed consent or withdraw from the trial.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the patient's source documents. The voluntary process of obtaining informed consent confirms the patient's willingness to participate in the study. It is the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP, EC requirements and country specific regulations. Study patients will be assured that they may withdraw from the study at any time and for any reason.

8.3 Baseline evaluation

All patients will have the following activities conducted prior to the PCI procedure:

- Baseline demographics and physical exam with pregnancy test (as required)
- Relevant medical and cardiac history
- Required anti-platelet medication(s)
- 12-lead electrocardiogram (within 72 hours)
- Cardiac biomarkers per standard of care and local practice is drawn prior to the index PCI procedure (within 24 hours prior to PCI). However it is preferred (if possible) to capture all 3 biomarkers: CK, CKMB and Troponin (I or T).
- Creatinine measurement (within 28 days prior to PCI)

8.4 Randomization

Randomization will be performed via web-based software with random blocks according to center. Randomization will occur after all inclusion criteria are met and no exclusion criteria are present and as soon as the baseline angiographic assessment confirms the patient matches enrolment criteria as mentioned in section 7.1 (items 2 and 3).

Patients will be randomized to one of two groups. Subjects will be randomized into either of MISTENT arm or XIENCE arm in the ratio of 1:1 respectively. All lesions for each patient treated at the index procedure should receive the same assigned stent type. Patients will not be informed of the treatment group they are assigned.

8.5 Measures to minimize/avoid bias

- Randomization will occur through a module in the eCRF.
- Patients will be randomized at a 1:1 ratio to the MISTENT or XIENCE treatment arm. This will result in two groups of an expected equal size.
- Other measures to avoid or minimize bias will include intent-to-treat principles of analysis and blinding of patients to treatment assignments.

8.5.1 Blinding

- The DESSOLVE III is a single-blind trial. Subjects will be blinded through the completion of 5-year follow-up. Care must be taken when explaining about procedure result to subject so that they may not identify assigned device(s).
- Investigators performing the index procedure will not be blinded as the investigational device is clearly identifiable from the comparator device by its appearance.

- The DSMB will remain blinded. However, if deemed necessary, the DSMB may review the data unblinded.
- Core Laboratory (e.g. event angio review) will not be blinded as the investigational device is clearly identifiable from the comparator device.

8.6 Stent implant Procedure

Please follow each manufacturer's respective Instructions for Use provided with the device. The investigator will choose the appropriate length and diameter of the stents to be implanted by visual estimate. The choice of the length of the stent should ensure complete coverage of the entire lesion. If multiple stents are required, the distal stent should be placed first and the second stent should be overlapping so that there are no gaps between stents with at least 5 mm overlap of stents. In case of insufficient stent expansion, the stent will be post-dilated with an appropriately sized balloon.

8.7 Staged procedures

If the patient requires a staged procedure, this should be documented at the time of the index procedure, and must not be in the same epicardial vessel as any index lesion, and must not occur more than 45 days post-index procedure. The patient should receive the same type study stent as during the original index procedure (MISTENT or XIENCE).

8.8 Concomitant Medical Therapy

8.8.1.1 Recommended Procedural Anti-Coagulation Strategy

Upon determination that a patient is eligible for PCI, an oral loading dose of

- 600 mg clopidogrel should be administered within 24 hours before PCI is performed. For patients already on chronic clopidogrel therapy of 75 mg (≥5 days), a loading dose of 300 mg may be administered at the physician's discretion prior to procedure.

- At sites in countries where it is approved and is commercially available, a loading dose of 60 mg of prasugrel or of 180 mg of ticagrelor at least 2 hours before the procedure can be used in place of clopidogrel or in accordance with local standard of care.

- Any patient not already taking daily chronic aspirin therapy will receive 100-300 mg (or dose per standard hospital practice) from 0 hours to preferably 24 hours before the procedure.

During the procedure, patients should receive bolus and maintenance doses of unfractionated heparin to avoid excess coagulation. The currently recommended target activated clotting time (ACT) is at least > 250 sec during coronary angioplasty. If Angiomax® (bivalirudin) is used in place of heparin an ACT does not need to be measured or recorded. Please refer to the package insert for bivalirudin for indications, contraindications, warnings and precautions.
In patients who do not receive GP IIb/IIIa inhibitors, a weight-adjusted unfractionated heparin bolus (70 to 100 IU per kg) will be administered to achieve a target ACT of >250 sec. In patients

who receive GP IIb/IIIa inhibitors, a weight-adjusted unfractionated heparin bolus (50 to 70 IU per kg) will be administered to achieve a target ACT of >200 sec. Post-procedural heparin infusions are not recommended during GP IIb/IIIa therapy. The currently recommended target ACT for eptifibatide and tirofiban is less than 300 sec during coronary angioplasty.

8.8.2 Post-procedural Antiplatelet Regimen

All stable coronary artery disease patients must receive dual anti-platelet therapy, being aspirin (ASA) and platelet aggregation inhibition therapy for at least *6 months* after PCI (as currently recommended by the ESC guidelines) followed by ASA monotherapy indefinitely.

All acute coronary syndrome patients must receive dual anti-platelet therapy, being aspirin (ASA) and platelet aggregation inhibition therapy for at least *12 months* after PCI (as currently recommended by the ESC guidelines) followed by ASA monotherapy indefinitely.

Extended DAPT will be at the discretion of the investigator. All DAPT (including start and stop times of interrupted DAPT) and cardiac medications will be recorded for data collection at each visit.

Antiplatelet Therapy
Please refer to the specific package insert for clopidogrel, ticlopidine, prasugrel or ticagrelor for indications, contraindications, warnings and precautions. The following is a recommendation for administration of DAPT but the final decision is up to the operator, local standard of care and drug availability.

All patients must receive a maintenance dose of clopidogrel 75 mg od. In case of prasugrel the maintenance dose is 10 mg od (the dose of prasugrel may be decreased to 5mg od in patients with a weight <60 kg or age >75 years) or in case of ticagrelor the maintenance dose is 90 mg bid.

It is important to avoid any imbalance in duration and type of DAPT between the study cohorts, i.e. one must adhere to the same DAPT treatment regimen in MISTENT and XIENCE randomized patients.

Note1: for ACS, order of preference is: ticagrelor, prasugrel (or clopidogrel) according to local practice and drug availability.
Note2: prasugrel and ticagrelor have no label for elective PCI.

Aspirin
Following the PCI procedure, subjects with no known aspirin allergy or bleeding risk should continue on aspirin (minimum of 75 mg/day up to 162 mg/day or dose per standard hospital practice) indefinitely.

Note3: avoid maintenance doses of aspirin above 100 mg daily for patients prescribed to ticagrelor.

8.9 Hospital Discharge (post-PCI to hospital discharge)

At discharge, from the hospital where the index procedure took place, an assessment of the cardiovascular drug use will be performed. Any Serious Adverse Events will be recorded and an ECG will be performed. The patient must be informed of the required DAPT medication and follow-up visits per protocol should be scheduled prior to discharge.

In addition, CK and CK-MB and Troponin (I or T) in the post-procedure hospitalization period should be taken approximately 6 hours post procedure.
The majority of historical coronary stent trial data does not utilize Troponin values to define myocardial infarction, thus, making it difficult to compare previous trials with this investigation where Troponin has become more the preferred biomarker of choice for the diagnosis of periprocedural MI. In an effort to compare event reporting between clinical trials it is required to collect all cardiac enzymes: CK, CK-MB and Troponin.
If cardiac enzymes are elevated (according to local upper limit of normal), serial measurements of cardiac enzymes must be taken until a decline is noted.

It is mandatory to keep all patients in the PCI (index) hospital for at least 6 hours after the PCI treatment.

8.10 Unscheduled Intervention

For all revascularizations and stent thrombosis, the angiogram must be sent to the Angiographic Core Laboratory, regardless of whether target or non-target vessel revascularization was performed. For all revascularizations performed including the target lesion (TLR) and target vessel (TVR), the Clinical Event Committee (CEC) will adjudicate the type of revascularization and determination as to whether the revascularization is clinically indicated or not clinically indicated. (See Appendix I: Definitions).

8.11 Follow-up Period

Hospital visits are planned at 1 month (+7 days) and 1 year (+30 days). An assessment of the anginal status, cardiovascular drug use and any Serious Adverse Events will be recorded during clinical follow-up visits. An ECG will be performed. Phone contacts are scheduled at 6 months (+14 days), 2 years (+30 days), 3 years (+30 days), 4 years (+30 days) and 5 years (+30 days).

All one-year follow-up visits must be scheduled at least at one year after randomization (and henceforth not earlier). This also applies to the scheduling of the 2, 3, 4 and 5 year visits.

8.12 Discontinuation of Follow-Up

At any time during the study, the subject may withdraw their participation from the study. Follow-up is only discontinued at the explicit request of the patient. This decision should be an independent decision that is documented in the patient study files. Survival status should be collected within legal and ethical boundaries for all subjects randomized who withdrew participation from the study. Data generated from any patient withdrawn from the trial will be included in the analysis unless the patient explicitly forbids the use of any data which should be documented by the patient.

All patients are encouraged to return for all scheduled follow-up visits, and to provide appropriate contact information to accommodate completion of required telephone follow-ups. The investigator will attempt to contact the patient at each follow-up visit, independent of any missed follow-ups. The investigator should make 3 documented attempts per required follow-up visit.

Patients who have discontinued the trial prematurely will not be replaced.

8.13 Subjects Lost to Follow-Up

A subject would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit. Survival status will be collected within legal and ethical boundaries for all subjects randomized. Vital status will be searched in public sources at the end of the 5 year follow-up period. If vital status is known, the subject will not be considered lost to follow-up.

9 STATISTICAL DESIGN AND ANALYSIS

9.1 Analysis Population(s)

9.1.1 Intent to Treat Population (ITT)

All clinical data in the ITT population will be analyzed according to randomized treatment. The ITT population set will consist of all patients who signed the written informed consent and are randomized, regardless if, and if so, which study stent was implanted.

9.1.2 Per Protocol (PP)

If required, an additional analysis of the Per-Protocol (PP) population will be conducted of the primary and secondary endpoints. The PP population consists of those patients who correctly received (only) the assigned study stent. If all patients correctly receive the assigned study stent(s), this analysis will not be required. If the patient has more than one lesion, for all lesions the assigned study stent must be used. If for a patient more than one lesion will be analyzed, no in-patient correlation will be taken into account.

9.2 Primary Analysis

The primary analysis is an ITT analysis of the primary endpoint, being TLF at 12-months. The study is powered at 85% to show non-inferiority for the MISTENT when compared to XIENCE. The analysis will also be conducted on the PP patient population, as required.

The primary endpoint of TLF will be analyzed and compared between the two treatment arms for non-inferiority of the MISTENT as compared to the control stent, XIENCE. The MISTENT expected TLF assumption is based on the assumption of no difference in event rates between MISTENT and XIENCE.

The 90% two-sided confidence interval for the difference in 12 months rates of TLF between the MISTENT and XIENCE arms will be calculated using Kaplan Meier estimates at 1 year and their standard deviations. If this 90% interval excludes the non-inferiority margin, MISTENT will be considered to be non-inferior to XIENCE (this accounts to one-sided non-inferiority testing at alpha = 5%).

9.3 Sample Size Calculations

Primary Analysis:

The study is powered at 85% to show non-inferiority for the MISTENT when compared to XIENCE. The primary analysis will be based on an intent-to-treat (ITT) patient population, that is, all patients who are randomized to the specific study stent. Randomization should occur only after all inclusion/exclusion criteria, including angiographic evaluation, have been met. A

secondary evaluation will be conducted on patients that received only the assigned study stent at the target lesion(s).

Study Sample Size Calculation: 1400 Subjects

Assumptions:

-A 1:1 treatment allocation ratio of MISTENT to XIENCE
-a one-sided significance level (alpha) of 0.05
-85% power to show non-inferiority of MISTENT to XIENCE
-a non-inferiority margin of 4%
-TLF event rate for XIENCE of 8.3% at 12M[5]
-TLF event rate for MISTENT of 8.3% at 12M
-maximum attrition rate of approximately 2%.

The 8.3% TLF rate is based on the XIENCE arm of the Resolute All Comers trial, the assumption is made that in DESSOLVE III the MISTENT arm will have the same event rate as the XIENCE arm. Using PASS software, and a standard normal distribution (Z-test) above assumptions require 682 subjects in the MISTENT arm and 682 in the XIENCE arm, for a total of 1364 patients, when not taking attrition into account. Accounting for loss to follow-up of approximately 2%, these numbers are increased to 700 and 700 respectively, for a total randomized sample of 1400 patients.

Primary Hypothesis and Statistical Analysis:

The primary endpoint of TLF will be analyzed and compared between the two treatment arms for non-inferiority of the MISTENT as compared to the control stent, XIENCE.

Secondary Endpoint Analysis:

Secondary endpoint analysis will occur at each follow-up visit and compared between the MISTENT and XIENCE groups.

For all clinical endpoints, the Kaplan-Meier method will be used.

For all secondary endpoints conventional p-values and 95% confidence intervals for the difference in Kaplan-Meier will be calculated.

Dichotomous variables will be evaluated using Fisher's exact tests. Continuous variables will be evaluated by a two-sample t-test.

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[5] Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, Kelbaek H, van Boven AJ, Hofma SH, Linke A, Klauss V, Wijns W, Macaya C, Garot P, DiMario C, Manoharan G, Kornowski R, Ischinger T, Bartorelli A, Ronden J, Bressers M, Gobbens P, Negoita M, van Leeuwen F, Windecker S. Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents. NEJM 2010;363:136-46.

For time-dependent analyses, Hazard Ratios will be evaluated using Cox proportional hazards model and Kaplan Meier estimates will be evaluated according to log-rank test.

9.4 Subgroup Analysis

For these pre-specified subgroups, the MISTENT arm and XIENCE arm will be compared on an ITT basis:

- Diabetes
- STEMI
- Renal insufficiency (serum creatinine > 2.5mg/dL, or creatinine clearance ≤ 30 mL/min)
- Small vessels (≤2.75mm)
- Multivessel treatment
- Long lesions (>18 mm)
- In-Stent restenosis
- Bypass graft
- Left Main treatment
- Bifurcation treatment
- Overlapping stents

For these subgroups, the primary endpoint and secondary endpoints will be evaluated. For these subgroups the study does not have significant power to demonstrate non-inferiority for the MISTENT arm to the XIENCE arm, meaning the results are considered exploratory (hypothesis-generating) only.

9.5 Missing data

Every effort will be undertaken to minimize missing data. The following approach to handling missing data will be adopted based on the type of the outcome and endpoint being analyzed.

Kaplan-Meier estimates will censor incomplete data at the last date of available follow-up information, assuming complete reporting of all events up to that date and event status unknown after that date.

9.6 Calculating days to event

When calculating the days-to-event, the date the event took place will always be compared to the index procedure date, also in case a staged procedure took place.

10 SAFETY REPORTING

10.1 Serious Adverse Events (SAEs) Definitions

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

An AE is classified as "serious" if the event:

- Led to death;
- Led to serious deterioration in the health of a patient that:
  - Resulted in a life threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in patients hospitalization or prolongation of existing hospitalization;
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

10.2 Anticipated Adverse Device Effects

Anticipated adverse device effects for both MISTENT and XIENCE are described in the Instructions For Use.

10.3 Device Malfunctions

If the investigator observes device malfunctions that led or might have led to a death or serious deterioration in health of a patient, user or other person, or has complaints with regard to defects in the medical devices, the investigator shall, within 24 hours of such observation, report such device malfunction or complaint to the device company, with a copy of the report to the sponsor. Sponsor shall be responsible to take necessary actions in response to a device malfunction to protect the safety of the trial subjects, e.g. temporary suspension of the trial. The Company shall be responsible for handling all complaints and reported device malfunctions in respect of the quality of medical devices, for determining the measures to be taken due to such observations or complaints and for ensuring that all necessary actions are taken including, but not limited to, any necessary action in connection with the recall of the medical devices or the reporting of incidents to competent authorities if deemed appropriate by the Company. Discussions regarding such device malfunction or complaints will be held between the Company and the Participating Site.

For definition refer also to Appendix II.

10.4 SAE Reporting

The investigator will monitor the occurrence of Serious Adverse Events (SAEs) for each subject during the course of the study. For the purpose of this protocol, the reporting of SAEs begins

directly after patient has signed informed consent through the last follow-up visit. If an event fulfills the criteria for SAE, then this shall be reported in the eCRF within 24 hours of the clinic study staff having become aware of this, including their judgment regarding causal relationship of the event to the trial. At the time the event is reported in the eCRF, no event-supporting source documentation needs to be sent. Event supporting source documents will be requested by the sponsor (via monitoring organization and/or CRO) for the purpose of potential clinical event adjudication and reporting purposes. All SAEs will be followed until the event has been resolved (with or without sequelae).

Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall review the investigator's assessment of all adverse events and determine and document in writing the sponsor's determination of seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), both opinions shall be reflected.

Safety reporting to the Competent Authorities and the local ECs will be in accordance with "Clinical investigation of medical devices for human subjects - Good clinical practice" (ISO 14155:2011,IDT) and the "guidelines on medical devices vigilance system" by the European Commission (MEDDEV2.12 rev 6, Dec 2009) and in compliance with local country law.

10.5 Risk Analysis

Percutaneous coronary interventions (PCI) and intravascular stenting may offer certain advantages as compared to conventional surgical techniques. In addition, coronary stenting with both BMS and DES have been performed successfully for several decades and is considered a standard treatment for coronary revascularizations. Furthermore, there is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the procedural risks in this study and existing stenting procedure will not be significantly different. Further, since the drug-polymer coating on the MISTENT is gone within 90 days, leaving a bare metal stent, this may diminish the potential concerns regarding long-term effect on vessel healing, late and very late thrombosis, and hypersensitivity. Aside from the potential direct benefits to the patient resulting from this study, there may be benefits to future patients based upon the results of the study.

With any procedure there are risks and complications. The following is a list of known adverse events (alphabetical order) that may result from stent intervention:

COMMON - More than 10%
Angina pectoris
Bleeding or hematoma (bruising) at the access site
Pain at the catheter insertion site
Unstable angina

LESS COMMON - 2% to 9%
Acute myocardial infarction
Arrhythmias

Bradycardia
Hypotension
Restenosis of the stented artery
Thrombus formation

RARE - 1% or less
Abrupt vessel closure
Allergic reaction to contrast media (dye), aspirin, heparin and Angiomax® (bivalirudin), clopidogrel bisulfate (Plavix), ticlopidine (Ticlid) Prasurgrel (Effient) or Ticagrelor (Brilinta), as prescribed
Aneurysm, pseudoaneurysm or arteriovenous fistula
Cardiac tamponade
Cerebral vascular event
Coronary artery aneurysm
Damage to the stent or injury to the artery requiring emergency heart surgery
Death
Device embolization
Dissection, perforation, or rupture of the coronary artery
Embolism (air, tissue, thrombus or device)
Hypersensitivity to cobalt-chromium
Hypersensitivity to sirolimus
Hypersensitivity to everolimus
Infection or fever
Pseudoaneurysm or fistula at the vascular access site
Stent misplacement
Stent thrombosis or occlusion
Stroke or transient ischemic attack (TIA)
Thromboembolic events
Vascular trauma

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Compliance to Standards and Regulations

The protocol, informed consent form and other study-related documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB). The study will be performed in accordance with the Declaration of Helsinki and Good Clinical Practices (GCP).

The trial will only start at a clinical site after written approval of the study has been obtained from the appropriate national EC/IRB.

11.2 Data Recording

It is the expectation of the Sponsor that all data entered into the eCRF has source documentation available at the clinical site. The site must implement processes to ensure this happens.

11.3 Quality Assurance and Monitoring

Monitoring the clinical investigation at the study site is the responsibility of the monitoring organization through trained and qualified Clinical Research Associates (CRAs).

The monitoring organization will discuss the investigator's patient enrollment prediction at the time of contracting.

Monitoring visits will be performed according to the monitoring plan. During on-site monitoring, the Informed Consent Forms will be checked and a sample of clinical data will be verified against eCRF data. Subject confidentiality will be maintained at all time. Emphasis will be on the complete reporting by the study staff of SAEs.

Each clinical site will be visited several times during the study to ensure a high degree of data quality. These site monitoring visits will be conducted to verify that the data are authentic, accurate and complete, that the safety and rights of subjects are protected, that the study is conducted according to the protocol, and that any other study agreements, GCP and all applicable regulatory requirements are met. The investigator and the head of the medical institution (where applicable) agree to allow the CRA direct access to all relevant documents. It is important that the investigator and the study staff are available during the monitoring visit and possible audits and that sufficient time is devoted to the process. Findings from the review and source documents will be discussed with the investigator. The number of monitoring visits will depend on Key Performance Indicators (KPI) derived from data management.

Remote site monitoring will also be performed to ensure complete quality study data and patient adherence to the protocol. On a regular basis, the monitoring organization will contact each site to discuss the progress of the study with respect to patient enrollment, timely attendance of patients to their follow-up visits and other relevant study aspects such as data query resolution.

Each participating clinic will receive a close-out visit to resolve any outstanding issues and to perform the final source data verification.

There will be regular teleconferences between the Sponsor and the monitoring organization to discuss site management issues.

11.4 Quality Assurance and Data management

The data collection will be performed through an electronic CRF (eCRF). The investigator or an authorized member of the investigational team must sign all completed eCRFs that require a signature by using an electronic signature (a password will be provided by the data management center at the start of the study).

Clinical data management will be performed in accordance with data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. angiographies, ECGs, etc.). Appropriate computer edit programs will be run to verify the accuracy of the database. The investigator will be queried on incomplete, inconsistent or missing data.

11.5 On-site Audits

To ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit, may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation, as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide may inspect the investigator during and after the study. The investigator should contact the sponsor immediately if this occurs, and must cooperate with the regulatory authority inspections as required.

12 ORGANISATION

12.1 Sponsor

In this investigator-initiated trial, the European Cardiovascular Research Institute (ECRI) will act as Sponsor (ECRI-Trials B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands,). The Sponsor's responsibilities are described in chapter 16.

12.2 Steering Committee

The Steering Committee is responsible of the overall management of the study at the highest level. Their names, roles and responsibilities are described in a separate Charter. The Steering Committee is responsible for global oversight of the trial progress (review and approval of the protocol and study design; review day-to-day trial progression (such as executional coordination, finances, safety, communication, delegation to committees); regular teleconference; and final approval of the investigational sites. The Steering Committee interacts with the Sponsor on study progress and related issues.

12.3 Data Safety Monitoring Board (DSMB)

Serious adverse events (events leading to serious disability or admission to hospital, life-threatening events or death) will be periodically reviewed and analyzed by an independent DSMB. Members of this board are not affiliated with any (interventional) cardiology site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise.

The composition, guiding policies, and operating procedures governing the DSMB are described in a separate DSMB Charter. Based on safety data, the DSMB may recommend that the Steering Committee modify or stop the clinical trial. All final decisions regarding clinical trial/investigation modifications, however, rest with the Steering Committee.

All analyses are carried out aiming to protecting the safety of the trial participants. If the data at hand suggests a substantial safety concern about the experimental treatment strategy, the DSMB will carefully balance the observed risk profile against possible signs of improved efficacy.

12.4 Clinical Event Committee (CEC)

The Clinical Events Committee (CEC) is an independent committee comprised of interventional cardiologists who are not participants in the study. The CEC is responsible for the categorization of Death, MI, revascularization and stent thrombosis, based on the definitions in the protocol. Prior to any CEC activity, a CEC Charter will be developed, which will describe the events to be adjudicated, the minimum amount of data required, and the algorithm followed in order to classify the events.

12.5 Data Management

Data management will be conducted by the Clinical Research Organization (CRO) Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands).

12.6 Site Management and Monitoring

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) will be responsible for site management and monitoring.

12.7 Safety Reporting

Sites are responsible for reporting of incidents, including device malfunctions, to the manufactures. Manufacturers are responsible for vigilance reporting of device malfunctions to competent authorities according to the "guidelines on medical devices vigilance system" by the European Commission (MEDDEV2.12 rev 6, Dec 2009).
No expedited safety reporting is foreseen.
The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for event reporting to the EC/IRB according to local and national requirements.

12.8 Statistical Analysis

The CRO Cardialysis (Cardialysis B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) is responsible for the statistical analysis.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documentation (SD)

Regulations require that investigators maintain information in the patient's medical records that corroborate data collected in the electronic Case Report Form (eCRF). In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained and made available as required by monitors and/or regulatory inspectors:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify investigational plan entry criteria;
- Dated and signed notes on the day of entry into the study, protocol number, clinical site, patient number assigned and a statement that informed consent was obtained and is on file in the patient medical chart;
- Notations on abnormal lab results;
- Adverse events reported and their resolution, including supporting documents such as discharge summaries, cath lab reports, ECGs, lab results;
- Notes regarding investigational plan-required and prescription medications taken during the study (including start and stop dates);
- Study patient's condition upon completion of or withdrawal from the study.

13.2 Record Retention

All eCRF information, study records, reports and source documents that support the eCRF must be retained in the files of the responsible investigator according to national requirements following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement. This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian.

14 PUBLICATION POLICY

The Steering Committee and investigators are committed to the publication and widespread dissemination of the results of the study. Data from this study will not be withheld regardless of the findings.

The DESSOLVE III trial is an investigator-initiated and scientifically driven study nested within the European Cardiovascular Research Institute (ECRI) and set up in collaboration with Stentys and Micell. All public presentations and manuscript generation and submissions will be led under the auspices of the Principal Investigators who will organize and lead a Publications Committee. However, this study represents a joint effort between investigators, ECRI and collaborators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

The final locked database will be housed at the data management center, Cardialysis. Cardialysis will not publicly release data or study-related material, presentations, or manuscripts without the express permission of the Principal Investigators. All Principal Investigators will be listed as authors on all abstracts and publications, and as such must agree to their submission. The publication and/or presentation of results from a single trial site are not allowed until publication and/or presentation of the multi-center results. All single site data for public dissemination must be generated from the central database – local database projects are not permitted. All proposed publications and presentations resulting from or relating to the study (whether from multicenter data or single site analysis) must be submitted to the Publications Committee for review and approval prior to submission for publication or presentation.

The Steering Committee will receive any proposed publication and/or presentation materials prior to submission of the presentation or the initial submission of the proposed publication in order for the materials to be timely reviewed by all parties.

15 INVESTIGATOR RESPONSIBILITIES

15.1 Investigator Responsibility/Performance

Prior to starting enrolment of patients, the investigator must read and understand this study protocol, and must sign and date the Protocol Signature page. The Investigator Site Agreement documents agreement to all conditions of the study protocol and agreement to conduct the study accordingly. This study will be conducted in accordance the Declaration of Helsinki and other applicable regulatory requirements or any conditions of approval imposed by the EC/IRB or regulatory authorities.

15.2 Required Documents

The following documents must be submitted to Sponsor, or designee prior to patient enrolment:

- Signed Protocol Signature Page
- Recent ($\leq$ 2 years old) signed and dated English Curriculum Vitae (CVs) of the Principal Investigator and co-investigators of the clinical site. These CVs should clearly show the investigator's and co-investigators' qualifications and experience.
- Copy of the written confirmation of the EC/IRB regarding approval of the protocol including version number and date, patient information sheet and informed consent form, including version and date and other adjunctive patient material.
- List of EC/IRB members, including name, title, occupation and any institutional affiliation of each member. If the EC/IRB member list is not available, the General Assurance or EC/IRB Recognition Number should be provided.
- Signed Investigator Site Agreement.

15.3 Ethics Committee (EC) / Institutional Review Board (IRB) Approval

According to the local regulations, the investigator must have all necessary approvals, including written approval from the EC/IRB of the clinical site or other accepted EC/IRB prior to enrolling patients in the study. A copy of the written approval must be provided to Sponsor and should include the following:

- Statement of EC/IRB approval for the proposed study at the clinical site
- Date the study was approved and the duration of the approval
- Listing of any conditions attached to the approval
- Identification of the approved Primary Investigator
- Signature of the EC/IRB chairperson
- Acknowledgement of the Co-Investigators
- EC/IRB approval of the informed consent form (if applicable)
- EC/IRB approval of the final protocol (if applicable).

Any substantial amendments to the protocol, as well as associated consent form changes, will be submitted to the EC/IRB and written approval obtained prior to implementation. Minor changes which do not affect the subject's safety will be subject to notification.

Serious Adverse Event (SAE) reports will be submitted to the EC/IRB as requested by the Sponsor, EC/IRB and/or local regulations. Annual and final reports will be provided to the EC/IRB as required.

15.4 Informed Consent

Prior to study start, the investigator must obtain written EC/IRB approval for the informed consent form. A copy of the Patient Information and the signed and dated informed consent will be provided to the study patient. The original must be retained in the patient medical records at the study site. The study must be explained to the study subjects in lay language. Study patients will be assured that they may withdraw from the study at any time and for any reason and receive alternative conventional therapy as indicated.

15.5 Reporting Requirements

The investigator should notify the EC/IRB in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to Competent Authority where required.

Site responsibilities for submitting data and reports:

Type of CRF/Report	Completed by Site Within	Process
Adverse Events	Ongoing Basis	Collected in the eCRF
Serious Adverse Event Notification eCRF (including death, Target Vessel Failure)	24 hours	Enter eCRF pages within 24 hours of knowledge of event
Randomization (study device assignment)	Immediate	Enter eCRF randomization page
Device Implant (# and size of devices opened – and implanted or not used)	Immediate	Enter eCRF device Accountability page
eCRF (Baseline, Follow-up visits, Patient Withdrawal)	Ongoing basis	Collected in the eCRF

Angiographic Films (if applicable) of Revascularizations and Stent Thrombosis	Ongoing basis	Collected by site and shipped to Core lab within 7 days
Device malfunctions	Ongoing basis	Collected by site and provided to manufacturer
Annual Reports	Forward as requested by EC/IRB	Copy to be provided to Sponsor and EC/IRB
Final Report	Forward within 3 months of study completion or termination	Copy to be provided to Sponsor and EC/IRB

15.6 Audits / Inspection

In the event that audits are initiated by the Sponsor (or its designee) or national/international regulatory authorities, the investigator allows access to the original medical records and provides all requested information. In the event that audits are initiated by a regulatory authority, the investigator will immediately notify the Sponsor.

16 SPONSOR RESPONSIBILITIES

16.1 Role of ECRI

As Sponsor, ECRI has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant competent authorities.

General duties

Prior to allowing the sites to start enrolling patients into the study, the Sponsor is responsible for selecting investigators, ensuring EC/IRB approvals are obtained where applicable, and signing the Investigator Site Agreement with the investigators and/or hospitals. It is the Sponsor's responsibility to ensure that the study is conducted according to ISO 14155, the Declaration of Helsinki, and other applicable regulatory requirements, the study protocol, and any conditions of approval imposed by the EC/IRB or regulatory authorities. Additionally, the Sponsor will ensure proper clinical site monitoring.

Selection of clinical investigators and sites

The Sponsor will select qualified investigators and facilities which have adequate study patient population to meet the requirements of the investigation.

Training of investigator and site personnel and site monitoring

The training of the investigator and appropriate clinical site personnel will be the responsibility of the Sponsor, or designee, and may be conducted during an investigator meeting, a site initiation visit, or other appropriate training sessions. Periodic monitoring visits will be conducted frequently enough to ensure that all clinical patient data are properly documented and that the study is properly conducted.

Documentation

The Sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents;

- All study relevant documents (protocol, Investigator's Brochure, EC/IRB approval and comments, competent authority notification and comments, patient information and informed consent template, relevant correspondence, etc.)
- Signed and dated Case Report Form (eCRF)
- Records of any Serious Adverse Events (SAEs) reported to the Sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- Final report of the clinical investigation

16.2 Supplemental Applications

As appropriate, the Sponsor will submit changes to the study protocol to the investigators to obtain EC/IRB re-approval.

16.3 Submitting Reports

The Sponsor will submit the appropriate reports identified by the regulations. This includes withdrawal of any EC/IRB approval, interim (if any) and final reports.

16.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, SAEs and other records related to the clinical study. The Sponsor will maintain records related to the signed Investigator Site Agreements according to requirements set forth by ISO14155.

CRO, Core Laboratories and clinical sites will maintain study records according to local requirements for this type of study.

16.5 Audit

The Sponsor is responsible for auditing the study to ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit and may arrange to conduct an on-site audit to assess the performance of the study at the study site and of the study documents originating there.

16.6 Confidentiality

All data and information collected during this study related to the participating subject will comply with the standards for protection of privacy based on applicable local/ national requirements for subject's confidentiality. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study subjects' names. Access to study subject files will be limited to authorized personnel of the Sponsor, the investigator, and research staff. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study, but all efforts must be made to remove the subject's personal data.

17 REFERENCES

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2. Stefanini G, Kalesan B, Serruys P, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomized non-inferiority trial. *Lancet 2011; 378:1940-1948*.
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9. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW; Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv. 2014 Jan 1;83(1):27-36*.

18 APPENDIX I: SCHEDULE OF INVESTIGATIONS

Schedule of Events	Baseline (prePCI)	Procedure	Post-procedure\ Discharge	30 days (+7 days)	6 months (+14 days)	1 year (+30 days)	2 year (+30 days)	3 years (+30 days)	4 year (+30 days)	5 years (+30 days)
				Visit	TC Contact	Visit	TC Contact	TC Contact	TC Contact	TC Contact
Inclusion/Exclusion Criteria	•									
Informed Consent	•									
History & Risk Factors	•									
Anginal status	•		•	•	•	•	•	•	•	•
Recording of Medications	•		•	•	•	•	•	•	•	•
12-Lead ECG	•[1]		•[2]	•		•				
Creatinine	•									
Cardiac enzymes (CK, CKMB, Troponin)	•[3]		•[4]							
Serious Adverse Events[5]		•	•	•	•	•	•	•	•	•

Notes:

[1] ECG at time of screening should be performed within 72 hours prior to PCI procedure.
[2] ECG within 24 hours post-procedure or at discharge, whichever comes first.
[3] Cardiac biomarkers per standard of care and local practice is drawn prior to the index PCI procedure (within 24 hours prior to PCI). However it is preferred (if possible) to capture all 3 biomarkers: CK, CKMB and Troponin (I or T).
[4] CK and CK-MB and Troponin (I or T) in the post-procedure hospitalization period should be taken approximately 6 hours post procedure. first). If cardiac enzymes are elevated (according to local upper limit of normal), serial measurements of cardiac enzymes must be taken until a decline is noted. It is mandatory to keep all patients in the PCI (index) hospital for at least 6 hours after the stent implantation.
[5] For all revascularizations (incl. stent thrombosis, etc.), the angiogram must be sent to the Monitor organization and/or CRO (Cardialysis),

Note: In the event of intercurrent illnesses, interventions, adverse events, or treatment failure, effort should be made to complete the required observations as much as possible.

19 APPENDIX II: DEFINITIONS

ACUTE SUCCESS DEFINITIONS

[Device Success (Lesion Basis)]

Successful delivery and deployment of (only) the assigned device at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of <30% (by visual estimation).

[Procedure Success (Patient Basis)]

Successful delivery and deployment of (only) the assigned device at the intended target lesion and successful withdrawal of the delivery system with attainment of final in-stent residual stenosis of <30% (by visual estimation) for all intended target lesions without the occurrence of TLF during the index procedure hospital stay (maximum of 7 days).

ACC/AHA CLASSIFICATION SCHEME OF CORONARY LESIONS

Type A Lesions (High Success, >85%; Low Risk)	
• Discrete (< 10 mm length)	• Little or no calcification
• Concentric	• Less than totally occlusive
• Readily accessible	• Not ostial in location
• Nonangulated segment, < 45°	• No major branch involvement
• Smooth contour	• Absence of thrombus
Type B Lesions* (Moderate Success, 60-85%; Moderate risk)	
• Tubular (10-20 mm length)	• Moderate-to-heavy calcification
• Eccentric	• Total occlusions < 3 mo old
• Moderate tortuosity of proximal segment	• Ostial in location
• Moderately angulated segment, > 45°, < 90°	• Bifurcation lesions requiring double guide wires
• Irregular contour	• Some thrombus present
* Type B1 lesions: One adverse characteristic * Type B2 lesions: ≥ two adverse characteristics	
Type C Lesions (Low Success, <60%; High Risk)	
• Diffuse (> 20 mm length)	• Total occlusions > 3 months old
• Excessive tortuosity of proximal segment	• Inability to protect major side branches

ADVERSE EVENT

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1 This includes events related to the investigational medical device or the comparator. NOTE 2 This includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3 For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1 This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, or the operation, or any malfunction of the investigational medical device. NOTE 2 This includes any event that is the result of a use error or intentional misuse.
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: 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. NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE Anticipated: is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.
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 labeling.
Device malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or study protocol.
Incident	Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.
Relationship of Adverse Event to the investigational treatment, device and/or procedure	• Certain: Event or laboratory test abnormality, with plausible time relationship to device use and/or procedure. It cannot be explained by disease or other drugs. • Probable: Event or laboratory test abnormality, with plausible time relationship to device and/or procedure. Unlikely to be attributed to disease or other drugs. • Possible: Event or laboratory test abnormality, with plausible time relationship to device and/or procedure. Could also be explained by disease or other drugs. • Unlikely: Event or laboratory test abnormality, with a time to device use and/or procedure that makes a relationship improbable (but not impossible). • Unassessable: Event or laboratory test abnormality, more data is needed for proper assessment.

ANGINA PECTORIS

Braunwald Classification of Unstable Angina:

Severity		Clinical Circumstances		
		A	**B**	**C**
		Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extracardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (postinfarction UA)
I	New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	IIA	IIB	IIC
III	Angina at rest within 48 hr (angina at rest, acute)	IIIA	IIIB Troponin negative IIIB Troponin positive	IIIC

Canadian Cardiovascular Society (CCS) Classification of Stable Angina:

CLASS	
0	Asymptomatic
I	Angina with strenuous exercise
II	Angina with moderate exertion
III	Angina with mild exertion · Walking 1-2 level blocks at a normal pace · Climbing 1 flight of stairs at a normal pace
IV	Angina at any level of physical exertion

I. Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

II. Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

III. Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

IV. Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

BLEEDING (HEMORRHAGIC) COMPLICATIONS

Bleeding will be classified according to the BARC[6] classification:

SEVERITY	
Major	Intracranial bleeding or clinically significant overt signs of bleeding associated with a decrease in hemoglobin ≥5 g/dL.
Minor	Spontaneous gross hematuria; spontaneous hematemesis; observed bleeding with a decrease in hemoglobin ≥3 g/dL but ≤5 g/dL.
Minimal	Any clinically overt sign of hemorrhage that is associated with a ≤3 g/dL decrease in hemoglobin.

[Transfusion and other bleeding complications]

All transfusions will be documented with accompanying bleeding complication, e.g., gastrointestinal (GI) bleed.

COMPOSITE ENDPOINTS

Device-Oriented Composite (DOCE)

- Cardiac death
- Myocardial Infarction (not clearly attributable to a non-target vessel)
- Clinically indicated target lesion revascularization

Major Adverse Cardiac Events (MACE)

- All cause death
- Any Myocardial Infarction (including non-target vessel territory)
- Any Target Vessel Revascularization (including all target and non-target lesion)

Patient-Oriented Composite Endpoint (POCE)

- All cause death
- Any Myocardial Infarction (including non-target vessel territory)
- Any Repeat Revascularization (including all target and non-target vessel)

Target Vessel Failure (TVF)

- Cardiac death
- Myocardial Infarction (not clearly attributable to a non-target vessel)
- Clinically indicated target vessel revascularization

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[6] Roxana Mehran, Sunil V. Rao, Deepak L. Bhatt, C. Michael Gibson, Adriano Caixeta, John Eikelboom, Sanjay Kaul, Stephen D. Wiviott, Venu Menon, Eugenia Nikolsky, Victor Serebruany, Marco Valgimigli, Pascal Vranckx, David Taggart, Joseph F. Sabik, Donald E. Cutlip, Mitchell W. Krucoff, E. Magnus Ohman, Philippe Gabriel Steg and Harvey White. Standardized Bleeding Definitions for Cardiovascular Clinical Trials : A Consensus Report From the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-2747.

Target Lesion Failure (TLF)

- Cardiac death
- Myocardial Infarction (not clearly attributable to a non-target vessel)
- Clinically indicated target lesion revascularization

DEATH

(ARC Circulation 2007; 115: 2344-2351)

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

- **Cardiac death:**
  Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all study procedure related deaths including those related to concomitant treatment.

- **Vascular death:**
  Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

- **Non-cardiovascular death:**
  Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

DISSECTION

National Heart, Lung, and Blood Institute [NHLBI] Dissection Classification System is used.

A. Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.
B. Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.
C. Extraluminal cap with persistence of contrast after dye clearance from the lumen.
D. Spiral luminal filling defects.
E. New persistent filling defects.
F. Non-A-E types that lead to impaired flow or total occlusion.

Note: Type E and F dissections may represent thrombus.

MYOCARDIAL INFARCTION (MI)

MI will be adjudicated based on multiple definitions:
1) WHO (Extended) Definition of MI *(Circulation 1979;59:607-609, Eurointervention 2010;5:871-874)*
2) Third Universal definition of MI *(European Heart Journal (2012) 33, 2551–2567)*
For peri-procedural MI an additional definition will be added: SCAI (*Catheter Cardiovasc Interv. 2014 Jan 1;83(1):27-36)*

NOTE: The primary endpoint for this trial (device-oriented composite endpoint, DOCE or TLF) will be assessed according WHO Extended Definition of MI!

1) [WHO Extended Definition]

I. PCI (Percutaneous Coronary Intervention)

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

Periprocedural <48 hours post PCI
A. New pathologic q waves in ≥ 2 contiguous ECG leads ***AND*** ▪ any CKMB > 1*URL ***or*** ▪ in the absence of CKMB: Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 1*URL ***or*** ▪ in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario
B. Appropriate cardiac enzyme data (respecting top-down hierarchy, b1 to b3): b1. **CK ≥ 2* URL Confirmed by:** ▪ **CKMB > 1*URL** ***or*** ▪ in the absence of CKMB:, Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CEC decision upon clinical scenario
OR b2. In the absence of CK: CKMB > 3*URL
OR b3. In the absence of CK and CKMB: Troponin > 3*URL

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

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

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

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

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

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

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

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

Spontaneous MI >48 hours(PCI)

A. Recurrent thoracic chest pain or ischemic equivalent ***AND***
New pathologic q waves in ≥ 2 contiguous ECG leads ***AND*** :

- any CKMB > 1*URL ***or***
- in the absence of CKMB: Troponin > 1*URL ***or***
- in the absence of CKMB and Troponin: CK > 1*URL ***or***
- in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario

B. Appropriate cardiac enzyme data:
b1. CK ≥ 2* URL Confirmed by:

- CKMB > 1*URL ***or***
- in the absence of CKMB: Troponin > 1*URL ***or***
- in the absence of CKMB and Troponin: CEC decision upon clinical scenario

OR

b2. In the absence of CK: CKMB > 3*URL

OR

b3. In the absence of CK and CKMB: Troponin > 3*URL

OR

b4. In the absence of CK, CK-MB and Troponin, clinical decision based upon clinical scenario.

II. CABG (Coronary Artery Bypass Grafting)

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

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

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

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

2) [Third Universal Definition of MI]

Type 1: Spontaneous myocardial infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new Ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI) Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (<99^{th} percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling **(*)**. In addition, either (i) symptoms suggestive of cardiac ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

(*) In patients with normal baseline cTn, a clinically relevant MI postPCI is diagnosed by a new biomarker elevation of CK-MB to ≥10x ULN or cTn (I or T) to ≥70x ULN (or by CK-MB to ≥5x ULN or cTn to ≥35x ULN plus the development of new pathologic Qwaves in ≥2 contiguous leads or new LBBB). **[SCAI Definition]**

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (<99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii)

angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

REVASCULARISATION

[Target Lesion Revascularization (TLR)]

TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR should be classified prospectively as clinically indicated [CI] or not clinically indicated by the investigator prior to repeat angiography. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

[Target Vessel Revascularization (TVR)]

TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion which includes upstream and downstream branches and the target lesion itself

[Non Target Lesion Revascularization (Non-TLR)]

Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

[Non Target Vessel Revascularization (Non-TVR)]

Revascularization of the vessel identified and treated as the non-target vessel at the time of the index procedure.

Note: TLR and TVR will be adjudicated by the Clinical Event Committee.

[Ischemia-driven Revascularization (CI-TLR/TVR)]

A revascularization is considered clinically indicated if associated with any of the following:

- Positive functional ischemia study including positive FFR
- Ischemic symptoms and angiographic diameter stenosis ≥50% by core laboratory QCA
- Angiographic diameter stenosis ≥70% by core laboratory QCA without angina or positive functional study

[Coronary Artery Bypass Graft Surgery]

CABG during follow-up is only considered as a clinically-indicated target lesion revascularization if coronary angiography indicates a diameter of stenosis ≥50% of the index lesion (core lab QCA assessment) associated with one of the following conditions:

- A positive history of recurrent angina pectoris presumably related to the target vessel
- Objective signs of ischemia (12-lead ECG, exercise test or equivalent) presumably related to the target vessel
- Abnormal results of any invasive functional diagnostic test (e.g. doppler flow velocity reserve, fractional flow reserve)

- A TLR/TVR with a diameter stenosis ≥70% (core lab QCA assessment) in the absence of the above mentioned ischemic signs or symptoms

STENT THROMBOSIS

(ARC Circulation 2007; 115: 2344-2351)

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

Timing:

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

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

Categories:

- Definite
- Probable
- Possible

Definitions of each category are as follows.

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

  Angiographic confirmation of stent thrombosis*
  The presence of a thrombus† that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:
  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical elevation or depression in cardiac biomarkers (refer to definition of spontaneous MI)
  - Nonocclusive thrombosis
    - Thrombus Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple

projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

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

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis.
† Intracoronary thrombus.

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

- **Probable stent thrombosis**
  Either of the following occurred after stent implantation will be considered a probable stent thrombosis:
  - Any unexplained death within the first 30 days‡
  - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

‡ For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

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

STROKE

[Cerebrovascular Accident (CVA) / Stroke]

Stroke is defined as a sudden onset of focal neurological deficits due to vascular lesions of the brain that persists >24 hours. Any neurological symptom that lasts < 24 hours is classified as transient ischemic attack (TIA). Stroke results from either of two types of cerebral vascular disturbance: ischemia or hemorrhage.

[Transient ischemic attack (TIA)]

TIAs are focal neurologic abnormalities of sudden onset and brief duration (i.e., lasting less than 24 hours) that reflect dysfunction in the distribution of the affected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.

TIMI FLOW GRADES

0. No contrast flow through the stenosis.
1. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
2. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
3. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.