# Study Protocol

# Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich's Combo StEnt (Japan-USA HARMONEE): Assessment of a Novel DES Platform For Percutaneous Coronary Revascularization in Patients with Ischemic Coronary Disease and NSTEMI Acute Coronary Syndrome

Phase: Japan Pivotal

U.S. Investigational Device Exemption

Date: March 16, 2015

Version: Amendment 1.02

Principal Investigators:

Shigeru Saito, MD
Director of Cardiology & Catheterization Laboratories and Vice President
Shonan Kamakura General Hospital
1370-1 Okamoto
Kamakura City 247-8533 Japan
Phone: +81-467-461717 Ext: 10490
e-mail: transradial@kamakuraheart.org

Mitchell W. Krucoff, MD
Professor, Medicine/Cardiology
Duke University Medical Center
Durham NC 27705
USA
Phone: +1-919-668-8422
e-mail: mitchell.krucoff@duke.edu

Sponsor:

OrbusNeich Medical K.K.
3-6-11 Uehara, Shibuya
Tokyo 151-0064
Japan
Phone: +81-3-5738-5765

OrbusNeich Medical, Inc.
5363 NW 35th Avenue
Fort Lauderdale FL 33309
USA
Phone: +1-954-730-0711

Notwithstanding the contents of this protocol, this clinical trial will be conducted in accordance with local regulations in each country. This document contains information that is privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. The information in this document is the property of the Duke Clinical Research Institute (DCRI) and may not be reproduced, published, or disclosed to others without written authorization from DCRI.

## PROTOCOL APPROVAL PAGE

**Study Title:** Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich's Combo StEnt (Japan-USA HARMONEE): Assessment of a Novel DES Platform for Percutaneous Coronary Revascularization in Patients with Ischemic Coronary Disease and NSTEMI Acute Coronary Syndrome

Version: Amendment 1.02

Date of Issue: March 16, 2015

Study Sponsor: OrbusNeich Medical

We, the undersigned, have read and approve this protocol and agree on its content.

Sponsor Representative

3-19-15
Date

Coordinating or Principal Investigator

3-16-15
Date

Coordinating or Principal Investigator

2015 / MAR / 20
Date

# PROTOCOL VERSION AND AMENDMENT TRACKING

| Version/Amendment Number | Approval Date |
|---|---|
| Regulatory 1.0 | |
| Regulatory 2.1 | October 23, 2013 |
| Regulatory 2.5 | December 13, 2013 |
| Regulatory 2.51 | February 5, 2014 |
| Regulatory 2.6 | May 5, 2014 |
| Amendment 1.0 | December 8, 2014 |
| Amendment 1.02 | March 16, 2015 |

# PROTOCOL SYNOPSIS

| | |
|---|---|
| Name of Company | OrbusNeich Medical |
| Product | Combo Stent (OMKK02 in Japan) |
| Protocol Number | VP-0601 |
| Protocol Title | Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich's Combo StEnt (Japan-USA HARMONEE): Assessment of a Novel DES Platform For Percutaneous Coronary Revascularization in Patients with Ischemic Coronary Disease and NSTEMI Acute Coronary Syndrome |
| Study Purpose | Treatment for coronary revascularization in patients with functionally significant ischemic heart disease, including unstable angina and non-ST-elevation myocardial infarction (NSTEMI), due to discrete *de novo* lesions (length 28 mm or less) in 1 or more native coronary arteries with a reference vessel diameter of 2.5 mm to 3.5 mm |
| Main Criteria for Inclusion | • Subject must be at least 20 years of age at the time of randomization<br>• Clinical or functional evidence of myocardial ischemia (eg, stable or unstable angina, stabilized NSTEMI confirmed by serum markers, ischemia by positive functional study, abnormal fractional flow reserve [FFR], or a reversible change in the electrocardiogram [ECG] consistent with ischemia)<br>• Acceptable candidate with anatomy for percutaneous coronary intervention (PCI) with a drug-eluting stent (DES)<br>• Agree to return for all study-related follow-up assessments, including invasive optical coherence tomography (OCT) follow-up assessment at 6 months (Cohort A) and at 1 year postprocedure (Cohorts A, B, and C)<br>• Acceptable candidate for coronary artery bypass graft surgery<br>Angiographic anatomy criteria:<br>• Target lesions must be located in a native coronary artery with visually estimated diameter of 2.5 mm to 3.5 mm, inclusive, and up to 3 de novo target lesions may be treated, with a maximum of 2 de novo target lesions per epicardial vessel, with a maximum of 2 target vessels.<br>• Target lesions should be treatable with a single stent and must measure 28 mm or less in length by visual estimation (2 mm or more of nondiseased tissue on either side of the target lesion should be covered by the study stent). |

| Name of Company | OrbusNeich Medical |
|---|---|
| Product | Combo Stent (OMKK02 in Japan) |
| | • If more than 1 target lesion will be treated, the reference vessel diameter and lesion length of each target lesion must meet the above criteria.<br>• Target lesions must be in a major artery or branch with a visually estimated stenosis of 50% or greater and less than 100% with a TIMI flow of 1 or greater.<br>• Previous percutaneous intervention of lesions in a target vessel (including side branches) is allowed if done 9 or more months before the study procedure and greater than 10 mm from the current target lesion.<br>• Nonstudy percutaneous interventions for lesions in a nontarget vessel are allowed if done 9 or more months before the study procedure, in the absence of documented ischemia or angiographic restenosis related to the vessel. |
| Main Criteria for Exclusion | • STEMI at index presentation or within 7 days of study screening.<br>• Current unstable arrhythmias or intractable angina with ECG changes or shock requiring pressors or mechanical circulatory assistance (eg, intraaortic balloon pump, left ventricular assist device, Impella).<br>• Known left ventricular ejection fraction less than 30%.<br>• Prior heart transplant or any other organ transplant or is on a waiting list for any organ transplant.<br>• Receiving or scheduled to receive anticancer therapy for malignancy within 30 days before or after the procedure.<br>• Receiving immunosuppression therapy, has known serious immunosuppressive disease (eg, human immunodeficiency virus), or has severe autoimmune disease that requires chronic immunosuppressive therapy (eg, systemic lupus erythematosus).<br>• Known hypersensitivity or contraindication to aspirin; both heparin and bivalirudin; all available P2Y12 inhibitors (clopidogrel, prasugrel, ticlopidine, and ticagrelor); or any everolimus, sirolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoro polymers; or hypersensitivity to contrast media that cannot be adequately premedicated.<br>• Has previously received murine therapeutic antibodies and exhibited sensitization through the production of human antimurine antibodies (HAMAs).<br>• Elective surgery planned within the first 12 months after the procedure that will require interruption or discontinuation of planned dual antiplatelet therapy.<br>• Known platelet count less than 100,000 cells/$mm^3$ or greater than 700,000 cells/$mm^3$, a white blood cell count of less than 3000 cells/$mm^3$, or documented or suspected liver disease (including laboratory evidence of hepatitis). |

| Name of Company | OrbusNeich Medical |
|---|---|
| Product | Combo Stent (OMKK02 in Japan) |
| | • Known renal insufficiency (eg, serum creatinine level of greater than 2.5 mg/dL or subject is on dialysis).<br>• History of bleeding diathesis or coagulopathy or will refuse blood transfusions.<br>• Has had a cerebrovascular accident or transient ischemic neurological attack within the past 6 months.<br>• Has had a significant gastrointestinal or urinary bleed within the past 6 months.<br>• Known extensive peripheral vascular disease that precludes safe 6 French sheath insertion.<br>• Known other medical illness (eg, cancer, chronic infectious disease, severe vascular disease, or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause noncompliance with the protocol, confound the data interpretation, or is associated with a life expectancy of less than 1 year.<br>• Currently participating in another clinical study that has not yet reached its primary endpoint.<br>• Currently pregnant or breast-feeding or is planning pregnancy in the period up to 1 year following index procedure. Female subjects of childbearing potential must have a negative pregnancy test within 7 days before the index procedure.<br>Angiographic exclusion criteria:<br>• Unprotected left main coronary artery location.<br>• Unprotected ostial (located within 2 mm of the origin) left anterior descending artery or left circumflex.<br>• Located within an arterial or saphenous vein graft or graft anastomosis, distal to a diseased arterial or saphenous vein graft (visually estimated graft diameter stenosis greater than 40%).<br>• Involves a bifurcation in which the side branch is 2 mm or greater in diameter AND would be covered by the planned stent.<br>• Involves a side branch requiring predilation.<br>• Total occlusion (TIMI flow 0) before wire crossing.<br>• Extreme tortuosity proximal to or within the lesion.<br>• Extreme angulation (90º or greater) proximal to or within the lesion.<br>• Heavy calcification, defined as multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion.<br>• Restenotic vessel from previous intervention.<br>• Received brachytherapy in any epicardial vessel (including side branches).<br>• Target vessel contains angiographically visible thrombus. |

| | |
|---|---|
| Name of Company | OrbusNeich Medical |
| Product | Combo Stent (OMKK02 in Japan) |
| | • Serial lesions or diffuse disease with high probability of bailout requiring 3 or more stents in a single vessel, more than 5 stents per subject, or more than 2 vessels.<br>• Target or nontarget vessel lesion (including all side branches) is present with a high probability of requiring PCI within 12 months after the index procedure.<br>• Stent overlapping is a planned treatment of the target lesion. |
| Study Device | Combo stent, a sirolimus-eluting and anti-CD34 antibody-coated stent |
| Comparator Device | Everolimus-eluting stent (EES) XIENCE family of stent systems: (Xience V, Xience Prime, Xience Xpedition, Xience Alpine stents, Abbott Vascular/Abbott Vascular Japan). The XIENCE Alpine stent system uses the identical stent and stent contacting balloon materials, and the identical drug coating formulation and drug dose density as the XIENCE Prime. Xience Prime, Xpedition, and Alpine utilized the clinical result of XIENCE V and is a product that obtains efficiency essentially equal to XIENCE V. |
| Study Objectives | <u>Primary</u><br>To demonstrate assurance of the safety and effectiveness of Combo—a combination sirolimus-eluting and anti-CD34 antibody-coated stent—through:<br>• Noninferior clinical effectiveness to state-of-the-art second-generation drug-eluting stent (DES), specifically<br>o Clinically, as comparable target-vessel failure (TVF) at 1 year<br>o Comparable freedom from ischemia assessed in primary target vessel by FFR ratio greater than 0.8 at 1 year<br>• Superior clinical effectiveness to imputed bare metal stent TVF at 1 year<br><u>Secondary</u><br>• To assess the effectiveness of Combo by OCT evaluation of healthy level of intimal tissue coverage at 1 year (Cohorts A and B combined)<br><u>Prespecified</u><br>• Evaluation of angiographic late lumen loss at 1 year (Cohorts A and B combined)<br>• To assess the safety of Combo by OCT evaluation of intracoronary thrombosis and stent malapposition at 1 year (Cohorts A and B combined)<br>• Serial observation of both Combo and EES at 6 and 12 months in the same patients (Cohort A) |

| | |
|---|---|
| Name of Company | OrbusNeich Medical |
| Product | Combo Stent (OMKK02 in Japan) |
| | • To assess the change in HAMA plasma levels at 30-day and 1-year follow-ups compared with baseline<br>• Comparable rates of death, myocardial infarction (MI), and stent thrombosis at 1 year |
| Study Design | Subjects will be randomized to receive the Combo stent as the investigational treatment arm or an EES as the active-control arm, in a multi-center, single-blind, noninferiority study.<br>Up to 50 sites are proposed in Japan and the United States.<br>Total sample size: 286 subjects (271 evaluable) in each of 2 arms, for a total sample size of 572 subjects (542 evaluable) who are admitted to the hospital for a planned (elective or urgent) percutaneous coronary artery intervention procedure. Investigators must declare an intended oral antiplatelet regimen and intended duration of antiplatelet therapy before randomization; postprocedure, subjects will receive aspirin indefinitely and P2Y12 inhibition for a minimum of 6 months (12 months for acute coronary syndrome diagnosis), according to regional standards of care. After stent implantation, subjects will be contacted for follow-up at 30 days; 6 months; and 1, 2, 3, 4, and 5 years. At 12 months a clinical evaluation will be completed before cardiac catheterization and angiographic assessment in all subjects.<br>The study population will be enrolled as 3 consecutive cohorts:<br>• Cohort A: 30 subjects (15 subjects per arm) will undergo all clinical follow-up assessments; receive OCT and angiographic assessments at 6 months; and receive OCT, FFR, and quantitative coronary angiographic (QCA) assessment at 12 months after device implantation. Cohort A will be the first cohort to enroll.<br>• Cohort B: 110 subjects (55 subjects per arm) will undergo all clinical follow-up assessments, with OCT, FFR, and QCA assessments at 12 months after device implantation. Cohort B will be the second cohort to enroll.<br>• Cohort C: 432 subjects (216 subjects per arm) will undergo all clinical follow-up assessments with FFR and angiographic assessments at 12 months. Cohort C will be the last cohort to enroll.<br>In addition, serum will be assessed for HAMA development at index, 30 days, and 12 months in Cohort B subjects. Human antimurine antibody plasma assessment will be with blood draws performed during index procedure, 30-day follow-up visit, and 1-year catheterizations.<br>Primary endpoint results will be reported after all subjects have completed 12 months of clinical and FFR follow-up. A total of 572 subjects (30+110+432) are enrolled to ensure that |

| | |
|---|---|
| Name of Company | OrbusNeich Medical |
| Product | Combo Stent (OMKK02 in Japan) |
| | 542 subjects are evaluable for the primary clinical endpoint, across all cohorts. |
| Duration of Study Participation | Primary endpoint: 1 year<br>Completed follow-up: 5 years |
| Number of Subjects | 572 (542 evaluable) |
| Number of Sites | Up to 50, in Japan and the United States |
| Primary Endpoint | TVF, defined as cardiac death, target-vessel MI, or ischemia-driven target-vessel revascularization (TVR) by percutaneous or surgical methods, at 1 year. |
| Secondary Endpoint | Mechanistic OCT healthy level of intimal tissue coverage, by OCT core laboratory at 1 year (Cohorts A and B, total N=140 subjects) |
| Additional Prespecified Endpoints | Efficacy:<br>• Angiographic late loss by quantitative coronary angiogram core laboratory at 1 year (Cohorts A and B combined).<br>• In-stent and in-segment angiographic binary restenosis at 1 year (Cohorts A and B combined). In-segment restenosis is defined as restenosis within a region including 5 mm proximal and 5 mm distal to the target lesion.<br>• In-stent and in-segment proximal and distal QCA measurement of late lumen loss at 1 year (Cohorts A and B combined).<br>• Clinically and functionally (FFR) ischemia-driven target-lesion revascularization (TLR) at 1 year.<br>• Device success, defined as attainment of less than 50% residual stenosis of the target lesion.<br>• Lesion success, defined as attainment of less than 50% residual stenosis using any percutaneous method.<br>• Procedure success, defined as lesion success without the occurrence of in-hospital death, nonfatal MI, stroke, or emergency revascularization.<br>• TVF, defined as cardiac death, target vessel MI, or ischemic-driven TVR by percutaneous or surgical methods at 30 days; 6 months; and 2, 3, 4, and 5 years.<br>• Death (all causes) at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.<br>• Cardiac death at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.<br>• Nonfatal MI at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.<br>• Target-vessel MI at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.<br>• TLR (ischemia driven) at 30 days; 6 months; and 1, 2, 3, 4, and 5 years. |

| Name of Company | OrbusNeich Medical |
|---|---|
| Product | Combo Stent (OMKK02 in Japan) |
| | • TVR (ischemia driven) at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.<br>• Target-lesion failure, defined as death, MI, and ischemia-driven TLR.<br><br>Safety:<br>• All-cause mortality at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years<br>• Cardiac mortality at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years<br>• ARC definite/probable stent thrombosis at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years<br>• ARC definite stent thrombosis at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years<br>• MI (using modified ARC definition[1]) at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years<br>• Stroke and TIA at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years<br>• OCT safety assessments for late malapposition and intracoronary thrombus by OCT core laboratory at 1 year (Cohorts A and B combined, N=140 subjects)<br>• Change in HAMA plasma levels at 30 days and 1-year follow-up compared with baseline (N=110, all subjects in Cohort B) |

## INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the investigator brochure, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by OrbusNeich Medical. I will discuss this material with them to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol.

I agree to provide all subjects with informed consent forms, as required by government regulations and International Conference on Harmonisation guidelines. I further agree to report to the sponsor any adverse device effects in accordance with the terms of this protocol, the Ministerial Ordinance on Good Clinical Practice for Medical Devices, Ordinance of the Ministry of Health and Welfare No. 36 (J-GCP) (for Japan), and U.S. Food and Drug Administration regulation 21 Code of Federal Regulations 812.150(a)(1) (for the United States).

_____
Site Principal Investigator Name (print)

_____
Signature

_____
Date

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## ABBREVIATIONS

| | |
|---|---|
| AAR | anti-antibody response |
| ACC | American College of Cardiology |
| ACS | acute coronary syndrome |
| ADE | adverse device effect |
| ADP | adenosine diphosphate |
| AE | adverse event |
| AHA | American Hospital Association |
| ARC | Academic Research Consortium |
| BDI | butane diisocyanate |
| BDO | butanediol |
| BMS | bare metal stent |
| CABG | coronary artery bypass graft |
| CCS | Canadian Cardiovascular Society |
| CD34Ab | anti-CD34 antibody |
| CEC | Clinical Events Classification Committee |
| CFR | Code of Federal Regulations (U.S.) |
| CK-MB | creatine kinase-myocardial band |
| CL | caprolactone |
| CRA | clinical research associate |
| CRC | clinical research coordinator |
| DAPT | dual antiplatelet therapy |
| DCRI | Duke Clinical Research Institute |
| DES | drug-eluting stent |
| DSMC | Data and Safety Monitoring Committee |
| EC | ethics committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EES | everolimus-eluting stent |
| EPC | endothelial progenitor cell |

| | |
|---|---|
| FAME | Fractional Flow Reserve (FFR) vs. Angiography in Multivessel Evaluation |
| FDA | Food and Drug Administration (U.S.) |
| FFR | fractional flow reserve |
| FKBP | FK-binding protein |
| GA | glycolide |
| GMP | Good Manufacturing Practice |
| HAMA | human antimurine antibody |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | investigator brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| ID | identification |
| IDE | Investigational Device Exemption |
| IFU | instructions for use |
| IRB | institutional review board |
| IXRS | interactive web response system |
| J-GCP | Ministerial Ordinance on Good Clinical Practice for Medical Devices. Ordinance of the Ministry of Health and Welfare No. 36 (Japan) |
| LA | lactide |
| LAR | legally authorized representative |
| LMWH | low-molecular-weight heparin |
| LVEF | left ventricular ejection fraction |
| mAbs | monoclonal antibodies |
| MACE | major adverse cardiac events |
| MI | myocardial infarction |
| MTC | mixed treatment comparison |
| mTOR | mammalian target of rapamycin |
| NSTEMI | non–ST-elevation myocardial infarction |
| OCT | optical coherence tomography |
| OD | optical density |
| OR | odds ratio |

| | |
|---|---|
| PCI | percutaneous coronary intervention |
| PEG | polyethylene glycol |
| PHI | protected health information |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency (Japan) |
| PTCA | percutaneous transluminal coronary angioplasty |
| PVC | premature ventricular contraction |
| QCA | quantitative coronary angiography |
| RR | risk ratio |
| SAE | serious adverse event |
| SOP | standard operating procedure |
| STEMI | ST-elevation myocardial infarction |
| TIA | transient ischemic attack |
| TIMI | thrombolysis in myocardial infarction |
| TLF | target-lesion failure |
| TLR | target-lesion revascularization |
| TVF | target-vessel failure |
| TVR | target-vessel revascularization |
| UADE | unanticipated adverse device effect |

# 1. ADMINISTRATIVE STRUCTURE

## Principal Investigators

Shigeru Saito, MD
Director of Cardiology & Catheterization Laboratories and Vice President
Shonan Kamakura General Hospital
1370-1 Okamoto
Kamakura City 247-8533 Japan

Mitchell W. Krucoff, MD
Professor, Medicine/Cardiology
Duke University Medical Center
Durham NC 27705
USA

## Data Coordinating Center

David F. Kong, MD
Duke Clinical Research Institute
Duke University
2400 Pratt Street
Durham NC 27705
USA

## OrbusNeich Medical Study Managers

Akira Sano
Manager, Clinical Development
OrbusNeich Medical K.K.
Oakhouse 201
3-6-6 Uehara, Shibuya
Tokyo, Japan

Debbie Morrell
Manager, Clinical Development
OrbusNeich Medical, Inc.
5363 NW 35th Avenue
Fort Lauderdale FL 33309
USA

## Data and Safety Monitoring Committee (DSMC)

Duke Clinical Research Institute
Duke University
2400 Pratt Street
Durham NC 27705
USA

## Clinical Events Classification Committee

Duke Clinical Research Institute
Duke University
2400 Pratt Street
Durham NC 27705
USA

**Site Management**

**Japan**

CMIC
7-10-4 Nishi-Gotanda
Shinagawa-ku
Tokyo, Japan

**United States**

Duke Clinical Research Institute
Duke University
2400 Pratt Street
Durham NC 27705
USA

**Human Antimurine Antibody Core Laboratory**

Celerion Switzerland AG
Allmendstrasse 32
8320 Fehraltorf, Switzerland

**Quantitative Coronary Angiographic Core Laboratory**

**Optical Coherence Tomography Laboratory**

Cardiovascular Research Foundation
111 East 59th Street, 12th Floor
New York NY 10022
USA

**Fractional Flow Reserve Core Laboratory**

University Hospitals of Cleveland
11100 Euclid Avenue
Cleveland OH 44194
USA

**Clinical Helpline**

ALMAC Clinical Technologies

25 Fretz Road
Souderton PA 18964
USA

# 2. INTRODUCTION

## 2.1 Background

One of the original limitations of percutaneous transluminal coronary angioplasty (PTCA) was restenosis, which occurred in 20% to 40% of patients.[2,3] The loss of luminal diameter resulting in restenosis is primarily due to 2 mechanisms: elastic recoil of the vessel and neointimal hyperplasia.

Coronary stenting reduced restenosis compared to balloon angioplasty alone by preventing acute elastic recoil.[4,5] However, stents still provoke increased neointimal hyperplasia with a consequent incidence of late luminal loss.[6,7] New bare-metal stent (BMS) designs with thinner struts are associated with restenosis rates around 12% to 15% in patients undergoing single-vessel revascularization and higher rates of restenosis in longer lesions, smaller vessels, multivessel percutaneous coronary intervention (PCI) procedures, and in patients with a diagnosis of diabetes. Adjunct therapies (eg, pharmacological therapy, coronary radiation, and coronary debulking) do not reduce restenosis more than stent placement alone.

Localized drug elution, in particular of -limus drug analogues, from stents coated with polymer loaded with inhibitory drugs has further reduced restenosis rates compared to bare metal platforms. A substantial body of evidence has emerged demonstrating that local delivery of cell cycle inhibitors from the stent surface dramatically reduces neointimal hyperplasia and subsequent restenosis. The longest historical data available are with stents using the drug sirolimus. More than a decade ago, Sousa, et al.[8,9] reported the safety and feasibility of a sirolimus-eluting stent; in this cohort of 30 consecutive patients who received active treatment, no patient exhibited restenosis at a 4-month angiographic follow-up. Evaluation of 2-year clinical outcomes revealed no deaths, 1 Q-wave myocardial infarction (MI) (unrelated to the target lesion), 1 coronary artery bypass graft (CABG) for an ostial left circumflex coronary artery progression, and 1 target-vessel revascularization (TVR) for lesion progression. Follow-up extended up to 39 months demonstrated that no new events had occurred. Event-free (death, MI, CABG, repeat PTCA) survival at 36 months for first-in-man patients was 90.1%.

In the SIRolImUS-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial, 556 patients were randomized to receive the sirolimus-eluting Cypher® stent and 545 to receive a bare metal Bx Velocity stent. Mean follow-up minimal luminal diameter on angiography was significantly different at 2.50 mm in the sirolimus group and 1.68 mm in the control. This led to a 10.5% mean diameter stenosis at follow-up vs 40.1% for the control group and a late loss reduction from 1.00 mm in the control to 0.17 mm in the sirolimus group. In-segment restenosis occurred in 8.9% of the sirolimus group and in 36.3% of the control group ($p < 0.001$). Stent thrombosis occurred in 2 patients (0.4%) in the sirolimus arm and in 4 patients (0.8%) in the control arm. The primary endpoint, target-vessel failure (TVF), was reduced by 59%, from 21.0% in the control group to 8.6% in the sirolimus group.[10,11]

While drug-eluting stents (DESs) have decreased the rates of in-stent restenosis compared with BMSs,[12,13] concerns about nonhealing of DES sites resulting in stent thrombosis, ST-elevation myocardial infarction (STEMI), and death were widely reported in 2006[14,15] and have led to extended use of dual antiplatelet therapy (DAPT) despite the risk of bleeding and costs associated with such extended therapy. Mechanisms associated with stent thrombosis, in addition to early interruption of DAPT, include strut malapposition or fracture, inhibition of endothelial cell recovery by mammalian target of rapamycin (mTor) inhibitors or paclitaxel, and persistent

inflammatory reactions to durable stent polymer. The end common pathway of all of these mechanisms is a thrombotic nidus consisting of incomplete reendothelialization within the stented segment, ie, the failed recovery of healthy neointima within the stented site.[14,16–18]

Thus, while effectiveness of DES platforms has reduced restenosis to less than 10%, concerns with late and very late stent thrombosis with these permanent coronary implants has led to a focus on long-term safety of these permanent implants in more than 10 million patients worldwide, with more than 1 million additional patients worldwide per year undergoing stenting. To address these rare but catastrophic safety concerns, many manufacturers of new DES platforms have focused on design features intended to augment safety without negating current high levels of effectiveness. A number of engineering modifications emerged in second-generation DES platforms, including the selection of more inert, biocompatible durable polymers (Endeavor, Endeavor Resolute, Xience V) and bioabsorbable polymers applied only to the abluminal stent surface (Nobori, Biomatrix, Combo).[19] Data comparing first- and second-generation DES platforms have been encouraging that these modifications have, indeed, improved safety at least in the setting of prolonged use of DAPT.[20,21] Endeavor platforms randomized against both Cypher and TAXUS first-generation DES platforms showed inferior late loss but noninferior clinical outcomes and superior safety (stent thrombosis) over 3-year follow up.[22–24] EES V platforms randomized against TAXUS first-generation DESs in multiple independent cohorts showed superior clinical outcomes and superior safety 3 to 5 years after PCI.[25–27]

Even with such improved outcomes, stent thrombosis rates of 0.3% to 0.6% per year over a patient's lifetime and the use of prolonged DAPT following more than 1 million stent procedures performed per year remains significant unmet clinical challenges. Dual antiplatelet therapy for 12 months or longer results in bleeding complications as well as elevated costs of care associated with PCI. Finally, the histopathological trauma associated with stent implantation continues to generate early stent thrombosis events at a rate of about 0.9% to 1.3% in the first 30 days, an event rate that is identical for both BMS and DES platforms. Thus DES platform engineering continues to direct itself toward better, safer medical device designs without compromising the very high level of effectiveness that generation 2 DESs have demonstrated.

New design features include DES platforms that do not use polymer at all; DES platforms that are completely made of bioabsorbable polymer; new metal alloys that support thinner struts but are resistant to strut fracture; and technologies designed to enhance the speed, completeness, and quality of reendothelialization following PCI. Of all currently advancing, safety-oriented designs, the OrbusNeich Medical Combo stent (Identification Mark: OMKK02 in Japan), combining abluminal only, bioabsorbable polymer with CD34 endothelial progenitor cells (EPCs)-capture technologies represents a unique potential to advance both short- and long-term safety with PCI.

Bone marrow-derived EPCs circulate in the peripheral blood and migrate to areas of vascular injury. It is hypothesized that the EPCs differentiate into mature endothelial cells, contributing to the vascular repair and formation of a functional endothelium.[28,29]

The ability to capture circulating EPCs was demonstrated by the Genous™ Endothelial Progenitor Cell Capturing Stent (OrbusNeich Medical Technologies, FL), a bare-metal stainless-steel stent coated with antihuman CD34+ antibodies that bind circulating EPCs. In animal studies, a rapid enhancement of EPCs binding to the stent struts was observed, and a confluent monolayer of adherent CD34+ cells was approached after 60 minutes of incubation.[30] In humans, the safety and efficacy of the bare-metal EPC-capturing stent was demonstrated in the nonrandomized Healthy

Endothelial Accelerated Lining Inhibits Neointimal Growth-First in Man (HEALING-FIM) study,[31] and the HEALING II study evaluating patients with noncomplex coronary lesions.[32] The HEALING-First-in-Man study included 16 patients. At the 9-month clinical follow-up, the composite of cardiac death, stroke, MI, and TVR was 6.3%, and no cases of stent thrombosis were reported. In the nonrandomized HEALING II study, 63 patients with noncomplex lesions were enrolled. At the 18-month clinical follow-up, no stent thrombosis was observed, and the composite of cardiac death, MI, and target-lesion revascularization (TLR) was 7.9%, mainly attributed to a relatively low (for a BMS platform) clinically driven TLR rate of 6.3%. In a subsequent single-center registry of 405 unselected patients treated percutaneously with the Genous bare-metal/EPC-capturing stent,[33] the primary endpoint, defined as the composite of cardiac death, MI, and TLR at 1 year, was 13.3%, mainly attributable to TLR, which was 10.9%—again, relatively encouraging for a BMS platform. The occurrence of definite and probable stent thrombosis was low, 0.5% and 0.7%, respectively. The data available today suggest that the use of the EPC-capturing stent technology is safe and that the results from nonrandomized trials can be replicated in patients with a variety of clinical and angiographic characteristics.

The OrbusNeich Combo platform advances this experience with CD34Ab on a bare-metal platform to the use of this technology in a safety-oriented (abluminal, bioabsorbable polymer) DES using sirolimus, the -limus analogue with the longest-standing experience in coronary stenting worldwide. In the REMEDEE study, Combo randomized 2:1 against TAXUS in 183 patients showed noninferior late loss, restenosis, and clinical outcomes (see Figure 1, Table 1, and Table 2).

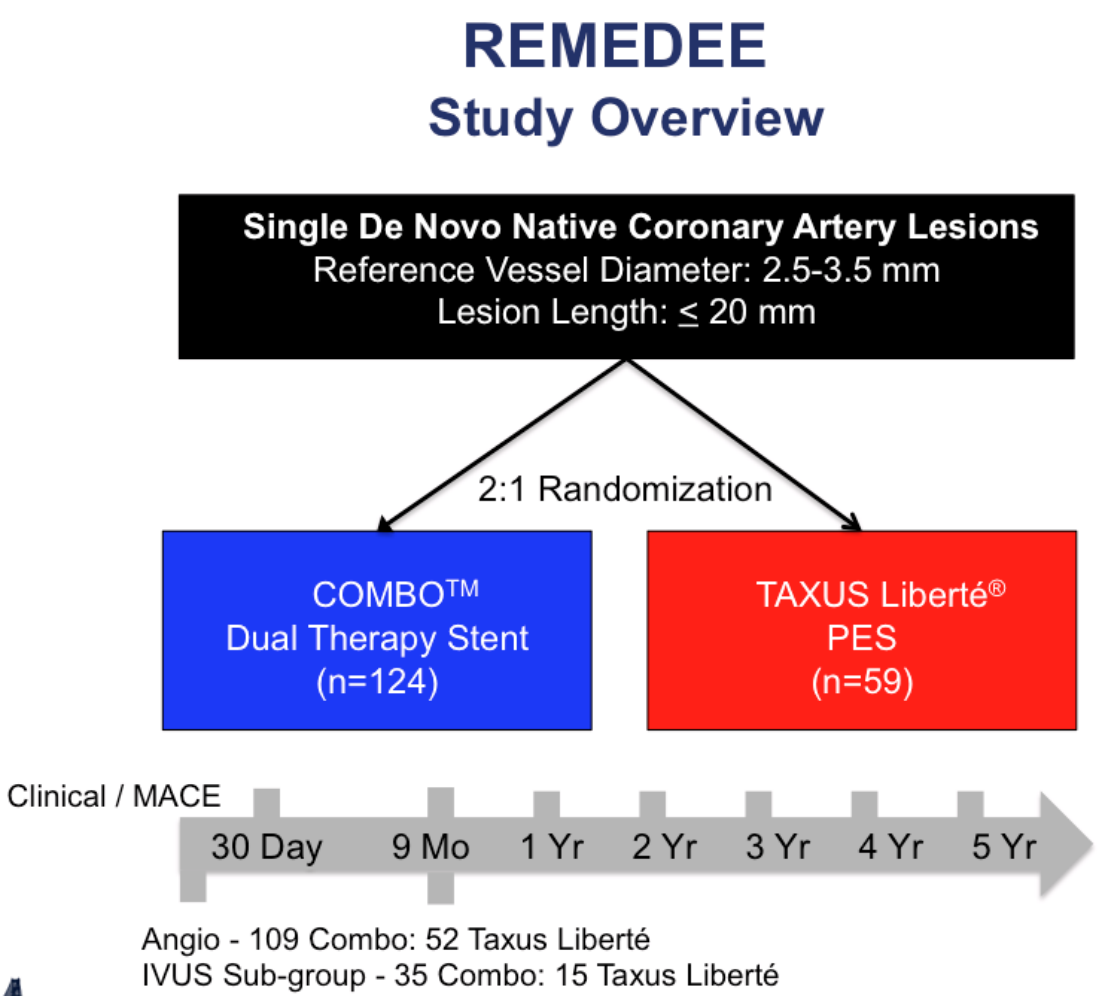



**Figure 1. REMEDEE Study Design**

**Table 1. REMEDEE 9-Month Binary Angiographic Restenosis and In-Segment Late Loss**

| | **Combo** (N=124) | **TAXUS** (N=59) | **P-value** |
|---|---|---|---|
| Restenosis | | | |
| In-stent | 5.5% | 9.6% | 0.34 |
| In-segment | 8.3% | 13.5% | 0.30 |
| Minimum lumen diameter (mm) | | | |
| In-stent, mean ± SD | 2.31 ± 0.58 | 2.30 ± 0.56 | 0.86 |
| In-segment, mean ± SD | 2.09 ± 0.56 | 1.97 ± 0.57 | 0.19 |
| In-stent late lumen loss (mm) mean ± SD | 0.39 ± 0.45 | 0.44 ± 0.56 | 0.55 |

| | **Combo** (N=124) | **TAXUS** (N=59) | **P-value** |
|---|---|---|---|
| In-segment late lumen loss (mm) | 0.27 ± 0.46 | 0.41 ± 0.54 | 0.08 |
| Proximal in-segment, mean ± SD | 0.19 ± 0.44 | 0.29 ± 0.53 | 0.24 |
| Distal in-segment, ± SD | 0.09 ± 0.30 | 0.13 ± 0.30 | 0.45 |

N, number; SD, standard deviation

**Table 2. REMEDEE 9-Month Secondary Effectiveness and Safety Endpoints**
(to 9 months + 30 days: protocol clinical assessment 270 + 30 days)

| | **Combo** (N=124) | **TAXUS** (N=59) | **P-value** |
|---|---|---|---|
| Measures at 9 Months | | | |
| Death | 1.0% | 0.0% | 0.49 |
| Cardiac death | 0.0% | 0.0% | N/A |
| Myocardial infarction (protocol definition) | 2.4% | 1.7% | 0.75 |
| Q-wave | 0.0% | 0.0% | N/A |
| Non–Q-wave | 2.4% | 1.7% | 0.75 |
| Clinically driven target-lesion revascularization | 5.2% | 9.5% | 0.35 |
| Major adverse cardiac events (protocol definition) | 8.7% | 11.0% | 0.69 |
| Stent thrombosis | 0.0% | 0.0% | N/A |
| Clinically driven target-vessel revascularization | 7.0% | 9.5% | 0.65 |
| Clinically driven target-vessel failure (protocol definition) | 10.4% | 11.0% | 0.97 |
| Clinically driven target-lesion failure (protocol definition) | 8.7% | 11.0% | 0.69 |

## 2.2 Preclinical Findings

The Combo stent has been shown to be biocompatible and safe through numerous laboratory and preclinical implant studies. The degradable polymer-based drug-elution technology, the immobilized anti-CD34 antibody cell-capture technology, and the combination thereof have been found to be nontoxic, nonirritating, nonimmunogenic, and blood compatible. The Combo stent, along with the constituent components of polymer-matrix and immobilized antibodies applied to stents, has been found to be well tolerated in preclinical implant studies. Further, the Combo stent has been shown in preclinical implant studies to be efficacious in sustained drug delivery to the local implant site tissue through PK studies, in controlling neointimal proliferation, and in enhancing reendothelialization of implanted stents.

In the preclinical studies, the Combo stent demonstrated significantly lower neointimal hyperplasia, while also showing improved endothelial coverage relative to other commercially available DESs. There was also a noticeably lower presence of inflammation and foreign-body reaction. Thus, the Combo stent appeared effective at inhibition of neointimal growth while enhancing endothelial coverage. These features might potentially result in low rates of in-stent

restenosis comparable to those of commercially available DESs and in reduced rates of late stent thrombosis.

## 2.3 Clinical Experience with Study Device

The study device has been previously evaluated in a Prospective, Randomized Study to Evaluate the Safety and Effectiveness of an AbluMinal Sirolimus CoatED Bio-Engineered StEnt (Combo Bio-Engineered Sirolimus Eluting Stent) Compared with a TAXUS® Liberté® Stent Control Arm for Treatment of Stenotic Lesions in Native Coronary Arteries (REMEDEE) trial. This study randomized 183 patients in a 2:1 fashion to Combo or TAXUS Liberté stents.

In the 12-month follow-up data set, the clinically driven target-lesion failure (TLF) rate was 8.9% for patients treated with the Combo stent, compared with 10.2% for those treated with the TAXUS stent. Clinically driven TLF was defined as a composite of death, MI, and clinically driven TLR. In addition, the rate of clinically driven TLR was 4.9% for patients treated with the Combo stent, compared with 8.5% for those treated with the TAXUS stent. There was no stent thrombosis in either of the groups.

## 2.4 Rationale

This study is intended to demonstrate that the Combo stent platform shows superiority to an imputed BMS performance goal, noninferior effectiveness and safety vs best-in-class second-generation everolimus-eluting stent (EES) (Xience V, Xience Prime, Xience Xpedition, Xience Alpine stents; [Abbott Vascular/Abbott Vascular Japan]), and evidence of mechanistic activity of the anti-CD34-Ab EPC capture technology with healthy level of intimal tissue coverage superior to that of the best-in-class EES.

To ensure the robustness and interpretability of results, the current proposal includes a number of unique design features:

- Largest randomized DES study ever performed in Japan
- Enriched population, including stabilized non-STEMI (NSTEMI) subjects with greater likelihood of plaque rupture associated with their clinical syndromes
- Collaboration between with Japan and the United States as a “Proof of Concept” program under the auspices of the Harmonization by Doing Initiative, WG 1, including concomitant enrollment in U.S.A. sites as an FDA-approved IDE study
- Head-to-head randomization against state-of-the-art EES platform control, analyzed for clinical noninferiority
- Statistical analysis vs imputed BMS analyzed for clinical superiority
- Fractional flow reserve (FFR) follow-up of 100% of subjects enrolled, providing clinically relevant physiologic assessment of all subjects for 1-year ischemia-driven TVR analysis
- Mechanistic OCT imaging observations in 140 subjects using 6 French catheters as follows:
    - Cohort A (30 subjects, 1:1 Combo and EES): Mechanistic imaging observations to provide serial 6-month and 1-year OCT evaluation of healthy intimal tissue coverage, intracoronary thrombosis, and stent malapposition and quantitative coronary angiographic (QCA) analysis to assess 1-year late loss.

  - Cohort B (110 subjects, 1:1 Combo and EES): Mechanistic imaging observations to assess 1-year OCT evaluation of healthy intimal tissue coverage, intracoronary thrombosis, and stent malapposition, and QCA analysis to assess 1-year late loss. Combined with the 12-month imaging of Cohort A, this study will provide OCT and QCA observations at 1 year in 140 patients, half with Combo and half with EES.

- In the 110 subjects in Cohort B, baseline, 30-day and 1-year human antimurine antibody (HAMA) titers will also be collected.

# 3. OBJECTIVES

## 3.1 Primary Objective

While EPC capture has intuitively attractive and exciting mechanistic novelty for both short- and long-term PCI safety, definitive demonstration of impact on stent thrombosis or the safety of shorter DAPT therapy with current stent thrombosis rates under 2% is not feasible for a premarket evaluation. Thus the objective for pivotal premarket approval is to demonstrate assurance of the safety and effectiveness of Combo—a combination sirolimus-eluting and anti-CD34 antibody-coated stent—through:

- Noninferior clinical effectiveness to state-of-the-art second-generation DES, specifically
  - Clinically, as comparable TVF at 1 year
  - Comparable freedom from ischemia assessed in primary target vessel by FFR ratio greater than 0.8 at 1 year
- Superior clinical effectiveness to imputed BMS TVF at 1 year

## 3.2 Secondary Objective

- Superior OCT evidence of healthy level of intimal tissue coverage at 1 year compared to EES considered mechanistically related to the activity of anti-CD34 Ab EPC capture and analyzed in an independent, blinded core laboratory (Cohorts A and B combined)
-

## 3.3 Prespecified Objectives

- Evaluation of angiographic late lumen loss at 1 year (Cohorts A and B combined)
- To assess the safety of Combo by OCT evaluation of intracoronary thrombosis and stent malapposition at 1 year (Cohorts A and B combined)
- Serial observation of both Combo and EES at 6 and 12 months in the same patients (Cohort A)
- To assess the change in HAMA plasma levels at 30-day and 1-year follow-ups compared with baseline
- Comparable rates of death, MI, and stent thrombosis at 1 year

# 4. SUBJECT SELECTION

## 4.1 Inclusion Criteria

To be eligible for this trial, subjects must meet all of the following criteria:

1. Subject is able to verbally confirm understanding of risks, benefits, and treatment alternatives of Combo vs EES stent, and the subject or a legally authorized representative (LAR) must provide written informed consent before any study-related procedures are performed.

2. Subject must be at least 20 years of age at the time of randomization.

3. Subject must have clinical or functional evidence of myocardial ischemia (eg, stable or unstable angina, stabilized non–ST-elevation MI confirmed by serum markers, ischemia by positive functional study, abnormal FFR, or a reversible change in the electrocardiogram [ECG] consistent with ischemia).

4. Subject must be acceptable candidate with anatomy suitable for PCI with a DES.

5. Subject agrees to return for all study-related follow-up assessments, including invasive OCT follow-up assessment at 6 months (Cohort A) and at 1 year postprocedure (Cohorts A, B, and C).

6. Subject is an acceptable candidate for CABG surgery.

Angiographic Anatomy Criteria—

7. Target lesions must be located in a native coronary artery with visually estimated diameter of 2.5 mm to 3.5 mm, inclusive, and up to 3 de novo target lesions may be treated, with a maximum of 2 de novo target lesions per epicardial vessel, with a maximum of 2 target vessels.

8. Target lesions should be treatable with a single stent, and must measure 28 mm or less in length by visual estimation (2 mm or more of nondiseased tissue on either side of the target lesion should be covered by the study stent).

9. If more than 1 target lesion will be treated, the reference vessel diameter and lesion length of each target lesion must meet the above criteria.

10. Target lesions must be in a major artery or branch with a visually estimated stenosis of 50% or greater and less than 100% with a TIMI flow of 1 or greater.

11. Previous percutaneous intervention of lesions in a target vessel (including side branches) is allowed if done 9 or more months before the study procedure and greater than 10 mm from the current target lesion.

12. Nonstudy percutaneous interventions for lesions in a nontarget vessel are allowed if done 9 or more months before the study procedure, in the absence of documented ischemia or angiographic restenosis related to the vessel.

## 4.2 Exclusion Criteria

If a subject meets any of the following criteria, he or she may not be enrolled in the study:

1. STEMI at index presentation or within 7 days of study screening.
2. Subject has current unstable arrhythmias or intractable angina with ECG changes or shock requiring pressors or mechanical assist device (intraaortic balloon pump, left ventricular assist device, Impella, etc.).
3. Subject has known left ventricular ejection fraction (LVEF) less than 30%.
4. Subject has received a heart transplant or any other organ transplant or is on a waiting list for any organ transplant.
5. Subject is receiving or scheduled to receive anticancer therapy for malignancy within 30 days before or after the procedure.
6. Subject is receiving immunosuppression therapy, has known serious immunosuppressive disease (eg, human immunodeficiency virus), or has severe autoimmune disease that requires chronic immunosuppressive therapy (eg, systemic lupus erythematosus).
7. Subject has known hypersensitivity or contraindication to aspirin; both heparin and bivalirudin; all available P2Y12 inhibitors (clopidogrel, prasugrel, ticlopidine, and ticagrelor); any everolimus, sirolimus, cobalt, chromium, nickel, tungsten, acrylic, or fluoro polymers; or hypersensitivity to contrast media that cannot be adequately premedicated.
8. Subject has previously received murine therapeutic antibodies and exhibited sensitization through the production of HAMAs.
9. Subject has elective surgery planned within the first 12 months after the procedure that will require interruption or discontinuation of planned DAPT.
10. Subject has known platelet count less than 100,000 cells/$mm^3$ or greater than 700,000 cells/$mm^3$, a white blood cell count of less than 3000 cells/$mm^3$, or documented or suspected liver disease (including laboratory evidence of hepatitis).
11. Subject has known renal insufficiency (eg, serum creatinine level of greater than 2.5 mg/dL or subject is on dialysis).
12. Subject has history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
13. Subject has had a cerebrovascular accident or transient ischemic neurological attack within the past 6 months.
14. Subject has had a significant gastrointestinal or urinary bleed within the past 6 months.
15. Subject has known extensive peripheral vascular disease that precludes safe 6 French sheath insertion.

16. Known other medical illness (eg, cancer, chronic infectious disease, severe vascular disease, or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin, etc.) that may cause noncompliance with the protocol, confound the data interpretation, or is associated with a life expectancy of less than 1 year.
17. Currently participating in another clinical study that has not yet reached its primary endpoint.
18. Currently pregnant or breast-feeding or is planning pregnancy in the period up to 1 year following index procedure. Female subjects of childbearing potential must have a negative pregnancy test within 7 days before the index procedure.

Angiographic Exclusion Criteria—

If the target lesion meets any of the following criteria, the subject may not be enrolled in the study:

19. Unprotected left main coronary artery location.
20. Unprotected ostial (located within 2 mm of the origin) left anterior descending artery or left circumflex.
21. Located within an arterial or saphenous vein graft or graft anastomosis, distal to a diseased arterial or saphenous vein graft (visually estimated graft diameter stenosis greater than 40%).
22. Involves a bifurcation in which the side branch is 2 mm or greater in diameter AND would be covered by the planned stent.
23. Involves a side branch requiring predilation.
24. Total occlusion (TIMI flow 0) before wire crossing.
25. Extreme tortuosity proximal to or within the lesion.
26. Extreme angulation (90º or greater) proximal to or within the lesion.
27. Heavy calcification, defined as multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion.
28. Restenotic vessel from previous intervention.
29. Received brachytherapy in any epicardial vessel (including side branches).
30. Target vessel contains angiographically visible thrombus.
31. Serial lesions or diffuse disease with high probability of bailout requiring 3 or more stents in a single vessel, more than 5 stents per subject, or more than 2 vessels.
32. Target or nontarget vessel lesion (including all side branches) is present with a high probability of requiring PCI within 12 months after the index procedure.
33. Stent overlapping is a planned treatment of the target lesion.

# 5. STUDY DESIGN

This study will be conducted in accordance with current Ministerial Ordinance on Good Clinical Practice for Medical Devices. Ordinance of the Ministry of Health and Welfare No. 36 (J-GCP) (Japan) guidelines, U.S. Food and Drug Administration (FDA) regulations and guidelines, International Conference on Harmonisation (ICH) guidelines on GCP (ICH E6, the principles of which have their origin in the Declaration of Helsinki), and all other applicable national and local laws and regulations.

## 5.1 Overview of Study

This is a multi-center, single-blind, randomized, active-controlled, clinical trial in PCI subjects. Subjects will be randomized to receive the Combo stent as the investigational treatment arm or an EES as the active-control arm, in a noninferiority study.

Up to 50 sites are proposed in Japan and the United States to enroll 286 subjects (271 evaluable) in each of 2 arms, for a total sample size of 572 subjects (542 evaluable) who are admitted to the hospital for a planned (elective and urgent) percutaneous coronary artery intervention procedure. Investigators must declare an intended oral antiplatelet regimen and intended duration of anti-platelet therapy before randomization; postprocedure, subjects will receive aspirin indefinitely and P2Y12 inhibition for a minimum of 6 months (12 months for acute coronary syndrome [ACS] diagnosis), according to recommended regional standards of care. After stent implantation, subjects will be contacted for follow-up at 30 days; 6 months; and 1, 2, 3, 4, and 5 years. At 12 months a clinical evaluation will be completed before cardiac catheterization and angiographic assessment.

There will be 3 consecutively enrolled cohorts of study subjects:

1. Cohort A: 30 subjects (15 subjects per arm) will undergo all clinical follow-up assessments; receive OCT and angiographic assessments at 6 months; and receive OCT, FFR, and QCA assessments at 12 months after device implantation. Cohort A will be the first cohort to enroll.
2. Cohort B: 110 subjects (55 subjects per arm) will undergo all clinical follow-up assessments, with OCT, FFR, and QCA assessments at 12 months after device implantation. Cohort B will be the second cohort to enroll.
3. Cohort C: 432 subjects (216 subjects per arm) will undergo all clinical follow-up assessments with FFR and angiographic assessments at 12 months. Cohort C will be the last cohort to enroll.

In addition, serum will be assessed for HAMAs development at index, 30 days, and 12 months in the in Cohort B subjects. When possible, HAMA plasma assessment will be from blood draws performed during catheterizations to minimize the need for additional needle punctures.

The primary clinical endpoint is TVF, defined as cardiac death, target-vessel MI, or ischemia-driven TVR by percutaneous or surgical methods, at 1 year. Primary endpoints will be reported after all subjects have completed 12 months of follow-up. A total of 572 subjects (30+110+432) are enrolled to ensure that 542 subjects are evaluable for the primary clinical endpoint, across all cohorts.

The secondary efficacy endpoint is mechanistic OCT healthy level of intimal tissue coverage, determined by the OCT core laboratory at 1 year for subjects in Cohorts A and B combined (total N=140 subjects).

Additional prespecified endpoints include clinically and functionally ischemia-driven TLR, including use of target-vessel FFR, analyzed dichotomously using the Fractional Flow Reserve (FFR) vs. Angiography in Multivessel Evaluation (FAME) study criteria of 0.8 during a 2-minute infusion of adenosine or adenosine triphosphate.[34] Abnormal FFR-driven interventions at 1 year will be included in the evaluation of ischemia-driven TLR.

Other prespecified endpoints are death, MI, composite cardiac death and MI, TLF composite and individual components, and stent thrombosis, to be assessed at each follow-up.

See Figure 2 for a schematic of the study design.

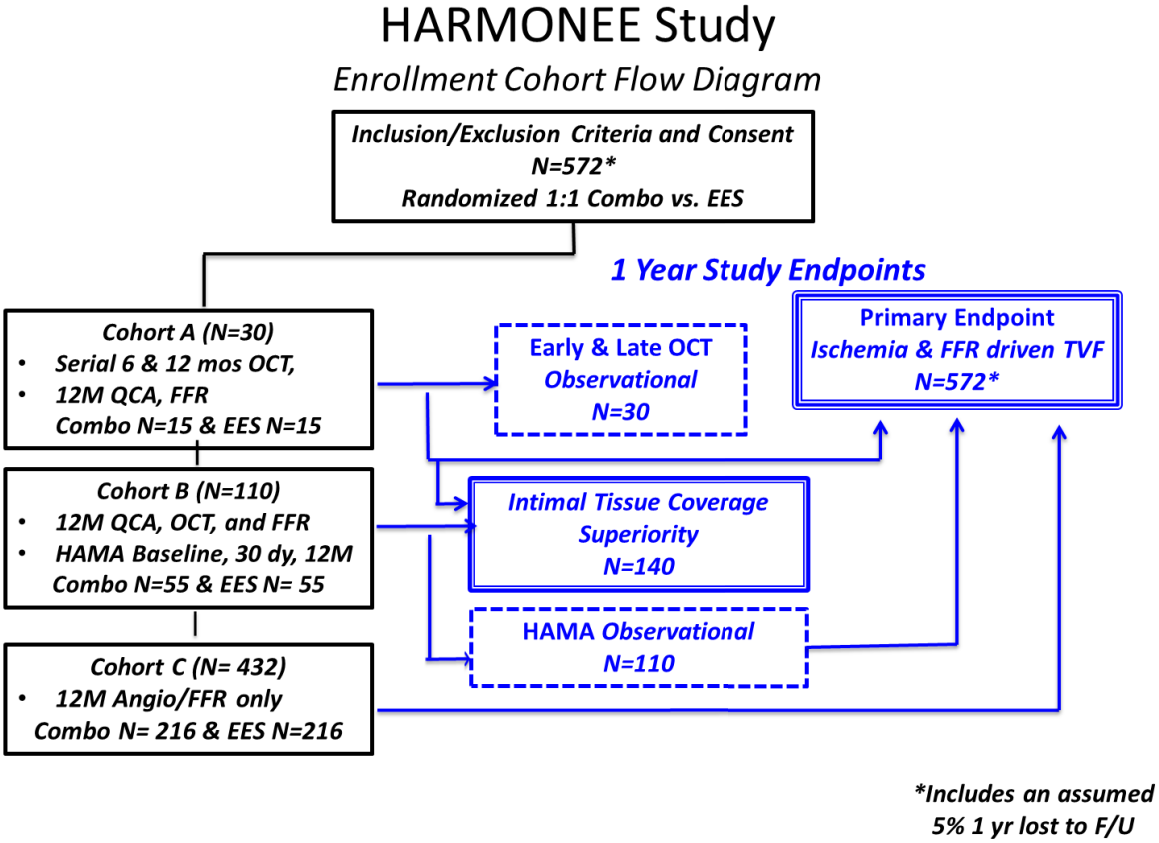



**Figure 2. Schematic of Study Design**

## 5.2 Study Procedures

Potentially eligible subjects will be identified by clinicians at the participating study sites, by review of catheterization laboratory schedules, or other means as locally relevant. Study personnel will assess each subject against each inclusion and each exclusion criterion, and the investigator will determine the subject's eligibility for study participation. Interested subjects will be asked to give written informed consent and undergo a screening evaluation to include a medical history,

physical assessment, laboratory tests, and review of concomitant and protocol-required medications. The informed consent form (ICF) for the enrolled subjects will include details of Cohorts A, B, and C. The ICFs will also include information regarding HAMA blood collections at baseline, 30 days, and the 12-month follow-up.

Subjects may qualify for enrollment based on prior diagnostic angiographic data obtained within the last 3 months. Females of childbearing potential must have a negative pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 7 days before each angiographic procedure. Subjects who have given written informed consent and meet all inclusion and no exclusion criteria will be randomized into 1 of 2 treatment arms in this study. The informed consent process and all assessments will be documented in the subject's medical record or comparable source document. Results from all study assessments on randomized subjects (as described below) will be entered in the eCRF.

The schedule of procedures is presented in Table 3.

**Table 3. Schedule of Procedures**

| | Screening and Prerandomization | Enrollment and Randomization/ Implantation | Postprocedure | 30 (± 7) Days | 180 (± 30) Days | 1 Year (± 30 Days) | Annual (± 60 Days) Follow-ups for 5 Years | Unscheduled Visits/ET |
|---|---|---|---|---|---|---|---|---|
| Inclusion/exclusion criteria | X | | | | | | | |
| Informed consent | X | | | | | | | |
| Medical history | X | | | | | | | |
| Physical assessment, including vital signs (weight, heart rate, blood pressure) | X[a] | | | X | | X[b] | | |
| Angina class[c] | X[a] | | X | X | X | X[b] | X | X |
| 12-lead ECG | X[a] | | X | | X[b.i] | X[b] | | X |
| Concomitant medications | X[a] | | | X | X | X[b] | X | X |
| Pregnancy test (serum or urine) | X[d] | | | | X[b,e,i] | X[b,e] | | |
| Troponin I or T, CK-MB | X, X[u] | | X | | | | | X |
| Chemistry panel and complete blood count[g] | X | | | | | | | |
| Lipid profile (total cholesterol, HDL, LDL, triglycerides) | X | | | | | | | |
| Protocol-required medications | X[a] | X | X | X | X | X[b] | X | X |
| Diagnostic angiogram (digital) | X[h, r] | | | | | | | |
| Pre-implant, target vessel angiogram (digital) | X[h,s] | | | | | | | |

| | Screening and Prerandomization | Enrollment and Randomization/ Implantation | Postprocedure | 30 (± 7) Days | 180 (± 30) Days | 1 Year (± 30 Days) | Annual (± 60 Days) Follow-ups for 5 Years | Unscheduled Visits/ET |
|---|---|---|---|---|---|---|---|---|
| Post-Implant angiogram (digital)[t] | | | X[h] | | | | | |
| Follow-up angiogram (digital)[t] | | | | | X[i] | X[h] | | |
| HAMA plasma samples[j] | | X[k] | | X | | X | | |
| FFR assessment[h,l] | | | | | | X | | |
| Implant device | | X | | | | | | |
| LVEF assessment[m] | | X | | | | | | |
| OCT[t] | | | | | X[i] | X[f,l] | | |
| Core Laboratory QCA[f, t] | | X | | | | X | | |
| Collection of all AEs | | X | X | X | | | | |
| Collection of all SAEs[q] | | X | X | X | X | X | | |
| Collection of AEs/SAEs related to study device only[q] | | X[n] | X[n] | X[n] | X[b,n] | X[b,n] | X[n] | X[n] |
| Event data collection for instances of specified cardiovascular endpoint events[q] | | | X | X | X | X | X | X |

AE, adverse event; CK-MB, creatine kinase-myocardial band; ECG, electrocardiogram; ET, early termination; FFR, fractional flow reserve; HAMA, human antimurine antibodies; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; OCT, optical coherence tomography; QCA, quantitative coronary angiogram; SAE, serious adverse event

[a]Within 24 hours before procedure.
[b]Complete before coronary angiogram and catheterization.
[c]Current Canadian Cardiovascular Society, Braunwald classifications
[d]Within 7 days or immediately before randomization.
[e]If not done within the previous 7 days.
[f]Only Cohorts A and B.
[g]Chemistry panel (alkaline phosphatase, aspartate amino transferase, alanine amino transferase, total bilirubin, calcium, sodium, potassium, glucose, creatinine, blood urea nitrogen); complete blood count (hemoglobin, hematocrit, platelets, white blood cell count, red blood cell count); C-reactive protein; N-terminal pro brain natriureticpeptide.
[h]All cohorts.
[i]Only Cohort A.
[j]Only Cohort B.
[k]Before stent implantation and heparin therapy. For subjects already receiving heparin, HAMA collection should occur 4-6 hrs post heparin therapy.
[l]Primary target vessel only.
[m]Within 14 days or immediately before randomization via echocardiogarphy, single photon emission-computed tomography, computed tomography, magnetic resonance imaging, or left ventriculography.
[n]All AEs and SAEs related to the device, anticipated and unanticipated adverse device effects, (Specified cardiovascular endpoint events data collection will be reported on the eCRF endpoint pages only)
[o]Includes death, myocardial infarction, stroke and transient ischemic attack, target lesion revascularization (ischemia driven), target vessel revascularization (ischemia driven), and stent thrombosis (Academic Research Consortium definition).
[q]Specified cardiovascular endpoint events collection as noted in o will be reported on the eCRF endpoint pages only

[r]Subjects may qualify for enrollment based on prior angiographic data obtained within the last 3 months. If a prior diagnostic angiogram is not available (within 3 months) a screening diagnostic angiogram is required prior to enrollment/randomization and can be completed at the same time as the Pre-implant, target vessel(s) angiogram. Randomized subjects' angiograms are to be provided to central image data center
[S]Pre-Implant, target vessel(s) (baseline) angiogram (all qualifying subjects, digital) will be used for the final assessment of subject eligibility. Randomized subjects angiograms to be provided to the central image data center
[t]Provided to central image data center
[u] For subjects with non-ST-elevation MI and abnormal serum markers, sufficient measurements should be obtained to show a decreasing trend in at least one serum marker consistent with stabilized NSTEMI.

## 5.3 Screening and Prerandomization Procedures

Patients to be admitted for a planned (elective or urgent) percutaneous coronary artery intervention procedure should be screened for study eligibility by a member of the study team (physician and/or research coordinator) previously trained to the study protocol. Subject selection factors to be assessed should include judgment regarding risk of antiplatelet therapy. Subjects who meet general eligibility criteria will be asked to sign an ICF.

After eligible subjects have signed the ICF, the following assessments should be completed as part of standard of care, from time of implant procedure:

- Medical history, including previous MI, previous PCI, previous CABG, peripheral vascular disease, stroke, hypertension, congestive heart failure, diabetes mellitus, cigarette smoking, chronic renal failure, hypercholesterolemia, angina status, and family history of coronary artery disease. If already completed within the past 30 days, those findings may be used.
- Physical assessment, including vital signs (height, weight, heart rate, blood pressure).
- Angina class
    - Stable Angina: Current Canadian Cardiovascular Society [CCS], where class 0=asymptomatic, class I=angina during strenuous physical activity without limitation, class II=slight limitation from angina only during vigorous physical activity, class III=moderate limitation from symptoms from everyday living activities, and class IV=severe limitation with inability to perform any activity without angina or angina at rest.
    - Unstable angina: Braunwald Classification where severity is new onset of severe angina or accelerated angina; no rest pain, angina at rest within past month but not within preceding 48 hours (angina at rest, subacute), angina at rest within 48 hours (angina at rest, acute). Clinical circumstance where develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary unstable angina); develops in absence of extracardiac condition (primary unstable angina); or develops within 2 weeks after acute MI (postinfarction unstable angina).
- 12-lead ECG; if already completed within the past 24 hours, this measurement may be used.
- Concomitant medications.
- Pregnancy test (serum or urine), performed within 7 days before the angiographic procedure.
- Troponin I or T, creatine kinase-myocardial band (CK-MB); if already completed within the past 48 hrs, those measurements may be used. For subjects with non-ST-elevation MI and abnormal serum markers, sufficient measurements should be obtained to show a decreasing trend in at least one serum marker consistent with stabilized NSTEMI.

- Chemistry panel (alkaline phosphatase, aspartate amino transferase, alanine amino transferase, total bilirubin, calcium, sodium, potassium, glucose, creatinine, blood urea nitrogen); complete blood count (hemoglobin, hematocrit, platelets, white blood cell count, red blood cell count); C-reactive protein; and N-terminal pro brain natriuretic peptide. If already completed within the past 30 days, those measurements may be used.
- Lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides). If already completed within the past 30 days, those measurements may be used.
- Protocol-required medications.
- Diagnostic angiogram (digital, all cohorts). Subjects may qualify for enrollment based on prior angiographic data obtained within the last 3 months. If a prior diagnostic angiogram is not available (within 3 months) a screening diagnostic angiogram is required prior to enrollment/randomization and can be completed at the same time as the Pre-Implant, target vessel(s) baseline angiogram. Randomized subjects' angiograms are to be provided to the central image data center.
- Pre-Implant, target vessel(s) (baseline) angiogram (all qualifying subjects, digital) will be used for the final assessment of subject eligibility. If a subject does not have a prior diagnostic angiogram, the preprocedure and diagnostic angiogram can be completed in one angiogram assessment for final eligibility assessment immediately prior to enrollment. Randomized subjects angiogram are to be provided to the central image data center. Subjects who do not meet angiographic inclusion criteria, including measurements that are taken after predilation, will not be randomized in this study but will be documented on a screening log.

A screening log will be provided to each study site to maintain a record of all of the subjects screened. This screening log must be completed and email (pdf) or faxed to the Data Coordinating Center on a weekly basis.

## 5.4 Enrollment and Randomization/Implantation

### 5.4.1 Enrollment

Subjects who have given written informed consent and meet all inclusion and no exclusion criteria will be eligible to be enrolled in this study.

### 5.4.2 Randomization/Implantation

After informed consent is obtained and it is confirmed that all clinical and angiographic inclusion criteria have been met and that no exclusion criteria are met, an interactive web response system (IXRS) will be used to randomize those subjects into 1 of 2 treatment arms. Subjects will be considered enrolled into the study when they are randomized into a treatment arm.

An IXRS system will centrally randomize eligible subjects, assign each subject a unique identification (ID) number, and identify the randomization arm for the subject. The study coordinator will access the IXRS system to obtain the randomization arm after the angiogram has confirmed that the subject meets all angiographic eligibility criteria. Subjects will be randomly assigned in a 1:1 ratio to receive either the Combo stent or the EES control. Randomization will be stratified based upon NSTEMI vs elective presentation and single-vessel vs multi-vessel disease. After randomization, the device will be implanted in the subject. If subjects are

randomized into a treatment arm and the study device is not delivered beyond the guiding catheter, the subjects will be followed through the 30-day visit and included in the intent-to-treat analysis.

At the time of randomization, the following assessments and procedures will be performed:

- Investigator declaration of antiplatelet therapy and duration.
- Protocol-required medications.
- HAMA plasma samples (Cohort B only) will be sent to the Central Laboratory. Samples to be collected prior to stent implantation and heparin therapy. For subjects already receiving heparin therapy HAMA collection should occur 4-6 hrs post heparin therapy.
- Device implantation per IFU/IB and clinical practice.
- LVEF (within 14 days of or immediately before randomization, via echocardiography, single photon emission-computed tomography, computed tomography, magnetic resonance imaging, or left ventriculography). Subjects presenting without documentation of prior LVEF assessment as described previously will be required to undergo ejection fraction assessment at the time of the pre-implant baseline angiogram to determine enrollment eligibility
- Pre-Implant target-vessel baseline angiogram (digital, all randomized subjects angiograms are to be provided to the central image data center). Cohort A and B subjects' angiogram will be provided to QCA Core Laboratory by central image data center manager.
- Collection of all AEs and SAEs

## 5.5 Postimplantation Procedures

### 5.5.1 Postprocedure

Following the implantation procedure, the following assessments and procedures will be performed within 24 hours post-PCI or before discharge:

- Immediate, post-implant target vessel(s) angiogram (all cohorts, digital, angiograms to be provided to the central image data center)
- Angina class (current CCS, Braunwald classifications)
- 12-lead ECG (PI signed and dated)
- Troponin I or T, CK-MB
- Protocol-required medications
- Collection of all AEs and SAEs. (Specified cardiovascular endpoint events collection as noted will be reported on the eCRF endpoint pages only)
- Cardiovascular Endpoint Event data collection for instances of
    - Death
    - MI
    - TLR (ischemia driven)
    - TVR (ischemia driven)
    - Stroke and transient ischemic attack (TIA)
    - Stent thrombosis (Academic Research Consortium [ARC] definition)

### 5.5.2 30 (± 7) Days

At 30 (± 7) days postprocedure, the following assessments and procedures will be performed:

- Physical assessment, including vital signs (weight, heart rate, blood pressure)
- Angina class (current CCS, Braunwald classifications)
- Concomitant medications
- Protocol-required medications
- HAMA plasma samples (only subjects enrolled in Cohort B) will be sent to the Central Laboratory
- Collection of all AEs and SAEs ., (Specified cardiovascular endpoint events collection as noted will be reported on the eCRF endpoint pages only)
- Cardiovascular Endpoint Event data collection for instances of
    - Death
    - MI
    - TLR (ischemia driven)
    - TVR (ischemia driven)
    - Stent thrombosis (ARC definition)
    - Stroke and TIA

### 5.5.3 180 (± 30) Days

At 180 (± 30) days postprocedure, the following information may be collected by telephone, unless noted for cardiac catheterization procedure (Cohort A only):

- Angina class (current CCS, Braunwald classifications)
- Concomitant medications
- Pregnancy test (serum or urine), performed within 7 days before the angiographic procedure (Cohort A only, complete before coronary angiogram and catheterization)
- 12-lead ECG (Cohort A only, complete before coronary angiogram and catheterization, PI signed and dated)
- Protocol-required medications
- Follow-up angiogram, target vessel (s) (only Cohort A, digital, angiogram to be provided to the central image data center for transfer to QCA Core Lab)
- OCT of the PRIMARY vessel (only Cohort A) will be provided to the central image data center for transfer to OCT Core Laboratory
- Collection of AEs/SAEs (Cohort A: complete prior to cardiac catheterization and coronary angiogram. Specified cardiovascular endpoint events data collection as noted will be reported on the eCRF endpoint pages only).
- Cardiovascular Endpoint Event data collection for instances of
    - Death
    - MI
    - TLR (ischemia driven)
    - TVR (ischemia driven)
    - Stent thrombosis (ARC definition)
    - Stroke and TIA

### 5.5.4 1 Year (± 30 Days)

At 1 year (± 30 days) postprocedure, the following assessments and procedures will be performed:

- Physical assessment, including vital signs (weight, heart rate, blood pressure) (complete before coronary angiogram and catheterization)
- Angina class (current CCS, Braunwald classifications) (complete before coronary angiogram and catheterization)
- 12-lead ECG (PI signed and dated, complete before coronary angiogram and catheterization)
- Concomitant medications (complete before coronary angiogram and catheterization)
- Pregnancy test, if not done within the previous 7 days (serum or urine; complete before coronary angiogram and catheterization)
- Protocol-required medications (complete before coronary angiogram and catheterization)
- Follow-up, target vessel(s) angiogram (all cohorts, digital, angiogram to be provided to the central image data center)
- HAMA plasma samples (before stent implantation; only subjects enrolled in Cohort B) sent to the Central Laboratory
- FFR assessment of PRIMARY target vessel only (all cohorts) will be provided to Core Laboratory
- OCT assessment of PRIMARY target vessel only (only Cohorts A and B) will be provided to the central image data center for transfer to the OCT Core Laboratory
- QCA of all target vessels (Cohort A and B only) will be provided to central image data center for transfer to Core Laboratory
- Collection of AEs/SAEs (complete prior to cardiac catheterization and coronary angiogram. Specified cardiovascular endpoint events data collection as noted will be reported on the eCRF endpoint pages only)

- Cardiovascular Endpoint Event data collection for instances of
    - Death
    - MI
    - TLR (ischemia driven)
    - TVR (ischemia driven)
    - Stent thrombosis (ARC definition)
    - Stroke and TIA

### 5.5.5 Annual (± 60 Days) for 5 Years Postprocedure

At 2, 3, 4, and 5 years (± 60 days) postprocedure, the following information may be collected by telephone:

- Angina class (current CCS, Braunwald classifications)
- Concomitant medications
- Protocol-required medications
- Collection of AEs/SAEs related to device only. (Specified cardiovascular endpoint events data collection as noted will be reported on the eCRF endpoint pages only)
- Cardiovascular Endpoint Event data collection for instances of
    - Death
    - MI
    - TLR (ischemia driven)

  - TVR (ischemia driven)
  - Stent thrombosis (ARC definition)
  - Stroke and TIA
- Interventional angiogram submission. It is recommended to submit any angiograms for clinical care treatment which were performed since the last patient visit and not previously submitted to the data central imaging center

### 5.5.6 Unscheduled Visits/Early Termination

Unscheduled visits are defined as subject visits outside of routine standard of care practice, outside of protocol defined visits, and contacts the study PI and is asked to return to the study PI clinic specifically for a study related concern. Additionally, all in-hospital cardiac events that occur outside of scheduled protocol visits should be captured as an unscheduled visit. At unscheduled visits or at early termination postprocedure, the following assessments and procedures will be performed:

- Angina class (current CCS, Braunwald classifications)
- 12-lead ECG (PI signed and dated)
- Concomitant medications
- Troponin I or T, CK-MB
- Protocol-required medications
- Collection of AEs/SAEs related to device only. (Specified cardiovascular endpoint events data collection as noted will be reported on the eCRF endpoint pages only)
- Cardiovascular Endpoint Event collection for instances of
  - Death
  - Myocardial Infarction
  - TLR (ischemia driven)
  - TVR (ischemia driven)
  - Stroke and TIA
  - Stent thrombosis (ARC definition)
- Interventional angiogram collection (for clinical standard of care treatment only) to be provided to the central image data center

All angiograms performed, including unscheduled angiograms for clinical care, will be sent to the Angiographic Core Laboratory for review.

# 6. STUDY DEVICE

## 6.1 Description of Study Device

The Combo stent™ (Figure 3) is a coronary balloon expandable vascular prosthesis, consisting of a 316L–stainless-steel alloy platform coated with a biocompatible, biodegradable polymer containing sirolimus (also known as rapamycin). Covalently attached to this matrix is a layer of murine, monoclonal, antihuman CD34 antibody. The immobilized antibody surface specifically targets CD34+ cells from the circulating blood, of which EPCs are CD34+. The base platform for the Combo stent is the OrbusNeich Medical R stent, which has a proprietary dual-helix stent design with a strut thickness of 0.0040". The 316L stainless-steel base platform (R stent) is coated sequentially with the drug/polymer matrix on the abluminal surface, then treated to immobilize antibody on the coated stent surface, and then finally treated with a stabilization treatment to preserve the antibody activity in the dried immobilized state on the stent. The treated stent is machine-crimped onto a low-profile, rapid-exchange PTCA dilation catheter, and then the crimped stent is subjected to visual inspection, verification of the outer diameter profile, and leak tested. Once found to be within specification, the mounted stent delivery system is placed into a high-density polyethylene hoop dispenser which in turn is placed into a Tyvek™/Mylar™ pouch. The pouch is heat-sealed and then labeled on the outside to maintain stent identity. Units are individually serialized to maintain unit identity, and the complete traceability of the manufacturing process flow is documented. The product is sterilized via an ethylene oxide sterilization process. Poststerile lot release testing includes total drug content, elution profile, antibody activity, endotoxin, and functional performance tests. The OrbusNeich Medical full quality assurance system is compliant to ISO 13485:2003, Medical Device—Quality Management Systems—Requirements for Regulatory Purposes and Directive 93/42/EEC for Medical Devices, Annex II (3) as verified by Intertek/American Manufacturing Trade Action Coalition Certification Services Limited (0473). The Combo stent conforms to the relevant provisions of the International Council of Electronic Commerce Consultants Council Directive 93/42/European Economic Community for Medical Devices dated 14 June 1993 and is in accordance with Annex II Conformity Assessment Procedure.

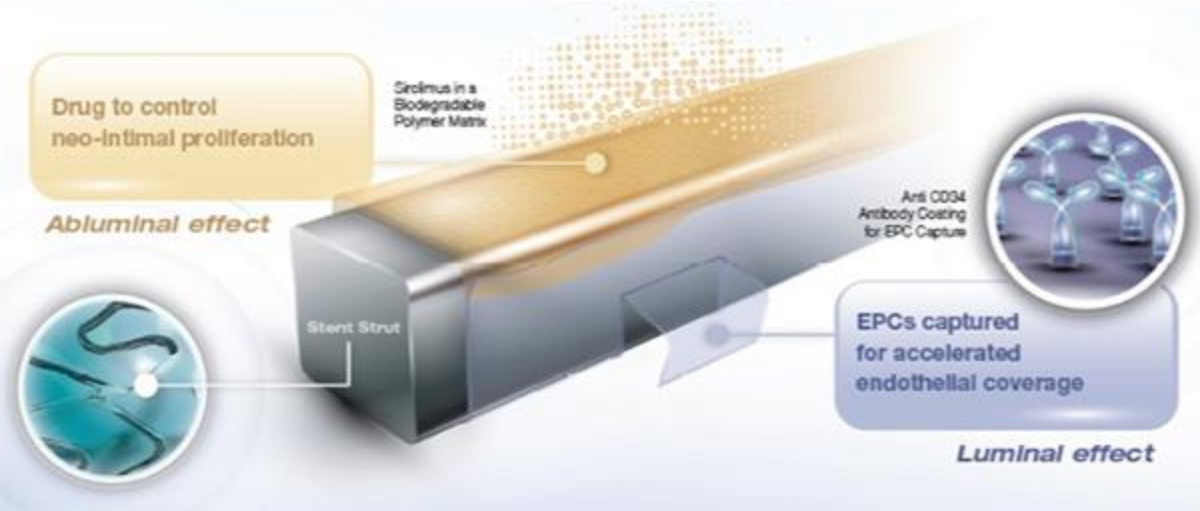


**Figure 3. Combo Stent**

### 6.1.1 Sirolimus

Sirolimus (rapamycin), the active ingredient in Rapamune® (Wyeth), has been tested extensively. The following is a brief summary of the available data; complete drug safety information is available through FDA.gov:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21083s017,21110s020lbl.pdf.

Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The chemical name of sirolimus is:

(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine1,5,11,28,29(4H,6H,31H)-pentone.

Its molecular formula is C51H79NO13, and its molecular weight is 914.2. The structural formula of sirolimus is shown in Figure 4 below.

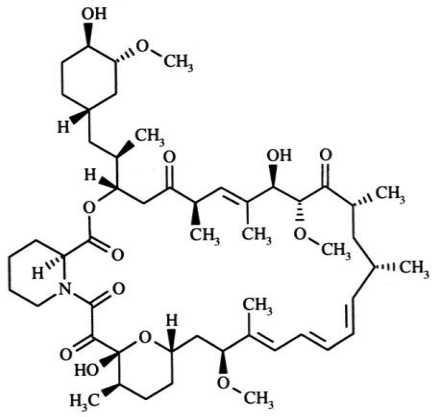


**Figure 4. Structural Formula of Sirolimus**

Sirolimus inhibits T-cell activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth-factor stimulation. Sirolimus binds to the immunophilin known as intracellular FK-binding protein (FKBP)12. The rapamycin-FKBP-12 complex binds to and inhibits activation of the mTOR, resulting in cell cycle arrest in the late Gap 1 phase and preventing progression to the synthesis phase.

The safety and efficacy of oral sirolimus (Rapamune, Wyeth), used as a prophylaxis of organ rejection in patients receiving renal transplants, were evaluated and established through 2 randomized, double-blind trials. Extensive studies have been conducted to investigate the mechanism of immunosuppressive activity, prevention of acute renal allograft rejection, clinical pharmacokinetics (PK), concentration-effect relationships, and therapeutic drug monitoring. Sirolimus has also been safely used in clinical studies as an antirestenotic drug component in the Cypher sirolimus-eluting coronary stent. Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at sirolimus doses 30 to 120 times higher than the 2-mg daily clinical dose (adjusted for body surface area), there was a statistically significant increase in

malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface area), hepatocellular adenoma and carcinoma in males were considered sirolimus related. In the 104-week rat study, at dosages equal to or lower than the clinical dose of 2 mg daily (adjusted for body surface area), there were no significant findings. Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay. Fertility was diminished slightly in both male and female rats following oral administration of sirolimus at doses approximately 10 times or 2 times, respectively, the clinical dose of 2 mg daily (adjusted for body surface area). In male rats, atrophy of testes, epididymides, prostate, seminiferous tubules, and/or reduction in sperm counts were observed. Reduction of sperm count in male rats was reversible upon cessation of dosing in one study. Testicular tubular degeneration was also seen in a 4 week intravenous study of sirolimus in monkeys at doses that were approximately equal to the clinical dose (adjusted for body surface area).

### 6.1.2 Bio-Engineered Drug-Eluting Coating

The Combo stent has a single-layer sirolimus-eluting coating that is applied to the abluminal stent surface. An anti-CD34 antibody surface modification is then applied to the entire stent surface (Figure 5).

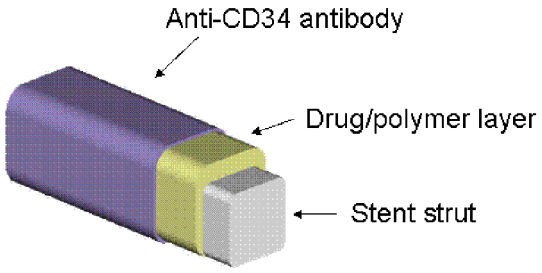



**Figure 5. Combo Stent Surface Modification**

To prevent restenosis, the drug/polymer coating consists of sirolimus loaded in the biodegradable SynBiosys™ polymer. The total drug content is approximately half the dose of the commercially available Cypher stent, but with the same release profile. The degradation of the polymer occurs in approximately 90 days. To promote healing, the anti-CD34 surface modification is applied to the entire stent such that the luminal surface of the deployed stent presents an immuno-affinity surface to promote the capture of circulating EPCs for the contacting blood.

Figure 6 (below) shows the in vivo elution profile of the final sterile Combo stent product compared with the commercially available Cypher stent.

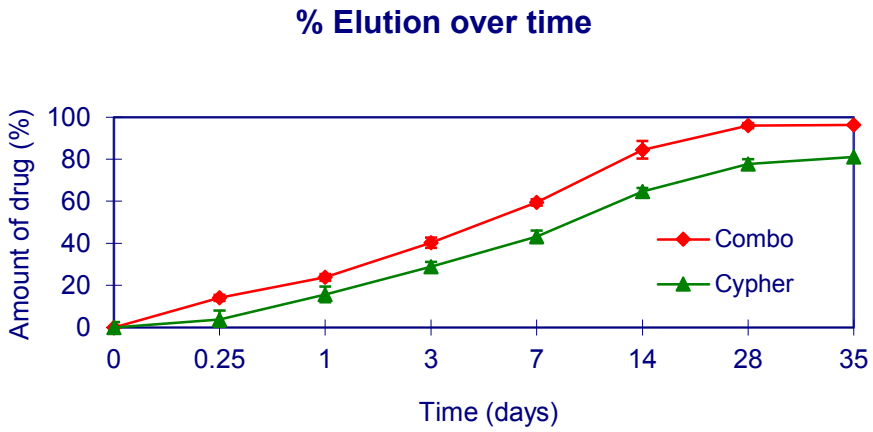



**Figure 6. In Vivo Elution of Combo Stent and Cypher (percentage of total drug eluted over time)**

### 6.1.3 SynBiosys™ Multi-Block Copolymer

The polymer coating of the Combo stent consists of a blend of the antiproliferative drug sirolimus with 2 bioabsorbable polymers, GLL01 and GPCGL01 (SynBiosys™ Polymer, Technology Transfer Specification, SurModics, December 2008). These copolymers, also referred to as SynBiosys copolymers, belong to a new class of proprietary bioabsorbable urethane-linked multi-block copolymers provided to OrbusNeich Medical by SurModics, Inc. Both copolymers are composed of prepolymers based on glycolide (GA), lactide (LA), and ε-caprolactone (CL), combined in various ratios and initiated with butanediol (BDO) or polyethylene glycol (PEG). The prepolymers are linked together by 1,4-butane diisocyanate (BDI) to create the multi-block architecture characteristic of these materials.

#### 6.1.3.1 Polymer In Vitro Degradation

The SynBiosys GLL01 and GPCGL01 are synthetic bioabsorbable urethane-linked multi-block copolymers, which degrade mainly by the hydrolysis of the ester and urethane bonds present in the polymer backbones. The hydrolytic degradation proceeds via a bulk erosion mechanism. First, the water diffuses into the material, which may induce a slight swelling of the polymer coating. Second, the ester and urethane bonds are randomly cleaved without producing soluble components. Third, the progressive chain scission leads to the formation of oligomers and monomers that are released from the coating layer, resulting in the actual mass loss of the material.

The degradation products of SynBiosys copolymers are mainly lactic acid, which is a naturally occurring compound in the human body, and glycolic acid. Both compounds degrade into pyruvic acid, which in turn is metabolized into carbon dioxide and water via the Krebs cycle. Caprolactone degrades into ω-hydroxyhexanoic acid, which is then eliminated via the urinary pathway. Polyethylene glycol and BDO are both excreted as such through the urinary pathway. Finally, the urethane moieties engendered by BDI during the polymerization process hydrolyze to form 1,4-butanediamine, also known as putrescine, which is also a naturally occurring compound in the human body. Putrescine is eliminated via the urinary pathway.

#### 6.1.3.2 6.1.3.2 Polymer Biocompatibility

Both the SynBiosys copolymers GLL01 and GPCGL01 are solely composed of biologically safe monomers and polymers already employed in numerous regulatory-approved and marketed biomedical implants and drug-delivery systems. These polymers are also widely used in fully bioabsorbable coronary stents and stent coatings.[35] The coating material of the BioMatrix® DES system (Biosensors International Group)[36] and the fully bioabsorbable Igaki-Tamai® stent (Kyoto Medical Planning) are based on poly(LA). The Igaki-Tamai stent and BioMatrix DES system were given their CE mark approvals in 2007 and 2008, respectively.[37]

Various studies have reported the biocompatibility of the substances released during the degradation of SynBiosys-like polymers. For instance, Guan et al. demonstrated that degradation products of polymers based on BDI, CL, PEG, and putrescine, which were collected over periods of 4 weeks, did not affect the endothelial cell viability.[38,39] Similarly, Asplund et al. showed that polymers based on BDI and CL did not release toxic products. The in vivo (subcutaneous) study of the materials revealed a typical foreign-body response such as the formation of macrophages and collagen after the first week and confirmed their biocompatibility over at least 6 weeks.[40] Van Minnen et al. showed that polymer foams based on D, L-LA, CL, BDO, and BDI that were implanted subcutaneously also induced a temporary increase in macrophages and giant cells upon implantation, but overall the foams remained biocompatible during a degradation period of 3 years.[41] The cytotoxicity, irritation, sensitization, and hemocompatibility of GLL01 and GPCGL01 were evaluated in vitro and in vivo upon implantation of polymer-coated stents.

### 6.1.4 Anti-CD34 Antibody

The Genous Bio-engineered Surface Technology is a surface treatment comprising a composite layer of covalently bound base matrix and a top layer of monoclonal antihuman CD34 antibody. The surface modification produces a cell binding immuno-affinity surface for capture of circulating CD34+ cells, including EPCs. Endothelial progenitor cells are a class of circulating, bone marrow-derived blood cells. The capture of circulating EPCs is the prohealing approach to reendothelialization.

The antibody used for the Genous Technology is a murine, monoclonal antibody directed towards the epitope class III of human CD34. The human CD34 is a monomeric cell surface antigen with a molecular mass of approximately 110 kDa that is selectively expressed on human hematopoietic progenitor cells. The anti-CD34 antibody is produced and purified under Good Manufacturing Practice (GMP) guidelines for production of therapeutic monoclonal antibodies.

#### 6.1.4.1 Antihuman CD34 Antibody Component

The antibody is a highly purified 1324-amino acid antibody that has an approximate molecular mass of 145 kDa. The antibody is a fully intact IgG2a immunoglobulin containing light and heavy chain variable and constant regions (Figure 7). The anti-CD34 antibody is current GMP produced in a hollow-fiber bioreactor perfusion system using a murine hybridoma in a nutrient medium containing 10% fetal bovine serum. The hybridoma was produced by the fusion of CD34 immunized BALB/c mouse sarcoma virus spleen cells with NS-0 myeloma cells. The antibody production purification process removed process and product impurities using protein A affinity chromatography, pH treatment, cation and anion exchange chromatography, filtration, and diafiltration.

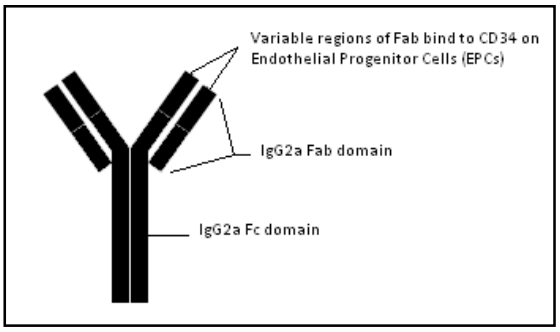



**Figure 7. Structure of Murine Antihuman CD34 Monoclonal Antibody**

#### 6.1.4.2 Genome Mechanism of Capture

The Genous Bio-engineered Surface Technology serves as a surface modification for antibody capture of EPCs from circulating blood onto the surface of the stent, thus promoting reendothelialization. CD34 is a cell surface protein found on the EPCs that are captured via immobilized anti-CD34 antibodies on the Genous-treated stent surfaces. The mechanism of EPC capture for the immune-affinity approach on an intravascular stent coated with immobilized antibody toward EPC cell surface antigens is shown in Figure 8.

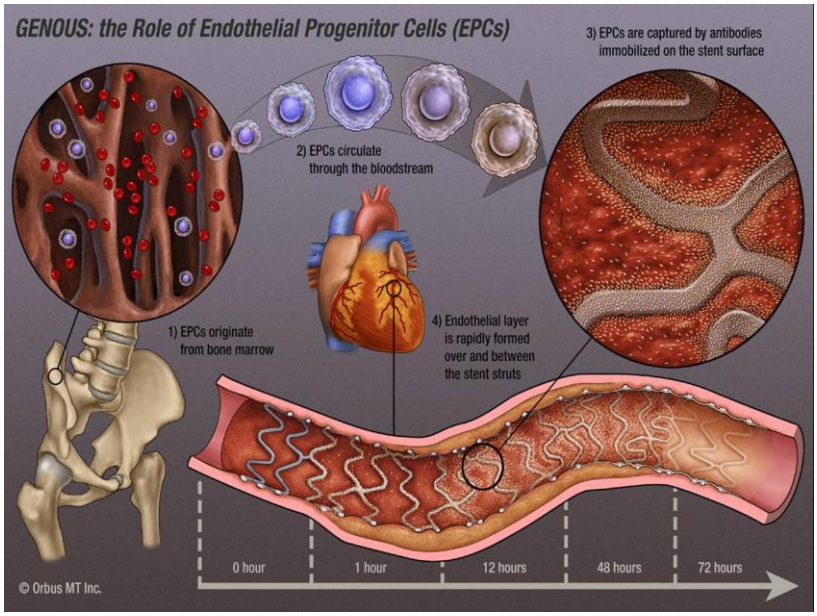



**Figure 8. Endothelial Progenitor Cell Capture**

By antibody recruitment of the patient's own EPCs to the site of vascular injury (eg, the site of a coronary stent implant), an acceleration and enhancement of the normal endothelialization process occurs. Functional endothelium is known to reduce inflammation; prevent thrombosis; and inhibit smooth muscle cell migration, proliferation, and the expression of extracellular matrix, along with functioning to maintain blood flow through vasodilation of the vessel. Rapid establishment of a functioning endothelial layer should help to promote the transformation of the injured site to a healthy state and reestablish vascular homeostasis.

### 6.1.5 Pharmacokinetics of the Combo Stent

The PK of sirolimus when released from the Combo stent were studied in a porcine model. Each animal had 5 stents implanted per time point. Whole-blood sirolimus PK parameters for this study are outlined in Table 4. Preclinical studies show that an equivalent amount of drug is delivered to blood vessels compared to commercially available sirolimus-eluting stents. However, the Combo stent releases less drug into the blood and downstream organs.

**Table 4. Pharmacokinetic Analysis for the Combo Stent**

| Pharmacokinetics Parameter | Value |
|---|---|
| Correlation coefficient of fit of the concentrations during the elimination phase based on a semi-log plot | 0.994 |
| Elimination constant (L/h) | 0.0028 |
| Terminal half-life (h) | 247.0 |

| Pharmacokinetics Parameter | Value |
|---|---|
| Time to maximum concentration (h) | 1.00 |
| Maximum concentration (ng/mL) | 3.98 |
| Time to last quantifiable sirolimus concentration (< 10 pg/mL) (h) | 672 |
| Last quantifiable sirolimus concentration (ng/mL) | 0.39 |
| Observed area-under-the-time-concentration curve (mg/mL*h) | 827.4 |
| Mean residence time (h) | 220.1 |

h, hour; L, liter; mg, milligram; mL, milliliter; ng, nanogram; pg, picogram

## 6.2 Delivery System Description

The Combo stent is mounted on a low-profile rapid-exchange percutaneous transluminal coronary stent delivery catheter with a working length of 138 cm. The balloon is inflated, and the stent is deployed by injecting diluted contrast medium solution through the trailing hub of the catheter. The guide wire lumen is accessed through the side port, which is located nominally 25 cm proximal to the leading tip of the catheter. A guide wire with a maximum diameter of 0.014" may be inserted through the side port. The delivery catheter has 2 shaft markers (90 and 100 cm from the distal tip) that indicate the relative position of the delivery catheter to the guiding catheter. The delivery system has 2 radiopaque marker bands; the inside edges delimit the working length of the balloon. The stent is mounted on the balloon between the marker bands. The stent and delivery system are available in the nominal lengths and diameters in Table 5. Although there is a 4.0 delivery system, it will not be included in this clinical trial.

**Table 5. Combo Stent Delivery System Size Matrix by Catalogue Numbers**

| Delivery Balloon Diameter (mm) | Nominal Stent Length (mm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 9 | 13 | 15 | 18 | 23 | 28 | 33 |
| 2.5 | 225-092-8 | 225-132-8 | 225-152-8 | 225-182-8 | 225-232-8 | | |
| 2.75 | 227-092-8 | 227-132-8 | 227-152-8 | 227-182-8 | 227-232-8 | | |
| 3.0 | 230-092-8 | 230-132-8 | 230-152-8 | 230-182-8 | 230-232-8 | 230-282-8 | 230-332-8 |
| 3.5 | 235-092-8 | 235-132-8 | 235-152-8 | 235-182-8 | 235-232-8 | 235-282-8 | 235-332-8 |

mm, millimeter

## 6.3 Implantation of Study Device

Use of a coronary stent and delivery system requires advanced angioplasty skills. Please refer to the Combo stent instructions for use (IFU)/investigator brochure (IB) for detailed technical guidance and instructions (Section 17.0). The following information provides general guidance but does not obviate the need for the physician to have undergone formal training as well as follow the IFU/IB for the treatment or control stent in the use of coronary stents and delivery systems.

Predilation with a balloon shorter than stent is required to avoid "geographical miss" (ie, balloon injury to any segment of the vessel that will not be entirely covered by the stent) during the

procedure. Postdilation is recommended based on investigator judgment. If postdilation is performed, it must be done with a balloon shorter than and within the boundaries of the stent to ensure complete apposition while avoiding injury to the unstented area.

### 6.3.1 Baseline Angiography

Baseline angiography of the target vessel will be completed per the Angiographic Core Laboratory Guidelines. Assessment of angiographic eligibility is based on a visual assessment of the immediate preprocedure angiogram obtained by the investigator. For accurate baseline QCA measurements, a 5 French or larger guide catheter must be used. Following intracoronary injection of nitroglycerin (dose per standard hospital practice), baseline angiography of the involved vessel will be performed for at least 2 orthogonal views showing the target lesion free of foreshortening or vessel overlap according to the Angiographic Core Laboratory Guidelines. Angiographic images of the target lesion must be sent to the Angiographic Core Laboratory per specified delivery method.

If there is more than 1 target vessel, operators will be asked to declare 1 target vessel as a primary target vessel before randomization. The primary target vessel will be analyzed with FFR at the 1-year follow-up visit for all subjects.

Angiography of nontarget vessels (if required) may be performed per site standard.

### 6.3.2 Left Ventriculography

Subjects presenting without documentation of prior LVEF assessment (echocardiography, single photon emission-computed tomography, computed tomography, magnetic resonance imaging, or left ventriculography) within the previous 14 days that meets enrollment inclusion criteria (30% or greater) will be required to undergo ejection fraction assessment at the time of the angiogram to determine enrollment eligibility. Documented left ventriculography should be performed with a pigtail catheter (even with radial access), ensuring that the left ventricle is fully opacified. At least 2 consecutive nonpremature ventricular contraction (PVC) or post-PVC beats must be present; otherwise, the ventriculogram should be repeated.

### 6.3.3 Predilation of Target Lesion

Predilation is to be performed per study stent IFU/IB, as follows:

- Predilation can be performed with an angioplasty balloon only (no cutting balloons, AngioSculpt balloons, or atherectomy).
- Predilation balloon must be shorter than the planned stent length to limit predilation injury within the area to be stented.
- It is recommended that a predilation balloon that is 0.5 mm smaller in diameter than the reference vessel be used.

Carefully inspect the sterile package before opening. Do not use the product after the “Use By” date. Do not use if any defects are noted.

### 6.3.4 Bailout Procedures

Bailout procedures may be performed if the subject experiences a major dissection requiring intervention or when an unplanned additional device is required to cover the target lesion. Bailout procedures may also be performed for an occlusive complication manifest as decreased target vessel flow, chest pain, or ischemic ECG changes that do not respond to repeat balloon inflations or intracoronary vasodilators (such as nitroglycerin, adenosine, verapamil, diltiazem, nicardipine, nitroprusside). Although a bailout procedure is not considered an endpoint event (unless the subject experiences death, MI, or CABG), bailout procedures should be avoided unless required for safe subject management. Use of bailout procedures should be uncommon. Ordinarily, each target lesion should be covered by a single stent, with a maximum of 2 target lesions per vessel and 3 target lesions per subject. Patients at high risk for bailout procedures (especially procedures exceeding 3 stents per vessel, 5 stents per subject, or more than 2 vessels) should be excluded from the protocol.

If a bailout stent is required for a target lesion (as in the case of edge dissection), a device from the assigned treatment group (Combo or EES) should be used. The bailout device should be a Combo stent if the target lesion has been treated with a Combo stent. Similarly, the bailout device should be an EES if the target lesion has been treated with an EES. The bailout device should overlap the previous device by 1 to 2 mm. If a stent of appropriate length and diameter of the same treatment assignment is not available, a commercially approved stent should be selected. Mixing different kinds of stents should be avoided unless there is no alternative. Other approved devices or therapies may be implemented in the treatment of occlusive complications at the investigator's discretion.

### 6.3.5 Postdeployment Angiography

In all subjects, the postprocedure target lesion angiography will be performed according to the Angiographic Core Laboratory Guidelines and must be captured in the similar manner used for the preprocedure images. These angiographic images should be performed after guide wire removal and intracoronary nitroglycerin if spasm is suspected. Two orthogonal views should be obtained using the same methods as the preprocedure angiogram. The procedure is considered complete after final angiographic recording of the treatment area and the guide catheter has been removed from the subject. Angiographic images of all target vessels for Cohorts A and B must be sent to the core laboratory per specified delivery method.

### 6.3.6 Risks

Risks associated with using the Combo stent are believed to be the same as those associated with percutaneous treatment procedures for a stenosed coronary artery using any other DES. There are potential additional risks of using this investigational device compared with a currently approved DES in that the frequency of AEs associated with stenting could possibly be increased with the Combo stent, although no such safety concerns have surfaced in the studies to date.

Use of this type of device is known to be associated with the following risks:

- Coronary or stent thrombosis
- Increased vascular and/or bleeding complications (due to anticoagulation)

- Increased length of hospital stay relative to length of stay for coronary balloon angioplasty alone. Judicious selection of subjects to receive this device rather than balloon angioplasty alone is strongly advised
- Infection secondary to contamination of the stent, which may lead to thrombosis, pseudoaneurysm, or vessel rupture
- Spasm, thrombosis, and/or distal embolization caused by implantation of the stent; stent could migrate from the site of implantation down the arterial lumen
- Rupture and life-threatening bleeding caused by excessive stretching of the artery
- Partial deployment of stents in particularly resistant lesions
- Stent dislodgment from the balloon surface during deployment and/or migration from the target site postdeployment
- Allergic reaction to this implant in subjects with an unknown hypersensitivity to stainless-steel alloy
- Sensitization towards murine antibodies
- Unknown long-term clinical outcome for this permanent implant

It is known from studies of oral sirolimus administration that the following drugs and foods may interact with sirolimus:

- Bromocriptine
- Carbamazepine
- Cimetidine
- Cisapride
- Clarithromycin
- Clotrimazole
- Cyclosporine
- Danazol
- Diltiazem
- Erythromycin
- Fluconazole
- Grapefruit juice
- HIV-protease inhibitors (eg, ritonavir, indinavir)
- Inducers of CYP3A4 and P-gp
- Inhibitors CYP3A4 and P-gp
- Itraconazole
- Ketoconazole
- Metoclopramide
- Nicardipine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
- Rifapentine
- St. John’s wort (hypericum perforatum)
- Strong inducers of CYP3A4 and P-gp
- Strong inhibitors of CYP3A4 and P-gp
- Telithromycin

- Troleandomycin
- Verapamil
- Voriconazole

Pregnancy, Category C: There are no adequate sirolimus or Combo stent-related studies in pregnant women.

Lactation, Category C: It is unknown whether sirolimus is excreted in human milk. A decision should be made whether to continue nursing or implant the Combo stent.

Potential complications and adverse effects (in alphabetical order) which may be associated with percutaneous coronary treatment procedures, including use of this product, include, but are not limited to, the following:

- Acute or subacute closure of the coronary artery
- Allergic reactions to stainless-steel alloy or contrast medium
- Aneurysm/pseudoaneurysm
- Arrhythmias, including ventricular fibrillation
- Arteriovenous fistula
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent thrombosis
- Coronary vessel dissection, perforation, rupture, or injury
- Death
- Distal embolization of stent
- Drug reactions, including to antiplatelet agents, anticoagulation agents, or contrast media
- Emergent coronary artery bypass surgery
- Failure to deliver the stent
- Fever
- Hemorrhage or bleeding complications that may require transfusion
- Hypotension/hypertension
- Immunologic reaction to murine antibodies
- Infection
- Myocardial ischemia/infarction
- Peripheral ischemia
- Renal failure
- Restenosis of stented segment
- Shock/pulmonary edema
- Stable or unstable angina
- Stent migration
- Stroke/cerebrovascular accident
- Target vessel and/or lesion revascularization
- Total occlusion of the coronary artery
- Vascular complications, including hematoma, pseudoaneurysm, or hemorrhage at the insertion site, which may require vessel repair

The occurrence of the above complications may lead to a repeat catheterization and/or PCI, MI, emergency bypass surgery, or death. Since the Combo stent is an investigational device, risks are not entirely known, but are believed to be similar to those that are associated with the standard, customary stenting of a stenosed coronary artery.

All efforts will be made to minimize these risks by selecting investigators who are experienced and skilled in using interventional devices and who are trained in the protocol and the Combo and EES IFUs/IBs.

The Cypher sirolimus stent is approved for use, and the risks associated with sirolimus are well documented. It is believed that the side effects with sirolimus on the Combo stent will be similar to those associated with sirolimus on the Cypher stent, but they may be slightly different (higher or lower) than those with the Cypher stent. The EES comparator stent contains everolimus, which is the 40-O-(2-hydroxyethyl) derivative of sirolimus and works similarly to sirolimus as an inhibitor of mTOR. Everolimus is approved in the United States under the name of Zortress by Novartis Pharmaceuticals for the prophylaxis of organ rejection in adult kidney-transplant recipients at low-moderate immunologic risk, at the dose of 1.5 mg/day when taken by mouth. Outside the United States, Zortress is sold under the brand name Certican in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor for the treatment of patients with advanced renal cell carcinoma (cancer) after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The amount of drug that circulates in the bloodstream following implantation of a XIENCE PRIME stent is several-fold lower than that obtained with oral doses (1.5 mg–20 mg/day). The following list includes the known risks of everolimus at the oral doses listed above:

- Abdominal pain
- Acne
- Anemia
- Anorexia
- Asthenia
- Coagulopathy
- Cough
- Diarrhea
- Dry skin
- Dysgeusia
- Dyspnea
- Edema, peripheral
- Epistaxis
- Fatigue
- Headache

- Hemolysis
- Hypercholesterolemia
- Hyperglycemia
- Hyperlipidemia
- Hypertension
- Hypertriglyceridemia
- Hypogonadism, male
- Increased serum creatinine
- Infections: wound infection; urinary tract infection; pneumonia; pyelonephritis; sepsis; and other viral, bacterial, and fungal infections
- Leukopenia or lymphopenia
- Liver function abnormality
- Lung and breathing problems
- Lymphocele
- Mucosal inflammation
- Myalgia
- Nausea
- Noninfectious pneumonitis
- Pain in extremity
- Pruritus
- Pyrexia
- Rash
- Renal tubular necrosis
- Stomatitis
- Surgical wound complication
- Thrombocytopenia
- Venous thromboembolism
- Vomiting

There may be other potential AEs that are unforeseen at this time.

### 6.3.7 Postprocedure Subject Management

It is recommended that immediately following the procedure:

1. Heparin or bivalirudin should be discontinued if an optimal procedural result is obtained.

2. Activated clotting time should be monitored in accordance with hospital protocol if femoral arteriotomy is performed.

3. Vascular sheaths should be removed according to standard hospital practice.

4. Additionally, management should be conducted in accordance with the processes of the respective medical institution.

Approved vascular closure devices may be used after femoral arteriotomies at the discretion of the investigator in accordance with the manufacturer's directions.

## 6.4 Follow-up Assessment Procedures

There are 3 overlapping mechanistic imaging cohorts.

1. Cohort A: 30 subjects will receive all clinical assessments, serial angiography assessments of all study vessels, QCA assessment of all study vessels at baseline. At 6 months Cohort A subjects will receive all clinical assessments and OCT assessment of primary target vessel only. At 12 months Cohort A subjects will receive all clinical assessments, angiographic and QCA assessment of all study vessels, OCT assessment of primary target vessel, and FFR assessment of primary target vessel only. Operators should follow the appropriate IFU/IB for the OCT system.
2. Cohort B: 110 subjects will receive all clinical assessments, angiographic and QCA assessment of all study vessels only at baseline. At 12 months Cohort B subjects will receive all clinical assessments, angiographic and QCA assessment of all study vessels, OCT assessment of primary target vessel, and FFR assessment of primary target vessel. Use of a 6 French guide catheter is recommended for these assessments. Operators should follow the appropriate IFU/IB for the OCT and FFR systems.
3. Cohort C: 432 subjects will receive all clinical assessments, angiographic assessments of all study vessels, and FFR assessment of the primary target vessel only at 12 months. Fractional flow reserve assessments may be obtained using a 4 French catheter. Operators should follow the appropriate IFU/IB for the FFR systems.

## 6.5 Recommendations for Evaluation of Fractional Flow Reserve Results and Revascularization Procedures

The recommendations for revascularization are based on the results of the Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Versus Optimal Medical Treatment Alone in Patients With Stable Coronary Artery Disease (FAME) 2 trial,[42] the 2011 American College of Cardiology (ACC) Foundation/American Hospital Association (AHA) PCI guidelines,[43] and the 2009 ACC/AHA Appropriateness Criteria for Coronary Revascularization.[44] Note that a positive FFR without subsequent PCI or CABG will not be considered revascularization.

For protocol-mandated angiograms at 12 months, FFR evaluation of the primary target vessel is required for all patients. Please also reference the FFR Core Laboratory Guidelines. In patients with more than one target vessel, FFR evaluation of the nonprimary target vessel is strongly recommended if the angiographic stenosis is ≥ 50% diameter reduction.

- If angiographic stenosis is < 50% diameter reduction, revascularization should not be performed.
- If an angiographic stenosis is ≥ 50% diameter reduction, revascularization should not be performed if the FFR is > 0.80. This rule applies even in patients with typical angina symptoms, patients with atypical angina symptoms, or subjects without chest pain but documented ischemia on noninvasive testing, based on the FAME 2 results that show that FFR-directed PCI is appropriate in this setting.
- If the angiographic stenosis is ≤ 60% diameter reduction, the patient is asymptomatic, and there is either no noninvasive testing or the noninvasive testing has equivocal results, revascularization should not be performed regardless of the results of the FFR.[44]

For catheterizations performed at times other than the scheduled angiographic study visits (12 months for subjects in Cohorts A, B, C; 6 months for subjects in Cohort A):

- If angiographic stenosis is < 50% diameter reduction, revascularization should not be performed.
- If an angiographic stenosis is ≥ 50% diameter reduction, FFR assessment of the lesion is strongly recommended. Revascularization should not be performed if the FFR is > 0.80. This rule applies even in patients with typical angina symptoms, patients with atypical angina symptoms, or patients without chest pain but documented ischemia on noninvasive testing, based upon the FAME 2 results that show that FFR-directed PCI is appropriate in this setting.
- If the angiographic stenosis is ≤ 60% diameter reduction or the patient is asymptomatic and there is either no noninvasive testing or the noninvasive testing has equivocal results, revascularization should not be performed regardless of the results of the FFR.[44]
- If FFR measurement is not possible, revascularization may be considered in the setting of MI (abnormal biomarkers or ST-elevation), unstable angina with ST-segment depression on ECG, or unstable angina accompanied by ischemia documented by noninvasive testing.

## 6.6 Potential Benefits of Combo Stent

Percutaneous transluminal coronary angioplasty has been widely used as an alternative to medical or surgical treatment in selected subjects with symptomatic coronary artery disease. The major limitations of PTCA (abrupt closure, intimal dissection, and restenosis from elastic recoil) are overcome to a significant extent with coronary stents.

The Combo stent can be expected to provide the same radial support as other coronary stents to minimize closure of a stenosed artery as is commonly indicated for coronary stenting. Additionally, the potential benefit of the Combo stent is its effectiveness in inhibition of neointima while enhancing endothelial coverage that may reduce rates of stent thrombosis or support shorter routine use of DAPT without increasing rates of restenosis compared with other commercially available DESs. Well-known components supporting these features include the elution of sirolimus and the use of abluminal, bioabsorbable polymer. The most novel feature of the Combo platform is the use of CD34 antibody coating, providing a unique endothelial progenitor cell-capture technology mechanistically targeted to promote faster, more complete healing of the stent site and struts.

## 6.7 Concomitant Medications/Therapies

### 6.7.1 Prepercutaneous Coronary Intervention Medications

#### 6.7.1.1 Aspirin

Preloading with aspirin at least 81 to 325 mg, according to regional standard of care therapy, at least 2 hours before the PCI is mandatory. For subjects already receiving chronic aspirin therapy, the loading dose of at least 81 to 325 mg of aspirin, according to regional standard of care therapy, should still be given. Either chewable or intravenous aspirin is mandatory for the loading dose in subjects not on chronic aspirin who will receive only 1 dose of aspirin before the PCI. Aspirin therapy will be at least 81 to 325 mg, according to regional standard of care therapy, for 1 month following the index PCI, then reduced to 81 to 325 mg daily, at the discretion of the investigator.

#### 6.7.1.2 Platelet Adenosine Diphosphate Receptor Antagonists

Platelet adenosine diphosphate (ADP) receptor antagonist preloading therapy is mandatory, using only approved agents at the time of enrollment. In subjects undergoing PCI, the platelet ADP receptor antagonist must be given before the start of the interventional procedure. The following schedule is recommended:

- Clopidogrel at least 75mg—600 mg more than 6 hours before PCI or 300 mg more than 12 hours before PCI (even if the subject is on chronic clopidogrel therapy), according to regional standards of care therapy; or
- Prasugrel at least 20 mg more than 1 hour before PCI, according to regional standards of care therapy; or
- Other approved adenosine diphosphate (ADP) receptor antagonists, designated before randomization. In the US, this includes ticagrelor, 180 mg more than 1 hour before PCI.

For subjects already receiving chronic platelet ADP receptor antagonist therapy, preloading is still mandatory. The choice of either clopidogrel, prasugrel, ticagrelor, or other approved thienopyridines is left to the discretion of the investigator. The intended duration of dual antiplatelet therapy is also left to the discretion of the investigator but must be recorded before randomized stent assignment.

#### 6.7.1.3 Other Medications

The use of other medications (eg, beta-blockers, angiotensin-converting enzyme inhibitors) before PCI is left to the discretion of the treating physicians. Best medical practice is recommended.

As additionally noted in the AC C/AHA PCI guidelines,[43] lipid management is strongly recommended. All concomitant cardiac medications must be recorded on the electronic case report form (eCRF).

### 6.7.2 Medications During Percutaneous Coronary Intervention

During the procedure, subjects will receive appropriate anticoagulation medications according to standard hospital practice. The use of any approved anticoagulant agent at the discretion of the investigator is acceptable.

The use of glycoprotein IIb/IIIa receptor inhibitors is allowed per the discretion of the investigator as long as the agents are approved for use in the participating country.

### 6.7.3 Postpercutaneous Coronary Intervention Medications

It is very important that the subject is compliant with the postprocedure antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medications could result in a higher risk of thrombosis, MI, or death. Before PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventionalist and subject should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI choice. If a DES is not appropriate, the subject should not be enrolled in the trial. Following PCI, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Subjects who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding should be monitored carefully for cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physician.

#### 6.7.3.1 Aspirin

Mandatory dosing with aspirin will be at least 81 mg or more post-PCI per day in the hospital and then at least 81 mg or more for 30 days, according to regional standard of care therapy. Dosing will then continue as at least 81 mg per day indefinitely. Daily aspirin must be given for the duration of the trial. Aspirin should not be discontinued for CABG or other reasons unless absolutely necessary.

#### 6.7.3.2 Platelet Adenosine Diphosphate Receptor Antagonists

Chronic daily platelet ADP receptor antagonist therapy using an approved agent requires that all subjects receive chronic daily DAPT therapy according to regional standard of care therapy, with the choice of agent left to the discretion of the investigator, either:

- Clopidogrel at least 50 mg per day; or
- Ticlopidine 250 mg every 12 hours; or
- Prasugrel at least 3.75 mg per day; or
- Ticagrelor 90 mg twice daily (if this drug is approved by national regulatory authorities)

Adenosine diphosphate antagonists should not be discontinued within the first 6 months after DES implantation, according to recommended standard of care, unless absolutely necessary due to major bleeding, major trauma, or major surgery (eg, intracranial surgery) necessitating discontinuation of antiplatelet therapy. Many surgeries can safely be performed while the subject is on DAPT. If a subject on DAPT requires surgery, strong consideration should be given to performing the surgery without antiplatelet agent discontinuation.

## 6.8 Packaging

The study device will be packed and shipped to sites and resupplied on an as-needed basis. EES comparator stents will be selected from the local clinical supply. The label of the study device includes the following information:

- Device is used for the clinical trial

- Lot number
- Storage condition
- Expiration date
- Name and address of sponsor

The study device will be stored at room temperature in the boxed state as supplied by the sponsor and will be used before the labeled expiration date. Study devices are to be stored separately from clinical supplies and accessible only to those who have appropriate authorization.

## 6.9 Product Stability and Shelf-Life

A stability study was conducted on the Combo stent, where total drug content and antibody activity were evaluated out to 12 months real-time aging. The total drug content and antibody activity for the Combo stent were found to remain stable and within the acceptance criteria for up to 12 months stored at 25°C/60% relative humidity. The Combo stent clinical product will have a product shelf-life of 12 months.

## 6.10 Blinding of Study

Single blinding practices for the study will include the following:

- Subjects: Subjects will be informed of the 1:1 randomization between the 2 stent systems (Combo:EES) but will remain blinded as to which stents they actually receive until after the 12-month follow-up.
- Implanting physician: It is not possible to blind the implanting physician due to the differences in the implant procedure for the treatment and the control stents.
- Follow-up physician: There will be no requirement that follow-up be performed by a physician other than the implanting physician. In follow-up reports, the follow-up physician will refer to either stent as a study stent so that these reports will not unblind anyone reviewing the report.
- Clinical research coordinators: Clinical research coordinators (CRCs) will not be blinded. In follow-up notes, the CRC will refer to either stent merely as a “study stent” so that these notes will not unblind anyone reviewing them. Clinical research coordinators will be instructed not to unblind subjects until after the 12-month follow-up visit.
- Monitors: Monitors will not be blinded. Monitoring reports will refer to either stent as the study stent to preclude inadvertent unblinding of those reading the reports.
- Data Management and Operations: Clinical trial operations at the Duke Clinical Research Institute (DCRI) currently utilize standard operating procedures (SOPs) for confidential data management that prohibit investigators, sponsor staff, subjects, families, or others from access to descriptor or outcomes data and/or its relationship to treatment assignment.
- Angiographic Core Laboratory: The angiographic core laboratory reviewers will be blinded to the treatment and the control stents.
- Clinical Events Classification Committee: The Clinical Events Classification Committee (CEC) may receive core laboratory reports regarding angiographic findings or blinded

angiographic films to adjudicate an event. To ensure that CEC members remain blinded to treatment assignment, information that will reveal how a subject was randomized will be redacted from medical record source documentation and event descriptions.

- Data and Safety Monitoring Committee: The DSMC will be blinded to treatment arm assignment. If it is determined by the DSMC that knowledge of treatment arm assignment is necessary to render opinion on the safety of trial design or conduct, this information will be disclosed to the DSMC. Material contained in each DSMC review is confidential, and all documentation is controlled in accordance with DCRI SOPs. The only exception to this policy is in the event that the DSMC recommends alteration to the trial and it is deemed essential that the Executive Operations Committee receive information that would implicitly result in their knowledge of treatment assignment.

## 6.11 Receiving, Storage, Dispensing, and Return

### 6.11.1 Receipt of Study Device

Upon receipt of the study device supplies, an inventory must be performed and a device receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator's site.

### 6.11.2 Return of Study Device

At the completion of the study, there will be a final reconciliation of study devices shipped, devices used, and devices remaining. This reconciliation will be logged on the device reconciliation form, signed, and dated. Any discrepancies noted will be investigated, resolved, and documented before the return of unused study devices. Any unused study devices are to be returned to the sponsor.

# 7. SUBJECT SAFETY AND ADVERSE EVENTS

## 7.1 Ethics Committees/Institutional Review Boards

Each site will submit the study protocol, ICF, and other study documents to their ethics committee (EC)/institutional review board (IRB) for approval. A copy of the signed and dated EC/IRB approval for each enrolling center will be stored at the Data Coordinating Center, in accordance with GCP. Any amendments to the protocol, other than minor administrative changes, must be approved by the site's EC/IRB before the changes are implemented at the site.

## 7.2 Definitions

### 7.2.1 Adverse Event

The reporting and recording of adverse events (AEs) is crucial to the evaluation of an investigational device and to the development of labeling information that appears in the IFU/IB. During a clinical trial, the reporting of adverse experience information can lead to important design changes in the new device, as well as provide integral safety data. The investigator will monitor each subject for clinical and laboratory evidence of AEs throughout the trial.

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.

Any pre-existing condition known to the investigator will not, in general, be reportable as an AE, unless the investigator believes that the participation of the subject in this study contributed to the progression of that condition.

When an AE has, by its nature, a prolonged course, the event will be considered a single event and not multiple events; for example, if a subject develops end-stage renal failure requiring regular dialysis, the event is considered end-stage renal failure, not multiple single renal events.

### 7.2.2 Serious Adverse Event

Any AE that:

- Led to death
- Led to a serious deterioration in the health of the subject that resulted in
    - Life-threatening illness or injury or
    - Permanent impairment of a body structure or a body function or
    - In-patient hospitalization or prolongation of existing hospitalization.
    - Medical or surgical intervention to prevent permanent impairment of a body structure or a body function
    - Led to fetal distress, fetal death, or a congenital abnormality or birth defect
    - The following hospitalizations are not considered AEs/SAEs:
        - Visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered "important medical event" or “event life threatening”).

- Elective surgery, planned before signing consent.
- Admissions per protocol for a planned medical/surgical procedure.
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and planned before entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

### 7.2.3 Anticipated Adverse Device Effects

A serious adverse device effect (ADE) that by its nature, incidence, severity or outcome has been previously identified as noted in the protocol risks section (6.3.6) or IFU/IB.

### 7.2.4 Unanticipated Adverse Device Effects

Per United States Code of Federal Regulations (CFR) Title 21, Part 812.3, an unanticipated ADE (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated ADEs will include events meeting either A or B as stated below:

A. Events meeting ALL of the following criteria:
   - Not included in the list of anticipated events (see IFU/IB)
   - Possibly, probably, or definitely related to the investigational device per the site investigator
   - Serious (meets <u>any</u> of the following criteria):
     - Life-threatening illness or injury
     - Results in permanent impairment of a body structure or a body structure
     - Necessitates medical or surgical intervention to prevent permanent impairment of a body function or a body structure
     - Led to fetal distress, fetal death, or a congenital abnormality or birth defect
     - Led to death

     (Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.)

B. Any other unanticipated serious problem associated with the investigational device that relates to the rights, safety, or welfare of subjects.

### 7.2.5 Device Failure and Device Malfunction

A device has failed or malfunctioned if it is used in accordance with the IFU/IB but does not perform according to the IFU/IB and negatively impacts the treatment. Device failures include:

- Inability to position at desired location
- Incorrect deployment of device

### 7.2.6 User Error

A device is used by the investigator in a manner that is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. The term "user error" refers to an error made by the person using the device, for example an error of use of the device outside of the IFU/IB.

## 7.3 Assessment

### 7.3.1 Causality Rating

| RELATIONSHIP | CAUSALITY | DEFINITION | REPORTING |
|---|---|---|---|
| **Not related to investigational device** | **Unrelated** | An event for which an alternative explanation (eg, concomitant drug or concomitant disease) is conclusively identified and/or the relationship in time suggests that a causal relationship is highly unlikely | All AEs/SAEs, regardless of relationship to the study device, occurring from randomization through the first 30 (± 7) days will be reported in the eCRF as soon as possible. Specified cardiovascular endpoint events collection will be reported on the eCRF endpoint pages only |
| **Not related to investigational device** | **Unrelated** | An event for which an alternative explanation (eg, concomitant drug or concomitant disease) is conclusively identified and/or the relationship in time suggests that a causal relationship is highly unlikely | All SAEs, regardless of relationship to the study device, occurring from randomization through the 1 year follow-up visit (+/- 30 days) will be reported in the eCRF as soon as possible. Specified cardiovascular endpoint events collection will be reported on the eCRF endpoint pages only |
| **Related to investigational device** | **Possible** | An event that might be due to the use of the study device. An alternative explanation (eg, concomitant drug or concomitant disease) is inconclusive. The | All AEs/SAEs related (possible, probable or definite) to the device, except events listed as protocol-specific endpoints, |

| | | | |
|---|---|---|---|
| | | relationship in time is reasonable; therefore the causal relationship cannot be excluded. | (section 7.6) occurring from randomization through the 5-year study period will be reported in the eCRF as soon as possible. Specified cardiovascular endpoint events collection will be reported on the eCRF endpoint pages only. |
| | **Probable** | An event that might be due to the use of the study device. An alternative explanation (eg, concomitant drug or concomitant disease) is less likely. The relationship in time is suggestive of causality. | |
| | **Definite** | An event that is due to the use of the study device. The event cannot be reasonably explained by an alternative explanation (eg, concomitant drug or concomitant disease). | |

### 7.3.2 Severity of Adverse Events

The severity of an AE will be rated as follows:

- **Mild:** AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe:** AE that prevents normal everyday activities; treatment or other intervention usually needed.

## 7.4 Reporting

It is understood that complete information about an event may not be known at the time the initial report is submitted. The investigator must assess the relationship of the event to the investigational device (including the rationale for the assessment) and should make every attempt to obtain as much information as possible concerning the event. Additional information pertaining to an event should be reported in the eCRF as it becomes available. Specified cardiovascular endpoint events will be reported on the eCRF endpoint pages only.

### 7.4.1 Time Frame

#### 7.4.1.1 Adverse Events

All AEs, except events listed as protocol-specific endpoints (Section 7.6), regardless of relationship to the study device, occurring from randomization through the first 30 (± 7) days will be reported in the eCRF as soon as possible.

All AEs related to the device, except events listed as protocol-specific endpoints, (Section 7.6) occurring from randomization through the 5-year study period will be reported in the eCRF as soon as possible.

#### 7.4.1.2 Serious Adverse Events

All SAEs, except events listed as protocol-specific endpoints (Section 7.6), occurring from randomization through the 1 year follow-up visit will be reported in the eCRF within 24 hours of knowledge of the event.

All events that lead to or result in death, device-related SAEs and UADEs occurring after randomization through the 5-year follow-up will be reported in the eCRF within 24 hours of knowledge of the event. If required, the site investigator or their delegate is responsible for notifying the site director of a reported SAE within the expected time frame. The investigator or qualified designee will enter the required information about the SAE into the AE/SAE page of the eCRF, which will be distributed to the appropriate sponsor contact. If only limited information is initially available, follow-up reports are required. As follow-up information becomes available, it should be entered into the eCRF within 24 hours.

If the eCRF reporting capability is not available, the SAE should be reported on the paper back-up SAE form and faxed or e-mailed to DCRI Safety Surveillance. If eCRF, e-mail, and FAX are not available, the event should be reported by telephone (see contact information below). If the report is initially given by e-mail, FAX, or telephone, then the required information about the SAE will be entered into the appropriate module of the eCRF immediately after the eCRF system is available by the site.

SAE FACSIMILE TRANSMISSION:

Duke Clinical Research Institute (DCRI) Safety Surveillance

Fax: +1-919-668-7138; toll-free within the U.S.: 1-866-668-7138

SAE e-mail: DCRISafetySurveillance@dm.duke.edu

SAE telephone: +1-919-668-8624 or toll-free within U.S.: 1-866-668-7799

All SAEs will be followed to resolution or stabilization. Resolution means that the subject has returned to a baseline state of health. Stabilization means that the investigator does not expect any further improvement or worsening of the AE.

Safety data will be periodically reviewed to monitor subjects safety through the study period, Study leadership will be notified if any events are occurring at an unexpected rate for this study population. Risks will be continually assessed to determine if a protocol or ICF revision is warranted.

### 7.4.2 Unanticipated Adverse Device Effects, Device Failures, Device Malfunctions, and User Error

In the case of a device failure or malfunction related to the investigational device, the Combo stent device must be returned to the manufacturing company, if possible. Device failure, device malfunctions, and user error will be reported on the device deficiency eCRF form within 24 hours of knowledge of the event. If the eCRF reporting capability is not available, the paper back-up device deficiency from should be emailed or faxed to DCRI Safety Surveillance as noted in section 7.4.1.2 within 24 hours of knowledge of the event.

## 7.5 Regulatory Reporting of Unanticipated Adverse Device Effects

There are situations that may necessitate rapid communication of the occurrence of AEs to the regulatory authorities. The DCRI Safety Surveillance medical monitor will determine if a device-related event meets "unanticipated" criteria (ie, is not identified in the IFU/IB or literature), reporting all findings to OrbusNeich Medical for the duration of the trial. All device-related AEs will be reported to OrbusNeich for the duration of the trial. Unanticipated ADEs will be reported by OrbusNeich Medical to the Pharmaceuticals and Medical Devices Agency (PMDA) (Japan), FDA, all reviewing ECs/IRBs, and all participating investigators within 10 working days of when DCRI Safety Surveillance was initially notified of the event or within accordance of country regulations.

In accordance with local regulations, OrbusNeich Medical will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IFU/IB). OrbusNeich Medical will immediately conduct an evaluation of any UADEs. If OrbusNeich Medical determines that a UADE presents an unreasonable risk to subjects, all investigations or parts of investigations presenting that risk shall be terminated as soon as possible. Termination shall occur no later than 5 working days after OrbusNeich Medical makes this determination and no later than 15 working days after they first received notice of the effect or within accordance of country regulations.

OrbusNeich Medical retains all regulatory reporting responsibility to the PMDA and the FDA.

Investigators are responsible for reporting UADEs to their reviewing EC/IRB within 10 working days of notification from sponsor.

## 7.6 Protocol-Specific Endpoint Events

The CEC will adjudicate the following protocol-specific endpoint events as defined in the CEC Charter:

- Death
- Cardiac death
- MI
- Target vessel MI
- TLR (ischemia driven)
- TVR (ischemia driven)
- Stroke and TIA
- Stent thrombosis (ARC definition)

These protocol-specific endpoint events will be reported on the appropriate pages in the eCRF within 24 hours of knowledge of the event. These events (with the exception of all events that lead to or result in death) will not be captured as SAEs and will not be reported to the regulatory authorities in an expedited manner.

## 7.7 Criteria for Withdrawal of Subjects from Study

Each enrolled subject shall remain in the study until completion of the required follow-up period; however, a subject's participation in any clinical study is voluntary, and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically indicated
- Subject lost-to follow-up

The reason for subject discontinuation must be documented on the eCRF and source documents. The investigator must also report any subject's discontinuation to his or her EC/IRB, as defined by his or her institution's procedure. When a subject discontinues or is withdrawn from the study before study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences that are ongoing at the time of discontinuation/withdrawal should be reported and followed up in accordance with the safety requirements outlined in Section 7.4.

# 8. EFFICACY ASSESSMENTS

The primary clinical endpoint is TVF, defined as cardiac death, target-vessel MI, or ischemia-driven TVR by percutaneous or surgical methods, at 1 year. The primary endpoint will be reported after all subjects have completed 12 months of follow-up.

The secondary efficacy endpoint is mechanistic OCT healthy level of intimal tissue coverage, determined by the OCT core laboratory at 1 year for subjects in Cohorts A and B combined (total N=140 subjects).

Additional prespecified efficacy endpoints are:

- Angiographic late loss by quantitative coronary angiogram core laboratory at 1 year (Cohorts A and B combined)
- In-stent and in-segment angiographic binary restenosis at 1 year (Cohorts A and B combined)
- In-stent and in-segment proximal and distal QCA measurement of late lumen loss at 1 year (Cohorts A and B combined)
- Clinically and functionally (FFR) ischemia-driven TLR at 1 year
- Device success, defined as attainment of less than 50% residual stenosis of the target lesion
- Lesion success, defined as attainment of less than 50% residual stenosis using any percutaneous method
- Procedure success, defined as lesion success without the occurrence of in-hospital death, nonfatal MI, stroke, or emergency revascularization.
- TVF, defined as cardiac death, target vessel MI, or ischemic-driven TVR by percutaneous or surgical methods at 30 days; 6 months; and 2, 3, 4, and 5 years
- The following clinical endpoints will be assessed at 30 days; 6 months; and 1, 2, 3, 4, and 5 years:
    - Death (all causes)
    - Cardiac death
    - Nonfatal MI
    - Target-vessel MI
    - TLR (ischemia driven)
    - TVR (ischemia driven)
    - TLF, defined as death, MI, and ischemic TLR

# 9. SAFETY ASSESSMENTS

Safety and tolerability will be assessed on the basis of reported AEs; changes in vital signs; and standard clinical laboratory tests, including routine hematology and blood chemistry. Safety endpoints will be assessed at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years as follows:

- All-cause mortality
- Cardiac mortality
- ARC definite/probable stent thrombosis
- ARC definite stent thrombosis
- MI (using modified ARC definition)[1]: Q-wave and non-Q-wave, cumulative, and individual
- Stroke and TIA
- OCT safety assessments for late malapposition and intracoronary thrombus by OCT core laboratory at 1 year (Cohorts A and B, total N=140 subjects)
- Change in HAMA serum levels at 30 days and 1 year follow-up compared with baseline (N=110, all subjects in Cohort B)

## 9.1 Adverse Events

The definitions of AEs and reporting responsibilities of the sponsor and investigator are described in Section 7 of this protocol.

## 9.2 Laboratory Testing

Clinical laboratory tests, requiring approximately 35 mL of blood, will be performed at specified times during the first year that each subject is under study. These times are detailed in the Schedule of Events in Section 5. Subjects participating in the HAMA blood collection will have an additional 12 mL of blood total collected for these assessments.

# 10. STATISTICAL ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

## 10.1 Statistical Design

This is a prospective, multi-center, 2-arm, symmetrically randomized, active-control clinical trial designed to assess the safety and effectiveness of the Combo stent in subjects with ischemic coronary disease and who are suitable for PCI. To support both the logistics of predominantly Japanese subject enrollment and a robust evaluation of both efficacy and safety, the analytic plan includes both superiority to imputed BMS control and noninferiority to best-in-class second-generation DES (Xience V) in 1-year TVF rates. In addition, FFR assessment to evaluate the physiology of target vessels in the entire population will augment the endpoint definition of ischemia-driven TVR. Finally, key safety considerations will be augmented with a subpopulation in whom imaging with OCT for strut coverage, late strut malapposition, and plaque volume, as well as serial HAMA assessments, will be reported.

For the primary efficacy endpoint, this study will include both an imputed BMS control performance goal and a randomized concomitant active-control EES stent cohort as reference comparators for superiority and noninferiority, respectively. The population studied will require enrollment of 572 subjects to get 542 evaluable (assuming a 5% lost-to-follow-up rate), randomized evenly to the 2 study arms, admitted to the hospital for a planned (elective) percutaneous coronary artery intervention procedure. Each subject will be followed for 5 years.

The primary analysis sample will be based on the principle of intention-to-treat. For this study, all subjects who meet the study-entry criteria, sign the written informed consent, and are randomized to a treatment arm will be counted in the primary analysis.

A secondary analysis will also be performed on the per-treatment population, defined as subjects with a successful procedure and follow-up information.

All statistical analyses will be performed using Statistical Analysis System (SAS), version 9.2 or higher, or other widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of results will be provided.

## 10.2 Primary Analysis

### 10.2.1 Primary Endpoint

The primary clinical endpoint is TVF, defined as cardiac death, target-vessel MI, or ischemia-driven TVR by percutaneous or surgical methods, at 1 year. The primary endpoint will be reported after all subjects have completed 12 months of follow-up. Target-vessel failure analysis will show noninferiority to an EES and superiority to an imputed BMS control (see Section 10.8.2.4). Clinical endpoints will be assessed before any protocol-mandated angiograms, to avoid bias from angiographic-triggered revascularization. Abnormal FFR during the protocol 1-year catheterization will be included with the clinical assessment for both 1-year TVF and ischemia-driven TVR calculations. The secondary efficacy endpoint will be 1-year ischemia-driven TVR, including use of target-vessel FFR, analyzed dichotomously using the FAME study criteria of 0.81 during a 2 minute infusion of adenosine or adenosine triphosphate.

### 10.2.2 Primary Endpoint Analysis

The primary endpoint will be evaluated using the relationship

$$\frac{\text{Odds of TVF for Combo}}{\text{Odds of TVF for BMS}} = \frac{\text{Odds of TVF for Combo}}{\text{Odds of TVF for EES}} \times \frac{\text{Odds of TVF for EES}}{\text{Odds of TVF for BMS}}$$

to determine the performance of Combo relative to bare metal stenting as a measure of clinical effectiveness.

## 10.3 Major Secondary Analyses

One-year protocol recatheterization will provide 3 genres of surrogate endpoint information to complement the safety and efficacy evaluation of both the investigational Combo platform and the control EES platform. Specifically these include physiologic flow as target-vessel FFR, angiographic assessment of late loss, and, in a cohort of 140 subjects, OCT imaging to quantify strut coverage, late stent malapposition, and plaque volume. Angiographic late loss and OCT image analyses will be conducted in independent, blinded core laboratories.

### 10.3.1 Secondary Efficacy Endpoint

- Mechanistic OCT healthy level of intimal tissue coverage by OCT core laboratory at 1 year (N=140 subjects)

### 10.3.2 Additional Prespecified Endpoints

#### 10.3.2.1 Efficacy

The following efficacy endpoints will also be assessed:

- Angiographic late loss by QCA core laboratory at 1 year (Cohorts A and B combined, N=140 subjects)
- In-stent and in-segment angiographic binary restenosis at 1 year (Cohorts A and B combined). In-segment restenosis is defined as restenosis within a region including 5 mm proximal and 5 mm distal to the target lesion.
- In-stent and in-segment proximal and distal QCA measurement of late lumen loss at 1 year (Cohorts A and B combined).
- Clinically and functionally (FFR) ischemia-driven TLR at 1 year.
- Device success, defined as attainment of less than 50% residual stenosis of the target lesion.
- Lesion success, defined as attainment of less than 50% residual stenosis using any percutaneous method.
- Procedure success, defined as lesion success without the occurrence of in-hospital death, nonfatal MI, stroke, or emergency revascularization.
- TVF, defined as cardiac death, target vessel MI, or ischemic-driven TVR by percutaneous or surgical methods at 30 days; 6 months; and 2, 3, 4, and 5 years.

- Death (all causes) at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.
- Cardiac death at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.
- Nonfatal MI at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.
- Target-vessel MI at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.
- TLR (ischemia driven) at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.
- TVR (ischemia driven) at 30 days; 6 months; and 1, 2, 3, 4, and 5 years.
- TLF, defined as death, MI, and ischemia-driven TLR.

#### 10.3.2.2 Safety

The following safety endpoints will be assessed:

- All-cause mortality at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years
- Cardiac mortality at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years
- ARC definite/probable stent thrombosis at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years
- ARC definite stent thrombosis at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years
- MI (using modified ARC definition[1]) at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years
- Stroke and TIA at postprocedure; 30 days; 6 months; and 1, 2, 3, 4, and 5 years
- OCT safety assessments for late malapposition and intracoronary thrombus by OCT core laboratory at 1 year (Cohorts A and B combined, N=140 subjects)
- Change in HAMA plasma levels at 30 days and 1-year follow-up compared with baseline (N=110, all subjects in Cohort B)

## 10.4 Optical Coherence Tomography Substudy Analyses

### 10.4.1 Introduction

Pathology studies have shown neointimal thickness to be predictive for completeness of stent strut coverage and endothelialization after DES implantation. At the typical observed levels of lumen loss after DES, ie, below 0.55 mm, angiographic late loss correlates poorly with stent strut coverage by healthy endothelium. Therefore, contemporary studies investigating new generation DES technologies have utilized intracoronary imaging to provide a direct measure of the amount of neointimal growth.

Intravascular OCT has emerged as a preferred method to investigate the healing response of intracoronary stent implants due to its high resolving power to detect strut tissue coverage and vascular healing. OCT can be used to detect morphologic and fine anatomic detail associated with stent site healing as well as with the occurrence of restenosis on a tissue level. OCT has also been used for the serial assessment of the human coronary response to DES implantation to detail the kinetics of stent site healing.

Some concerns have been expressed with regard to over-interpretation of in vivo OCT imaging for ultra-thin tissue layers such as endothelium, in particular with regard to reflectivity artifacts as well as fibrin or other noncellular substrates to mimic, and hence undermine, strut coverage quantification in vivo. Recently, ex vivo assessment of human coronary artery stent explants have compared OCT imaging with histopathology assessment, reporting that a neointimal thickness > 80 microns covering struts by OCT showed a much-improved correlation with histopathology of healthy mature tissue covering DES struts. These observations, grounded in human histopathologic correlations, provide the most robust basis for a quantitative approach to the use of OCT imaging to assess the recovery of healthy endothelium following DES implantation, especially when executed by an independent, blinded, and experienced core laboratory facility.

A unique aspect of the Combo stent device is the incorporation of an immobilized anti-CD34 antibody on the stent blood-contacting surface with the intended effect of providing an affinity surface for circulating CD34+ cells that are key for neointimal formation and vascular healing. Anti-CD34 antibody stents have been shown in acute human ex vivo shunt studies to have rapidly adherent cells, which express endothelial markers while showing less thrombus formation. In preclinical studies, conventional DESs treated with the immobilized anti-CD34 antibody have been shown to have an enhanced endothelial coverage and expression of endothelial functional markers over the DES alone. Likewise, the Combo device has also been shown in preclinical studies to have an enhanced endothelial coverage and expression of endothelial functional markers over conventional DESs while showing similar modulation of the neointimal response expected from a DES.[45] In the REMEDEE first-in-man randomized trial of the Combo device, the device was shown to be noninferior to conventional DESs in the control of neointimal proliferation and prevention of restenosis, while intravascular ultrasound and OCT imaging show a more homogeneous healing reaction with the Combo stent compared with a contemporary DES, with less evidence of inflammation and neoatherosclerosis.[46] Therefore, given the unique vascular healing behavior of the Combo stent due to the dual nature of sirolimus control of neointima and anti-CD34 antibody effect on endothelialization and vessel healing, a subset of patients in both cohorts will be assessed with OCT to characterize and compare the neointimal responses, both quantitatively and qualitatively, as a surrogate marker of the mechanistic role of the novel biologic anti-CD34 antibody component of the device.

### 10.4.2 Objective

Optical coherence tomography assessment of a subset of patients in the trial will provide important mechanistic insight into the healing response of the Combo stent compared with the DES comparator. Unlike angiographic late loss studies of DES effectiveness to control restenosis, where lower late loss or less tissue is viewed as better, in this OCT assessment a higher neointimal thickness without signs of hemodynamic compromise (by FFR) will be viewed as superior, since neointimal thickness has been shown to correlate histopathologically with mature endothelialization and more mature vessel healing.[47] The hypothesis of the imaging-physiology substudy is that Combo and the DES comparator have similar low rates of physiologic intrastent coronary obstruction at 12-months post-DES implantation, with superior strut level tissue coverage thickness observed in the Combo platform. This concept of a “well-healed” stent with healthy neointimal coverage while maintaining a good physiological blood flow is illustrated in Figure 9.

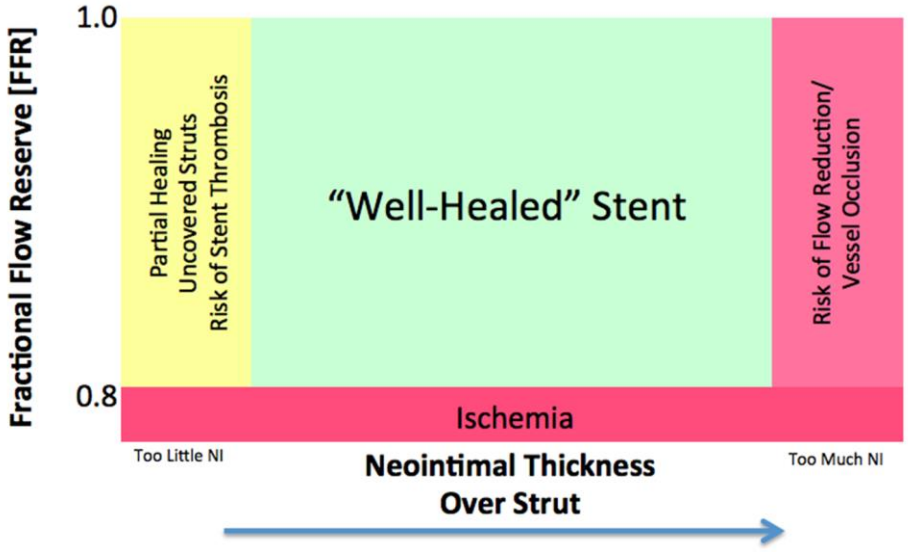



**Figure 9. Illustration of the Balance Between Achieving Adequate Neointimal Coverage to Protect Against Stent Thrombosis While Maintaining Adequate Blood Flow to Prevent Ischemia**

The primary OCT metric will be "strut level tissue coverage thickness" at 1 year in subjects with normal FFR, based on automated measurements performed from the center of the luminal surface of each strut blooming and its distance to the lumen contour. All visible struts at 0.6-mm intervals along the entire stented segments will be measured. Other secondary OCT metrics will include percentage of covered struts; percentage of malapposed struts; qualitative and quantitative assessment of intraluminal thrombus; and quantitative analysis of lumen, stent and neointimal volumes.

### 10.4.3 Sample Size

To test the difference in mean struts neointimal thickness between the Combo and Xience stent types at mean neointimal thickness (subject level), 86 subjects with an allocation ratio 1:1 yield > 99% power to detect the difference in neointimal thickness of struts between the 2 stent types. The sample size assumes a neointimal thickness of struts difference between 2 stent types equal to 0.050 mm, a common standard deviation of 0.050 mm, and utilizes a 2-sided, alpha level = 0.05. If abnormal positive FFR event rate is estimated as 4% for each stent type, the sample size needed for each treatment arm should be adjusted to 43/(1 – 0.04) = 45. Therefore, when accounting for a 20% dropout rate for follow-up, 57 subjects are required to be randomized in each study arm for the OCT substudy.

### 10.4.4 Optical Coherence Tomography Image Acquisition

The following recommendations are required for proper OCT data acquisition according to the study. Please reference the OCT Core Laboratory Guidelines:

- Select ≥ 6French guiding catheter without side holes.

- Give the intracoronary nitroglycerin injection (100–200 mcg) before introduction of the OCT device into the coronary.
- The coronary vessel should be flushed with nondiluted angiographic contrast injected through a power injector.
- Cine should be obtained during the pullback/contrast injection.

### 10.4.5 Primary Neointimal Thickness Quantification by Optical Coherence Tomography

Strut level analysis of the neointimal thickness will be performed by measuring the distance from the center of the stent blooming to the lumen centromere. This measurement will take into consideration every strut available in a cross-section image at every 0.6-mm longitudinal interval (every third frame). Measurements are illustrated in Figure 10.

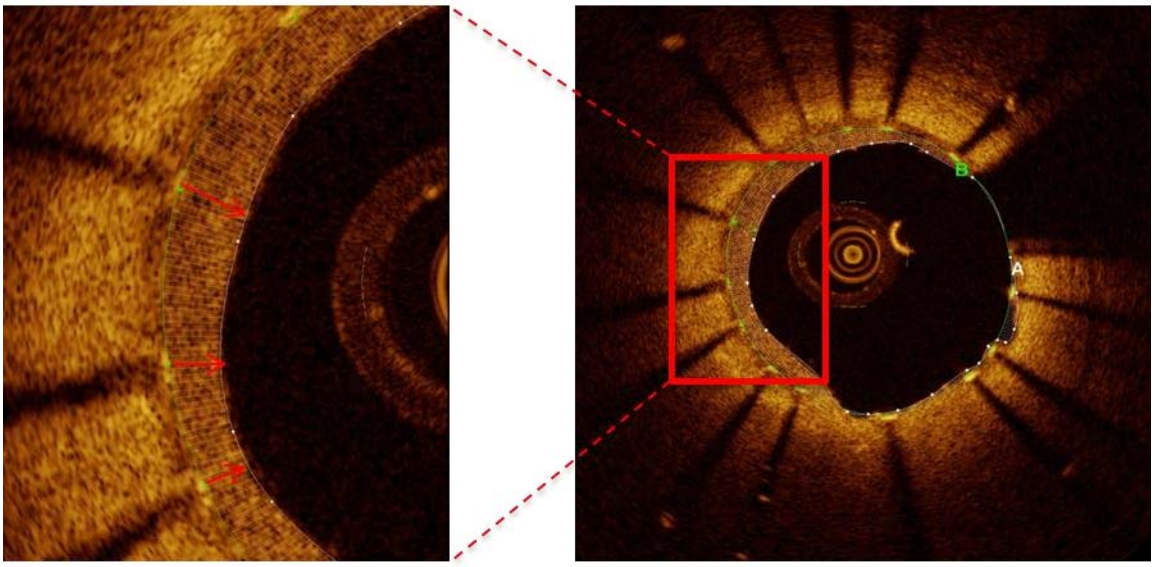


**Figure 10. Strut Level Analysis of the Neointimal Thickness**

Strut level analysis of the neointimal thickness will be performed by measuring the distance from the center of the stent strut blooming to the lumen centromere for each individual strut (red arrows).

### 10.4.6 Secondary Optical Coherence Tomography Assessment

The OCT image assessment will include the determination of stent morphometric characteristics, identification of surrogate endpoints of stent healing and safety, and tissue characterization. These secondary assessments are outlined below and endpoints defined in the Appendix: Optical Coherence Tomography Image Analysis Parameters.

### 10.4.7 Stent Morphometric Parameters

Optical coherence tomography images will be assessed for quantification of neointimal tissue thickness and lumen area and lumen volume compared with the reference segments.

Characterization of stent deployment will include strut coverage and apposition, stent length, stent expansion and deformation, and intrastent residual stenosis.

### 10.4.8 Surrogate Safety Parameters

Optical coherence tomography images will be assessed for evidence of edge dissections, stent associated vascular positive remodeling, evidence of stent deformation and stent strut fracture and gaps, and the presence of intramural thrombus.

### 10.4.9 Tissue Characterization

The OCT imaging will be used to characterize the nature of the neointimal tissue through semi-quantitative assessment of optical density to differentiate fibrin from a mature tissue. A qualitative assessment will be performed to differentiate homogeneous predominantly fibrotic tissue (neointima) from neoatherosclerosis, defined as tissue with characteristics suggestive of lipid and/or calcium.

## 10.5 Angiographic Late Loss Analysis

### 10.5.1 Introduction

As a surrogate endpoint, late loss has provided useful information on the range of long-term luminal dimensions that mechanistically correlate with clinical outcome. Direct comparisons between stent platforms, however, may yield statistically significant p-values whose clinical relevance is unclear. Logistic regression models have reliably estimated TLR rates for DES and BMS based upon angiographic late loss measures.[48] However, because of the curvilinearity of the logistic model, trials comparing 2 effective DESs can have statistically significant differences in angiographic late loss, but small expected differences in TLR risk, especially at the lower ranges of late loss.

Thus an objective performance goal for late loss is highly relevant to interpretation of angiographic late loss in new DES platforms. In this study, both the Combo and EES platforms are compared to a performance goal to ensure that performance of the Combo is comparable to currently approved DES (and superior to BMS).

### 10.5.2 Performance Goal Justification

To understand the relationships between late loss among approved DESs, (a network meta-analysis was performed evaluating DESs, including Cypher, TAXUS, Endeavor, Xience, Nobori, Resolute, and Combo to estimate the overall expected differences among each of the stents with regard to in-segment and in-stent late loss using a Markov chain Monte Carlo method, treating all BMSs as a single therapy (data on file, OrbusNeich Medical). The results are displayed in Figure 11 and Figure 12.

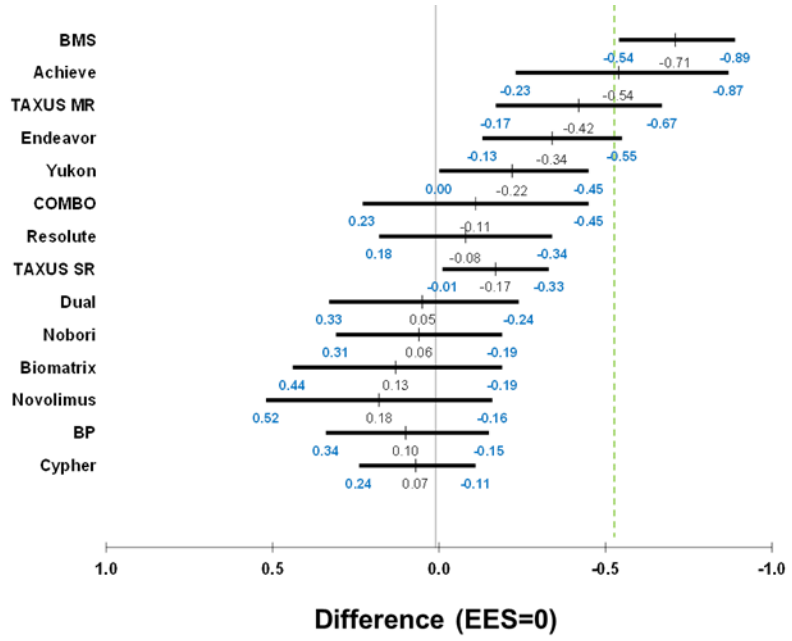



**Figure 11. In-Stent Late Loss Performance Goal vs Everolimus-Eluting Stent**

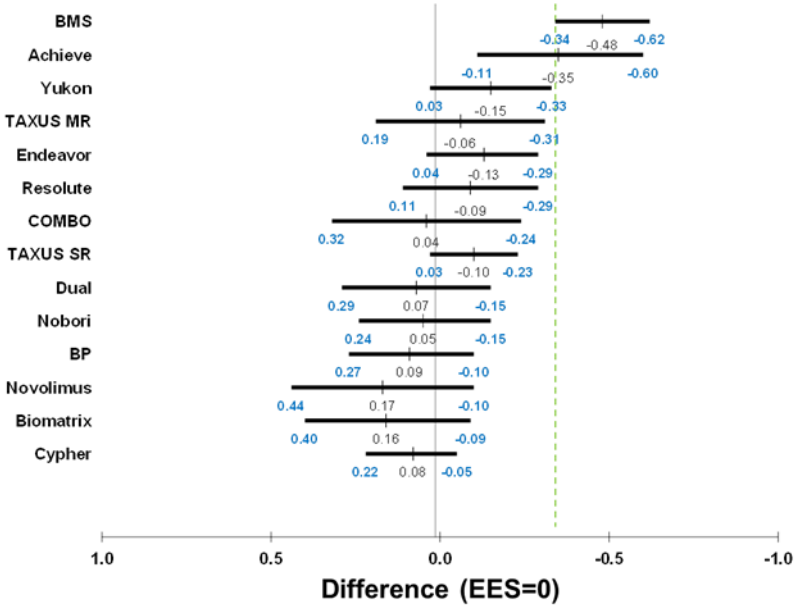



**Figure 12. In-Segment Late Loss Performance Goal Relative to Everolimus-Eluting Stent**

Consequently, based upon the REMEDEE results alone, the Combo stent is superior to BMS with regard to in-stent late loss, in the indirect comparison using the Bayesian network methods to account for the indirect relationships in the existing evidence.

Based upon the lower 95% credible limit observed for BMS in the network meta-analyses, the maximum difference (delta) relative to EES that would still preserve superiority to BMS is -0.54 mm for in-stent late loss and -0.34 mm for in-segment late loss. This boundary constitutes the performance goal for the HARMONEE late loss analysis.

If we assume the mean late loss is similar to the results observed in SPIRIT III and REMEDEE, and a 1-sided alpha of 0.025, then a subsample of 80 subjects (40 per arm) would have 91% power to detect noninferiority for in-stent late loss and 62% power to detect noninferiority for in-segment late loss and satisfy the performance goal. The primary analysis of late loss will include subjects from cohorts A and B evaluated using this performance goal. As a sensitivity analysis, angiographic late loss will be assessed including all subjects who have QCA performed as a study procedure.

While late loss measured as a continuous variable may report highly statistically significant differences of no clinical relevance, physiologic measurement of lesion severity using FFR dichotomously analyzed at the 0.81 threshold has been shown in 2 independent, prospective randomized trials to be highly predictive of later clinical events. Thus, for this study, although late loss will be reported as a mechanistic observation, abnormal FFR will provide a unique and reliably unbiased component of the ischemia-driven TVR secondary endpoint.

## 10.6 Human Anti-Murine Antibody Analysis

Up to 55 patients assigned to the Combo stent will submit blood samples at baseline, at 30 days, and at 12 months for measurement of HAMA levels. All patients will provide written informed consent for collection of the plasma samples. A core laboratory will provide binary determination of changed HAMA antibody levels indicative of anti-antibody response.

### 10.6.1 Introduction

Murine monoclonal antibodies (mAbs) have proved tremendously useful. However, when used in the treatment of patients with various ailments, their effect is not always sustained. This is often due to the development of human anti-mouse antibodies, leading to clearance of the murine mAb and adverse events.[49] Over the past 2 decades these fears have been somewhat allayed as allergic reactions have generally proven to be minor and readily reversed.[50,51] Hwang and Foote have classified therapies as having negligible immunogenicity when the anti-antibody response was reported in less than 2% of patients.[52] Immunogenicity this low represents an ideal, with very reassuring safety. Immunogenicity is tolerable if detectable in 2% to 15% of patients, with use of the antibodies warranted for catastrophic or life-limiting disease. Immunogenicity with anti-antibody response greater than 15% are usually clinical failures with regulatory concerns likely to preclude clinical use.

HAMA antibody levels have been obtained in at least 120 subjects enrolled in previous evaluations of the COMBO stent, and there have been no significant changes in HAMA levels detected in previous studies (data on file, OrbusNeich Medical).

### 10.6.2 Objective

The HAMA analysis will evaluate the frequency of change in HAMA plasma levels at 30 days and at the 12-month follow up compared to baseline.

### 10.6.3 Sampling Procedure

Patients will have blood drawn through vascular access sheaths or by venipuncture at baseline, at 30 days, and at the 12-month follow-up. All samples will be submitted to a central core laboratory. Blood draws will be performed in all Cohort B patients to preserve blinding to treatment assignment. The samples obtained from the 55 patients assigned to the Combo stent in Cohort B will assure a minimum of 40 complete sets of samples in case of missed visits, losses to follow-up, or nonevaluable samples.

Sampling procedure:

1. Recommended sampling device: Vacutainer red, without additives.

   For example: Becton Dickinson No. 367812 (4 mL)

2. Centrifuge clotted samples immediately and separate serum into the PP tubes supplied by the core laboratory. Samples should be frozen within one hour after collection.
3. Storage temperature: < -20°C until delivery.
4. Hemolyzed and lipemic samples are to be avoided.

### 10.6.4 Human Anti-Murine Antibody Data Analysis Plan

Analysis of the HAMA prespecified endpoint will include the frequency of increased HAMA antibody levels, as determined by the core laboratory. A minimum sample size of 40 patients is designed such that assuming alpha = 0.05 and an underlying seroconversion rate of 5 per thousand, there will be 86.5% power to exclude an anti-antibody response (AAR) upper bound of 8.0%. Further, when a total of 160 device exposures is considered (120 from previous studies and 40 from the present substudy), the upper 95% binomial confidence limit will exclude an AAR rate greater than 2.28% if no anti-antibody response is detected.

## 10.7 Other Planned Analyses

### 10.7.1 Analysis of Baseline Characteristics

All clinically relevant baseline variables will be tabulated and compared among subjects assigned the Combo stent and an EES stent control arm of the study. Categorical variables will be tested using appropriate contingency table analyses (exact or chi-square approximations), and continuous variables will be tested using unpaired Student's t-test or Wilcoxon rank-sum test, depending on variable distribution. Statistical significance on baseline variables will be declared if the 2-sided P-value is less than 0.05.

### 10.7.2 Additional Consistency Analyses

IF and ONLY IF the overall primary noninferiority endpoints are met, additional consistency analyses will be performed:

- Superiority testing of primary endpoint of Combo vs EES control
- Subgroup analyses for consistency of effect:
  - Age
  - Sex
  - Diabetes
  - Renal impairment
  - Clinical presentation
  - Ejection fraction
  - Lesion length
  - Reference vessel diameter
  - Multivessel

## 10.8 Statistical Methods

### 10.8.1 General Statistical Methods

Noninferiority testing of the primary endpoint with an absolute difference delta of 7.0% will be performed (Section 10.8.2.2). Additionally, superiority testing to an imputed BMS control will be performed to ensure assay sensitivity (Section 10.8.2.4).

### 10.8.2 Power and Sample Size

#### 10.8.2.1 Event-Rate Estimates

Event-rate estimates were obtained for an all-comers population based upon the Bern-Rotterdam Registry (N=12,339), from which 385 patients were excluded due to loss to follow-up, 1060 patients were excluded due to LVEF less than 20%, and 210 patients were excluded due to cardiogenic shock. Of the remaining 10,684 patients, 3046 were excluded for STEMI, leaving a population of 7638 patients who would meet the inclusion and exclusion criteria for the proposed study. Clinical-event rates for this population are shown in Table 6 below:

**Table 6. 12-Month Event Rates Among All-Comers in Bern-Rotterdam Registry, Excluding ST-Elevation Myocardial Infarction Subjects, N=7638**

| | Everolimus-Eluting Stent (N=1980) N (%) | Sirolimus-Eluting Stent (N=2860) N (%) | Paclitaxel-Eluting (Stent N=2798) N (%) |
|---|---|---|---|
| Cardiac death/MI/TVR (=TVF) | 179 (9.0) | 342 (12.0) | 364 (13.0) |
| Cardiac death | 53 (2.7) | 64 (2.2) | 81 (2.9) |
| MI | 35 (1.8) | 63 (2.2) | 87 (3.1) |
| TVR | 116 (5.9) | 256 (9.0) | 258 (9.2) |

MI, myocardial infarction; N, number; TVF, target-vessel failure; TVR, target-vessel revascularization

Notably, the TVF rates for stable coronary artery disease and ACS subgroups within this population were similar to the event rates observed for the overall population. This consistency of effect across subgroups supports evaluation of a broad subject population in the present clinical trial (Table 7).

**Table 7. 12-Month Event Rates Among Subgroups in Bern-Rotterdam Registry**

| **Stable Coronary Artery Disease (N=4575)** | **Everolimus-Eluting Stent (N=1148) N (%)** | **Sirolimus-Eluting Stent (N=1749) N (%)** | **Paclitaxel-Eluting Stent (N=1678) N (%)** |
|---|---|---|---|
| Cardiac death/MI/TVR (=TVF) | 101 (8.8) | 197 (11.3) | 209 (12.5) |
| Cardiac death | 23 (2.0) | 30 (1.7) | 38 (2.3) |
| MI | 12 (1.1) | 38 (2.2) | 50 (3.0) |
| TVR | 75 (6.5) | 152 (8.7) | 151 (9.0) |
| **ACS, excluding STEMI (N=3042)** | **Everolimus-Eluting Stent (N=831) N (%)** | **Sirolimus-Eluting Stent (N=1105) N (%)** | **Paclitaxel-Eluting Stent (N=1106) N (%)** |
| Cardiac death/MI/TVR (=TVF) | 78 (9.4) | 143 (12.9) | 154 (13.9) |
| Cardiac death | 30 (3.6) | 33 (3.0) | 43 (3.9) |
| MI | 23 (2.8) | 25 (2.3) | 37 (3.4) |
| TVR | 41 (4.9) | 103 (9.3) | 106 (9.6) |

ACS, acute coronary syndrome; MI, myocardial infarction; N, number; STEMI, ST-segment elevation myocardial infarction; TVF, target-vessel failure; TVR, target-vessel revascularization

Based upon these observations, the statistical analysis plan considers potential TVF event rates between 7% and 15%.

### 10.8.2.2 Identification of a Clinically Acceptable Margin (Delta)

The clinically acceptable margins used in previous trials of next-generation DESs vary widely, as shown in Table 8.

**Table 8. Absolute Delta Values for Clinical Trials of Next-Generation Drug-Eluting Stents, Assuming 1-Sided Alpha of 0.05**

| Trial | Stent Comparison | Absolute Difference Delta |
|---|---|---|
| PLATINUM | Promus Element vs Promus/Xience | 3.5% given TLF 5.5% |
| Resolute | Resolute vs Endeavor | 3.3% given TLF 6.5% |
| LEADERS | Biolimus vs Cypher | 4% given TVF 8% |
| TWENTE | Resolute vs Xience | 4.48% given TVF 12.8% |

TLF, target -lesion failure; TVF, target vessel failure

The PLATINUM noninferiority trial comparing the Promus Element stent to the Promus/Xience stent used an absolute difference delta of 3.5%, assuming a 1-year TLF rate of 5.5% and 1-sided alpha of 0.05.[53] The Resolute noninferiority trial comparing the Resolute stent to a historical control of Endeavor stents used an absolute difference delta of 3.3%, assuming a 1-year TLF rate of 6.5% and 1-sided alpha of 0.05.[54] The LEADERS trial comparing a biolimus stent to Cypher used an absolute difference delta of 4%, assuming a 9-month TVF rate of 8% and a 1-sided alpha of 0.05.[55] Finally, the TWENTE trial of Resolute vs Xience stent used an absolute difference delta of 4.48%, assuming a 1-year TVF rate of 12.8%, as observed in Endeavor III. Again, the noninferiority boundary was expressed for the upper limit of a 1-sided 95% CI assuming a 1-sided alpha of 0.05. These boundaries have been determined empirically in the above studies.

To investigate whether Combo is noninferior to EES, the appropriate null hypothesis is that EES is better than Combo by at least the noninferiority margin (delta). The alternative hypothesis is that Combo is not worse than EES by the noninferiority margin (delta). The quantification of delta should be clinically relevant and statistically feasible. Selection of an appropriate delta value, while ideally based on prior data and expectations of performance, should be determined by what is clinically meaningful.

In addition to EES, there are several DESs that are approved for clinical use in Japan, including Cypher, Nobori, TAXUS, and Endeavor. There are several studies that have compared these DESs to each other and to BMS in various combinations. The effect size of each of the currently approved DESs in subjects similar to those in the proposed study population can be summarized in a network meta-analysis. The 95% upper credible limit (a Bayesian parameter analogous to the upper 95% confidence limit) of these estimates relative to EES indicates a maximum reduction in therapeutic response that has already been considered acceptable by the clinical community.

#### 10.8.2.3 Bayesian Network Meta-Analysis

There are 21 studies that evaluated currently approved DESs in subjects similar to the proposed study population and measured TVF between 12 and 18 months. The treatment arms in each study, TVF events, and sample sizes are provided in Table 9 below:

**Table 9. Network Meta-Analysis of 21 Studies of Currently Approved Drug-Eluting Stents vs Everolimus-Eluting Stents**

| Study | Treatment | TVF Events | N |
|---|---|---|---|
| Bern-Rotterdam Registry | Xience | 179 | 1980 |
| | Cypher | 342 | 2860 |
| | TAXUS | 364 | 2798 |
| | | | |
| COMPARE | TAXUS | 82 | 903 |
| | Xience | 56 | 897 |

| Study | Treatment | TVF Events | N |
|---|---|---|---|
| | | | |
| COMPARE II | Xience | 41 | 912 |
| | Nobori | 87 | 1795 |
| | | | |
| | | | |
| Endeavor II | BMS | 100 | 591 |
| | Endeavor | 58 | 592 |
| | | | |
| Endeavor III | Cypher | 13 | 110 |
| | Endeavor | 42 | 316 |
| | | | |
| Endeavor IV | TAXUS | 72 | 751 |
| | Endeavor | 58 | 754 |
| | | | |
| REALITY | TAXUS | 86 | 669 |
| | Cypher | 82 | 684 |
| | | | |
| Resolute AC | Xience | 108 | 1126 |
| | Resolute | 101 | 1119 |
| SIRIUS | Cypher | 52 | 533 |
| | BMS | 130 | 525 |
| | | | |
| SIRTAX-LATE | TAXUS | 74 | 509 |
| | Cypher | 46 | 503 |
| SORT-OUT II | TAXUS | 120 | 1033 |
| | Cypher | 106 | 1065 |
| | | | |
| SORT-OUT III | Cypher | 53 | 1170 |
| | Endeavor | 113 | 1162 |
| | | | |
| SORT-OUT IV | Cypher | 105 | 1384 |
| | Xience | 99 | 1390 |

| Study | Treatment | TVF Events | N |
|---|---|---|---|
| | | | |
| SORT-OUT V | Cypher | 68 | 1239 |
| | Nobori | 82 | 1229 |
| | | | |
| SPIRIT II | TAXUS | 7 | 77 |
| | Xience | 10 | 220 |
| | | | |
| SPIRIT III | TAXUS | 37 | 319 |
| | Xience | 56 | 655 |
| | | | |
| SPIRIT IV | TAXUS | 92 | 1195 |
| | Xience | 134 | 2416 |
| | | | |
| TAXUS IV | BMS | 127 | 652 |
| | TAXUS | 66 | 662 |
| | | | |
| TAXUS V | BMS | 115 | 567 |
| | TAXUS | 82 | 560 |
| | | | |
| TWENTE | Xience | 56 | 692 |
| | Resolute | 57 | 695 |
| | | | |
| ZEST | TAXUS | 125 | 884 |
| | Cypher | 73 | 878 |
| | Endeavor | 90 | 883 |

BMS, bare metal stent; N, number; TVF, target-vessel failure

The results of these studies were combined using network meta-analysis to estimate the effect of each treatment relative to EES. Network meta-analysis, or mixed treatment comparison (MTC) is a technique to meta-analyze networks of trials comparing 2 or more treatments at the same time.[56,57] Using a Bayesian hierarchical model, all direct and indirect comparisons are taken into account to arrive at a single, integrated estimate of the effect of all included treatments based on all included studies. A Markov chain Monte Carlo model was created with 10 Markov chains, each using 20,000 tuning iterations followed by 50,000 simulation iterations. Satisfactory convergence was verified for all model parameters using the Brooks-Gelman-Rubin method.[58]

The relative effects and 95% credible intervals are shown for each stent in Figure 13 below:

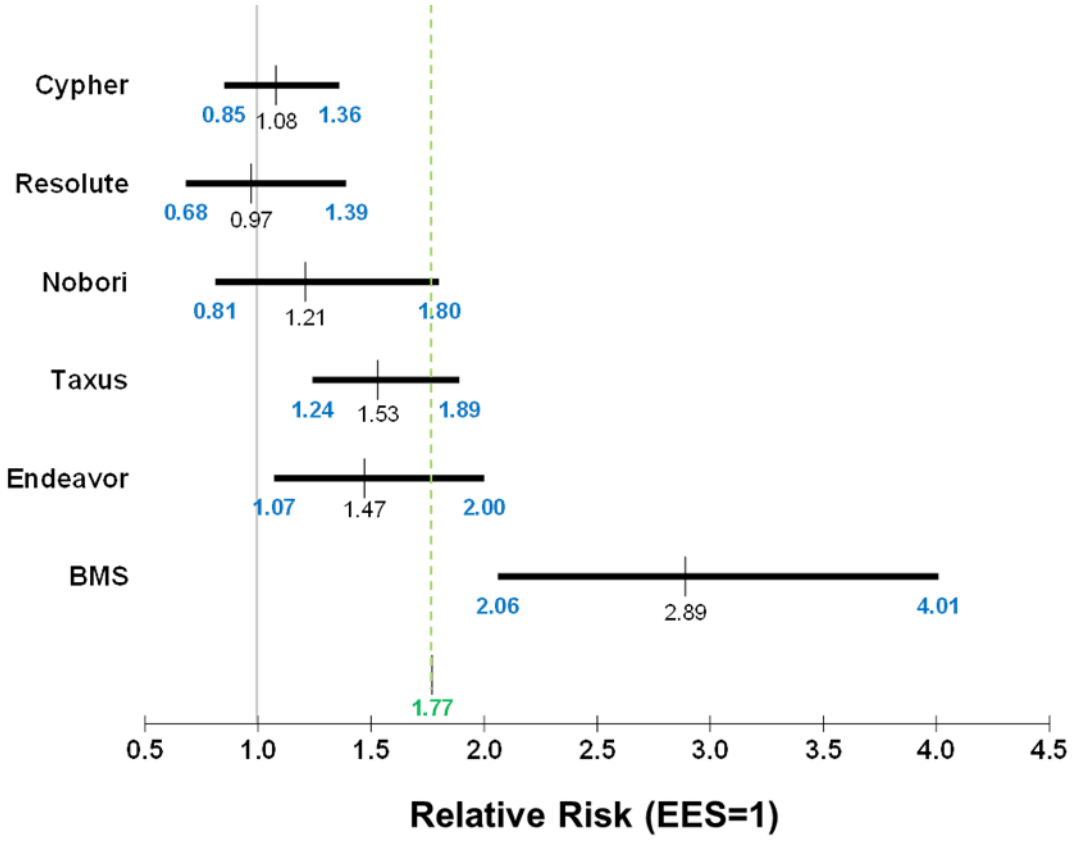



**Figure 13. Relative Risk (95% credible interval) of Currently Approved Drug-Eluting Stents vs Everolimus-Eluting Stents**

Each of the DESs has a 95% credible interval consistent with superiority to BMS. Clinical acceptance by healthcare providers of the Endeavor, TAXUS, and Nobori stents in this patient population on the basis of currently available studies indicates acceptance of an upper 95% credible limit greater than 1.80 relative to EES. Relative to EES, an upper bound of 1.77 would be more conservative than the upper bounds for 3 of the 5 approved DESs (Endeavor, TAXUS, and Nobori). If the TVF rate is 9% for the EES control arm, a relative upper bound of 1.77 corresponds to an absolute margin (delta) of 7%. Based on this evidence, this analysis shows a margin (delta) of 7% is clinically justified.

In the Combo study, we are assuming a 2-sided alpha of 0.05. For a trial population of 542 evaluable subjects (271 per arm), the study has 81% power to detect noninferiority using an absolute difference delta of 7%, assuming a 1-year TVF rate of 9% (Figure 14).

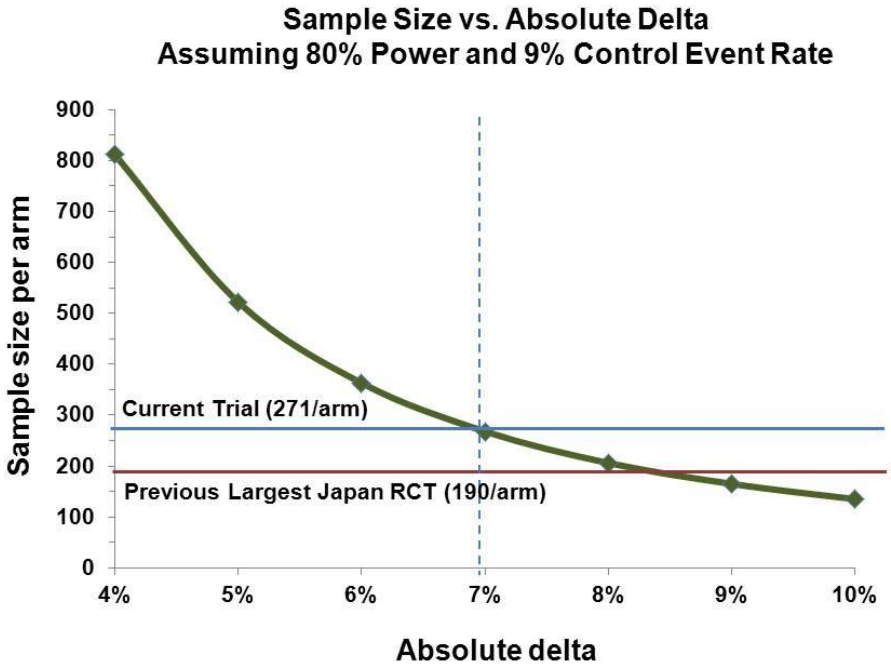



**Figure 14. Absolute Delta for Various Sample Sizes**

To date the largest randomized device trial in Japan succeeded in enrolling fewer than 400 subjects.[59] In this proposal more than 542 subjects are proposed, the largest randomized clinical trial ever conducted for medical devices in Japan. Thus, to create a robust and logistically feasible study to support this noninferiority analysis, superiority to an imputed BMS will also be required to fulfill the primary endpoint and demonstrate assay sensitivity, as is described below.

### 10.8.2.4 Comparison to an Imputed Bare Metal Stent Control

An important statistical consideration for the noninferiority evaluation of next-generation DESs is "drift"—the risk that a series of active-control trials might push the general therapy in the wrong direction by accepting therapies that are worse than previously approved therapy. In order to evaluate Combo stent effectiveness and assay sensitivity, the analysis should examine whether the effect of Combo on TVF is superior to the effect of a BMS on TVF, had a BMS arm been present. The evaluation of Combo as a third-generation product requires 2 indirect comparisons (Xience vs TAXUS, TAXUS vs bare metal) in addition to the direct comparison observed in the trial (Combo vs EES). In this particular circumstance, the mandate for assay sensitivity is actually more stringent (requiring a risk ratio [RR] difference between 1.1 and 1.3) than the requirement for noninferiority (estimated as an RR difference between 1.35 and 1.40).

The techniques for creating indirect comparisons of a new treatment to placebo have been described by several investigators, including Eddy et al. (1992),[60] Bucher et al. (1997),[61] Fisher (1998),[62] Hauck and Anderson (1999),[63] and Hasselblad and Kong (2001).[64] Simon (1999)[65] gave an equivalent Bayesian method.

Using these methods it is possible to estimate how Combo would have performed against a BMS had a BMS arm been present. The method takes into account the uncertainty in the trial of the investigational stent (Combo) as well as the uncertainty about the active-control stent (EES). The imputed control calculations for the trial will be based on the results of the TAXUS IV, TAXUS V, SPIRIT II, SPIRIT III, and SPIRIT IV trials.

First consider the SPIRIT II, SPIRIT III, and SPIRIT IV trials, which evaluated Xience V vs TAXUS Express stents, with 1-year TVF rates available in the Xience V IFU. The trial results can be summarized as a combined estimate using an Empirical Bayes random-effects model as described by Hedges and Olkin (1985).[66] This estimator has the property that it reduces to a fixed-effects estimator if no heterogeneity is present. The estimates were computed using FAST*PRO Software (Eddy and Hasselblad, 1992).[67] The 1-year TVF rates in these trials are summarized in Table 10.

**Table 10. One-Year Target-Vessel Failure Rates in the SPIRIT Trials**

| Trial | Xience V | TAXUS | Odds Ratio, 95% CI | Relative Risk, 95% CI |
|---|---|---|---|---|
| SPIRIT II | 4.5% (10/220) | 9.1% (7/77) | 0.48 ( 0.17, 1.30) | 0.50 (0.20, 1.27) |
| SPIRIT III | 8.5% (56/655) | 11.6 (37/319) | 0.71 ( 0.46, 1.11) | 0.74 (0.50, 1.09) |
| SPIRIT IV | 5.5% (134/2416) | 7.7% (92/1195) | 0.70 (0.53, 0.93) | 0.72 (0.56, 0.93) |
| Combined | | | 0.69 (0.55, 0.87) | 0.71 (0.57, 0.88) |

Next consider the TAXUS IV, and TAXUS V trials, which compared TAXUS Express to bare metal controls in a variety of anatomic settings[11] (TAXUS IFU[68]; personal communication). The 1-year TVF results can be summarized as a combined estimate using an Empirical Bayes random-effects model (Table 11).

**Table 11. One-Year Target-Failure Rates in the TAXUS Trials**

| Trial | TAXUS | Control (Bare Metal Stent) | Odds Ratio, 95% CI | Relative Risk, 95% CI |
|---|---|---|---|---|
| TAXUS IV | 10.0% (66/662) | 19.4% (127/652) | 0.46 ( 0.34, 0.64) | 0.51 (0.39, 0.68) |
| TAXUS V | 18.7% (105/560) | 25.0% (142/567) | 0.69 ( 0.52, 0.92) | 0.75 (0.60, 0.94) |
| Combined | | | 0.57 ( 0.43, 0.76) | 0.63 (0.49, 0.82) |

The following method is taken from Hasselblad and Kong (2001).[64] From these estimates, we can obtain an imputed comparison of EES to BMS by multiplying the summary odds ratios (ORs):

$$\frac{\text{Odds of TVF for EES}}{\text{Odds of TVF for BMS}} = \frac{\text{Odds of TVF for EES}}{\text{Odds of TVF for TAXUS}} \times \frac{\text{Odds of TVF for TAXUS}}{\text{Odds of TVF for BMS}}$$

Because these are all independent estimates, the variance of the imputed EES vs BMS estimate is the sum of the variances of the EES vs TAXUS estimate variance of the TAXUS vs BMS estimate.

Using the meta-analytic estimates above, the OR for EES BMS is 0.395 with 95% CI 0.275, 0.567. Next, consider the relationship between Combo and bare metal:

$$\frac{\text{Odds of TVF for Combo}}{\text{Odds of TVF for BMS}} = \frac{\text{Odds of TVF for Combo}}{\text{Odds of TVF for EES}} \times \frac{\text{Odds of TVF for EES}}{\text{Odds of TVF for TAXUS}} \times \frac{\text{Odds of TVF for TAXUS}}{\text{Odds of TVF for BMS}}$$

$$\frac{\text{Odds of TVF for Combo}}{\text{Odds of TVF for BMS}} = \frac{\text{Odds of TVF for Combo}}{\text{Odds of TVF for EES}} \times \frac{\text{Odds of TVF for EES}}{\text{Odds of TVF for BMS}}$$

Again, because these are all independent estimates, the variance of the imputed Combo vs BMS estimate is the sum of the variances of the Combo vs EES trial and the estimates for EES vs TAXUS and TAXUS vs BMS.

Using these methods, for any particular control event rate and sample size, we can define a delta boundary where there is superiority over BMS (and assay sensitivity). For example, if one selects an RR delta of 1.2, assay sensitivity is preserved over the following range of sample sizes, depending on the control event rate (Table 12).

**Table 12. Boundary Sample Size and Control Event Rate, Combo vs Everolimus-Eluting Stent; Combo vs Bare Metal Stent**

| EES Event Rate | Boundary Event Rate | Boundary Sample Size | | Trial Result (Combo vs EES) | | | Imputed Result (Combo vs Bare Metal Stent) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Relative Risk Ratio | 95% CI | | Relative Risk Ratio | 95% CI | |
| 0.07 | 0.084 | 540 | (270 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |
| 0.08 | 0.096 | 482 | (241 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |
| 0.09 | 0.108 | 438 | (219 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |
| 0.10 | 0.120 | 402 | (201 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |
| 0.11 | 0.132 | 374 | (187 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |
| 0.12 | 0.144 | 350 | (175 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |
| 0.15 | 0.180 | 300 | (150 per arm) | 1.2 | 0.71 | 2.02 | 0.54 | 0.29 | 1.00 |

EES, everolimus-eluting stent

Consequently, if one selects a sample size of 542 evaluable subjects (which would provide assay sensitivity with an RR delta of at least 1.2 at control event rates of 9% and greater), the boundary deltas to assure assay sensitivity are as in Table 13.

**Table 13. Boundary Sample Size and Boundary Relative Risk Delta: Combo vs Everolimus-Eluting Stent; Combo vs Bare Metal Stent**

| EES Event Rate | Boundary Event Rate | Boundary Relative Risk Delta (Combo vs EES) | Trial Result (Combo vs EES) | | | Imputed Result (Combo vs Bare Metal Stent) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Odds Ratio | 95% CI | | Odds Ratio | 95% CI | |
| 0.07 | 0.084 | 1.200 | 1.22 | 0.65 | 2.30 | 0.48 | 0.23 | 1.00 |
| 0.08 | 0.099 | 1.238 | 1.26 | 0.70 | 2.29 | 0.50 | 0.25 | 1.00 |
| 0.09 | 0.114 | 1.265 | 1.30 | 0.74 | 2.27 | 0.51 | 0.26 | 1.00 |
| 0.10 | 0.129 | 1.285 | 1.33 | 0.78 | 2.26 | 0.52 | 0.28 | 1.00 |
| 0.11 | 0.143 | 1.304 | 1.35 | 0.81 | 2.26 | 0.54 | 0.29 | 1.00 |
| 0.12 | 0.158 | 1.317 | 1.38 | 0.84 | 2.25 | 0.54 | 0.30 | 1.00 |
| 0.15 | 0.205 | 1.367 | 1.42 | 0.91 | 2.22 | 0.56 | 0.32 | 1.00 |

EES, everolimus-eluting stent

### 10.8.2.5 Power to Detect Noninferiority Based on Assay Sensitivity Boundary Conditions

In the proposed trial, if one assumes that the control and experimental event rates are equal, then the power to exclude the assay sensitivity boundaries shown in Figure 13 (above) for each event rate is equal to the area to the left of the boundary delta value. On that basis, the power by each EES event rate is as shown in Table 14 for a sample size of 542 evaluable subjects:

**Table 14. Power to Exclude Assay Sensitivity Boundaries for Each Event Rate**

| EES Event Rate | Boundary Event Rate | Boundary Relative Risk Delta (Combo vs EES) | Power to Detect Noninferiority Assuming Combo Rate = EES Rate |
|---|---|---|---|
| 0.07 | 0.084 | 1.200 | 0.716 |
| 0.08 | 0.099 | 1.238 | 0.764 |
| 0.09 | 0.114 | 1.265 | 0.800 |
| 0.10 | 0.129 | 1.285 | 0.830 |
| 0.11 | 0.143 | 1.304 | 0.856 |
| 0.12 | 0.158 | 1.317 | 0.877 |
| 0.15 | 0.205 | 1.367 | 0.933 |

EES, everolimus-eluting stent

# 11. DATA AND SAFETY MONITORING

## 11.1 Safety Monitoring

It is the responsibility of the investigator to oversee the safety of the study at his or her site. This safety monitoring will include careful assessment and appropriate reporting of AEs/SAEs, and UADEs as noted in Section 7, as well as the construction and implementation of a site data and safety monitoring plan (Section 13.4). Medical monitoring will include a regular assessment of the number and type of adverse device events.

## 11.2 Data Management to Maintain Blinding

Data that may potentially reveal treatment assignment will be handled with special care, so that before unblinding, such data will be available to only data management staff for purposes of data cleaning.

# 12. DATA MONITORING AND QUALITY CONTROL

## 12.1 Required Data

The full study dataset will be collected for subjects who enter the randomization phase of the study. All required data for this study will be entered into the eCRF.

## 12.2 Data Collection and Tracking

Qualified study staff at each site will perform primary data collection from source document reviews. OrbusNeich Medical or their delegate will perform clinical monitoring, including review of eCRFs with verification to the source documentation.

This study will use Web-based e-CRFs developed through a validated platform that enables electronic-reporting-electronic-signatures–compliance platform (21 CFR Part 11). Before initiation of the trial, each site will be assessed as to computer availability, hardware specifications, and Internet connectivity, to evaluate the site's capability to use this type of data-collection system. The investigator's site staff members who will be entering data will receive training on the system, after which each person will be issued a unique user ID and password.

For security reasons, and in compliance with regulatory guidelines, it is imperative that only those persons trained in the system use the system, and each must do so using his or her own unique access code. Access codes are nontransferable. Site personnel who have not undergone training may not use the system and will not be issued user ID and password until appropriate training is completed.

During monitoring visits, the site will ensure that system access is available to the clinical research associate (CRA), so that the CRA may verify the data entries against source documentation. At the conclusion of the study, each enrolling site will be provided with a copy of its own subjects' data that includes entries and changes made by the site (ie, the audit trail of changes made to the database). This will be maintained at the site according to the requirements for records retention.

# 13. STUDY RESPONSIBILITIES

This is a global, multi-site trial that will be conducted at up to 50 sites in Japan and the United States. This clinical trial is sponsored by OrbusNeich Medical. The Steering Committee for this study will have overall responsibility for the oversight and management of the trial. The Steering Committee will include Drs. Saito and Krucoff, PIs, and DCRI representatives. Representatives from OrbusNeich Medical will be liaisons to the Steering Committee.

## 13.1 Investigator Responsibility/Performance

By signing this protocol, OrbusNeich Medical and DCRI agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol; accepted standards of J-GCP; GCP; and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The investigator will provide current copies of the study protocol to all subinvestigators or other site personnel responsible for study conduct.

The investigator will provide OrbusNeich Medical with copies of all EC/IRB reports regarding the study.

## 13.2 Study Data Reporting and Processing

Each page of the eCRF will be reviewed by the investigator at the site. The investigator is required to sign the eCRF on the appropriate pages to verify that he or she has reviewed the recorded data. This review may be delegated to a qualified physician appointed as a subinvestigator by the investigator. The transfer of duties to a subinvestigator will be recorded on the delegation list (which is kept on file at the site). The investigator shall inspect the eCRFs prepared by the subinvestigators and, upon confirming the content thereof, shall sign and seal, or sign the forms. The investigator must ensure that all site staff involved in the conduct of the trial are familiar with the protocol and all study-specific procedures, and that they have appropriate knowledge of the study agents.

## 13.3 Training

The training of appropriate clinical site personnel will be the responsibility of OrbusNeich Medical or their delegate. The investigator is responsible for ensuring that his or her staff conducts the study according to the protocol. To ensure proper administration of study agents, uniform data collection, and protocol compliance, OrbusNeich Medical or their delegate will present a formal training session to study site personnel, to include instructions for study procedures, the investigational plan, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by OrbusNeich Medical or their delegate in the course of regular site monitoring.

## 13.4 Monitoring the Investigational Sites

As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of J-GCP, GCP, and applicable regulations, an OrbusNeich Medical study monitor or their delegate will visit the study sites regularly and will maintain frequent telephone and written communication.

Periodic monitoring visits will be made at all active investigational sites throughout the clinical study to assure that the investigator obligations are being fulfilled and all applicable regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the EC/IRB has approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to OrbusNeich Medical or their delegate and the EC/IRB, study device and study device inventory are controlled, and the investigator is carrying out all agreed-upon activities.

During monitoring visits, the monitor will perform a review of inclusion/exclusion criteria, informed consent, HIPAA (Health Insurance Portability and Accountability Act) authorization (U.S.), events meeting criteria for expedited event reporting, as well as safety and efficacy endpoints. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. Any discrepancies will be noted and resolved.

During monitoring visits, the site will ensure system access is available to the CRAs so that they may verify the data entries against the source documentation.

## 13.5 Study Documentation

Study documentation includes all eCRFs, source documents, monitoring logs, appointment schedules, sponsor-investigator correspondence, and regulatory documents (eg, signed protocol and amendments, EC/IRB correspondence and approvals, approved and signed subject consent forms, Statement of Investigator form, and clinical supplies receipts and distribution records).

The investigators will prepare and maintain complete and accurate study documentation in compliance with U.S. and Japan GCP standards and applicable country, federal, state, and local laws, rules, and regulations; and, for each subject participating in the study, promptly complete all eCRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with OrbusNeich Medical or their delegate.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to OrbusNeich Medical or their delegate by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of OrbusNeich Medical or their delegate or responsible government agencies as required by law.

The investigator agrees to promptly take any reasonable steps that are requested by OrbusNeich Medical or their delegate as a result of an audit to cure deficiencies in the study documentation and eCRFs.

## 13.6 Source Documentation

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts, pharmacy records, and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Regulations require that investigators maintain information in the study subject's medical records that corroborate data collected on the eCRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by OrbusNeich Medical or their delegate's monitors and/or regulatory inspectors:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.
- Medical record documenting that informed consent was obtained for the subject's participation in the study.
- Dated and signed notes for each subject visit, including results of examinations.
- Notations on abnormal laboratory results and their resolution.
- Dated printouts or reports of special assessments (eg, ECG reports).
- Description of AEs and follow-up of the AEs (minimally, event description, severity, onset date, duration, relation to study drug/device, outcome, and treatment for AE).
- Notes regarding concomitant medications taken during the study (including start and stop dates).
- Subject's condition upon completion of or withdrawal from the study.

## 13.7 Protocol Deviations

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the study according to the investigational plan or the Investigator Agreement.

Investigators are required to obtain approval from the OrbusNeich Medical or their delegate's medical monitor before initiating deviations from the investigational plan or protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Significant deviations and approval will be documented in writing and maintained in study files. Unless OrbusNeich Medical or their delegate has consented to any such deviations in writing, OrbusNeich Medical will not assume any resulting responsibility or liability. Preapproval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control, (eg, subject did not attend scheduled follow-up visit, blood sample lost by laboratory); however, the event is still considered a deviation.

Deviations will be reported to OrbusNeich Medical or their delegate regardless of whether medically justifiable, preapproved by the medical monitor, or taken to protect the subject in an emergency. Subject-specific deviations will be reported. Nonsubject-specific deviations will be reported to OrbusNeich Medical or their delegate in writing.

The EC/IRB will be informed of all protocol changes by the sponsor in accordance with applicable regulations and the EC/IRB's established procedures. No deviations from the protocol of any type will be made without complying with all the EC/IRB's established procedures.

Investigators will maintain documentation of the dates and reasons for each deviation from the protocol, in compliance with J-GCP guidelines and U.S. 21 CFR 812.140.

## 13.8 Study Supply Accountability

The investigator (and in Japan, the Device Storage Manager) will maintain records of the receipt and disposition of all investigational devices. When the enrollment is complete, the investigator (and in Japan, the Device Storage Manager) will be notified by the OrbusNeich Medical or their delegate and, in a timely manner, will return all study devices as directed by OrbusNeich Medical or their delegate.

## 13.9 Data Transmittal and Record Retention

Required data will be entered in the eCRF at the time of or as soon as possible after the subject visit or the availability of test results. Study sites will transcribe subject source data into eCRFs using a computerized electronic data capture (EDC) system. The EDC system is compliant with all relevant aspects of GCP. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate and complete data collection. Data will be transmitted via the Internet from investigational sites to a central site, utilizing state-of-the-art encryption mechanisms to ensure security and confidentiality.

Copies of protocol-specified source documents (eg, hospital discharge summaries, operative/procedural reports, and other source documents, as applicable) will be provided to the Data Coordinating Center as necessary. Copies of study-related documentation will also be retained at the site.

The investigator will maintain the records of device disposition, final eCRFs, worksheets, and all other study-specific documentation (eg, study file notebooks or source documentation) until notified by the sponsor that records may be destroyed. OrbusNeich Medical or their delegate will be contacted if the investigator plans to leave the institution, so that arrangements can be made for the transfer of records. If a marketing application is not filed or is withdrawn, the investigator will maintain the records for at least 3 years after the formal discontinuation of the clinical development program for this product. In Japan, the head of the medical institution shall appoint a record keeping manager, who must retain the relevant records for the specified period.

As this study is being conducted under a U.S. Investigational Device Exemption application, FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- At least 2 years following the date on which an Investigational Device Exemption Application is approved by the U.S. FDA
- 2 years after OrbusNeich Medical or their delegate notifies the investigator that no further application is to be filed with the U.S. FDA

The investigator will not dispose of any records relevant to this study without either (1) obtaining written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator takes responsibility for maintaining adequate and accurate hard-copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by OrbusNeich Medical or their delegate as well as the FDA and other regulatory agencies, as provided by law.

## 13.10 Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved), OrbusNeich Medical or their delegate will notify the site of closeout, and a closeout visit will be performed. All unused study materials will be collected and returned to the OrbusNeich Medical or their delegate. The monitor will ensure that the investigator's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the EC/IRB of study closure.

## 13.11 Audit/Inspections

OrbusNeich Medical or their delegate's quality assurance personnel may conduct audits at the study sites. Audits will include, but not be limited to, audit trail of data handling and processes, SOPs, device supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to accommodate and participate in audits conducted at a reasonable time and in a reasonable manner, as needed.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the sponsor immediately if this occurs and must fully cooperate with governmental (eg, FDA, PMDA) audits conducted at a reasonable time and in a reasonable manner.

## 13.12 Publication Policies

Members of the steering committee will be primarily responsible for creation, review, and submission of publications and presentations relating to the major aspects of the study and approved ancillary analyses within a timely fashion after completion of the study.

The manuscript containing the overall study results will be distributed to OrbusNeich Medical for review before submission to a peer-reviewed journal, but the final content will be at the discretion of the Steering Committee. Any other manuscripts containing these data, including abstracts, will be distributed to OrbusNeich Medical before submission, with a reasonable period for review. Submitted publications will conform to international standards for biomedical manuscripts, including those regarding authorship.

## 13.13 Study Committees

### 13.13.1 Principal Investigators and National Coordinators

Dr. Shigeru Saito (Shonan Kamakura General Hospital) and Dr. Mitchell Krucoff (Duke University) will provide academic leadership and day-to-day scientific oversight of the study. They will report to the Steering Committee. Drs. Saito and Krucoff will also serve in the role of liaison between the Steering Committee and site investigators as well as between the DSMC and the Steering Committee. The study will be coordinated on a national basis by Dr. Shigeru Nakamura (Kyoto Katsura Hospital) in Japan and Dr. Roxana Mehran (Mount Sinai Hospital) in the United States.

### 13.13.2 Steering Committee

A Steering Committee will be chaired by Dr. David Kong (Duke Clinical Research Institute), providing scientific and operational oversight to the study. The study chair will also serve as the liaison to the DSMC. The Steering Committee will monitor all aspects of the study, offer suggestions to the Executive Committee based on the DSMC recommendations, and oversee the presentation of the trial results and any publications.

### 13.13.3 Executive Operations Committee

The Executive Operations Committee will be responsible for the day-to-day administrative management of the study. This committee will meet periodically by teleconference to monitor subject enrollment, clinical site progress, and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.

### 13.13.4 Data and Safety Monitoring Committee

The study will be conducted under the auspices of an independent DSMC, whose activities will be described in a DSMC charter.

### 13.13.5 Clinical Events Classification Committee

The CEC will adjudicate the following protocol-specific suspected cardiovascular events as defined in the CEC Charter:

- Cardiac death
- MI
- TLR (ischemia driven)
- TVR (ischemia driven)
- Stroke and TIA
- Stent thrombosis (ARC definition)

The CEC will be blinded to subject treatment assignment as well as the primary results of the study.

# 14. ETHICAL CONSIDERATIONS

By signing this protocol, the investigator agrees to conduct the study in compliance with the protocol; OrbusNeich Medical or their delegate's SOPs and/or guidelines; the FDA regulations; J-GCP ordinance, based on the ICH guidelines on GCP (ICH E6, the principles of which have their origin in the Declaration of Helsinki); and all other applicable national, federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

## 14.1 Role of Sponsor

As the study sponsor, OrbusNeich Medical has overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the PMDA, U.S. FDA and regulatory requirements of international regulatory agencies appropriate to the conduct of the study in centers outside of the United States. In this study, OrbusNeich Medical will have certain direct responsibilities and will delegate other responsibilities to DCRI. DCRI will ensure adherence to the sponsor's general responsibilities (21 CFR 812.40) and other responsibilities as agreed between DCRI and the sponsor, eg, selection of investigators (21 CFR 812.43), monitoring (21 CFR 312.46), and protocol amendments (21 CFR 312.35). OrbusNeich Medical and DCRI will ensure compliance with relevant local regulations and guidelines in the conduct of the study in centers outside of the United States.

## 14.2 Informed Consent

The investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the study. Written informed consent will be obtained from all subjects (or their LAR) before any study-related procedures (including any pretreatment procedures, such as preprocedure sedation) are performed or given.

Written informed consent will be documented on an ICF approved by the same EC/IRB responsible for approval of this protocol. The ICF will conform to J-GCP regulations, FDA regulations in 21 CFR Part 50, and to the institutional requirements for informed consent and applicable regulations. The investigator agrees to obtain approval from OrbusNeich Medical or their delegate of any ICF intended for use in the study, before submission for IRB approval.

The ICF will be reviewed with the prospective study subject or his or her LAR, and the investigator or qualified designee will be available to answer questions regarding procedures, risks, and alternatives.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators or qualified designee, and it is felt that the subject understands the implications of participating, the subject or his or her LAR will sign and date the EC/IRB-approved written ICF. The subject will receive a copy of the signed ICF. The original signed and dated ICF will be kept in the site's regulatory file. Documentation of the subject's informed consent for and participation in this trial will be noted in the subject's medical record.

If the subject is illiterate, an impartial witness is required to be present during the entire informed consent reading and discussion. Afterward, the subject should be asked to sign and date the ICF, if capable. The witness should also sign and date the ICF along with the individual who read and discussed the informed consent (ie, study staff personnel).

The subject or his or her LAR will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information to the subject will be documented.

## 14.3 Confidentiality of Subjects

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject ID code (ID number and subject name code) will be used that allows identification of all data reported for each subject.

Subject information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated by U.S. HIPAA and as mandated in Title 45 CFR Parts 160 and 164 (U.S.) and J-GCP (Japan). All records will be kept confidential, and the subject's name will not be released at any time. Subject records will not be released to anyone other than OrbusNeich Medical or their delegate or its designees and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is protected.

## 14.4 Authorization for Use and Disclosure of Protected Health Information (HIPAA)

An authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule (45 CFR § 164.102 *et seq*) will be obtained from every trial subject before or at the time of enrollment. It will be presented to, and signed by, the subject at the same time as the ICF. The investigator is responsible for obtaining subjects' (or their LARs') authorizations and signatures and for explaining the elements of the HIPAA authorization form if necessary.

HIPAA authorization may be either a separate form or included in the study ICF, dependent upon local requirements.

The HIPAA authorization form will contain all elements required under the HIPAA Privacy Rule. By law, site IRB approval of the sponsor-provided authorization form for use in this study is not required, and no such approval will be sought or requested..

The investigator or the site will promptly inform OrbusNeich Medical or their delegate of any restrictions on the use or disclosure of PHI of any subject to which the site or the investigator have agreed under the Privacy Rule. The investigator or the site will also promptly inform OrbusNeich Medical or their delegate of any written revocation of any subject's HIPAA authorization.

## 14.5 Insurance

This study is covered under the sponsor's liability insurance policy. A certificate of insurance and/or an information leaflet containing essential information about the insurance coverage can be provided by study sites upon request.

## 14.6 Human Subject Protections

There will be no exclusion from participation in the study on the basis of ethnicity or race. Subjects younger than 20 years of age will be excluded from the study, as the target population is adults. Women of childbearing potential will have pregnancy testing before randomization to avoid potential fetal exposure. Cognitively impaired individuals, prisoners, or other institutionalized persons will be allowed to participate only after documented consultation with and approval by the EC/IRB.

Subjects who are admitted to the hospital for a planned (elective) percutaneous coronary artery intervention procedure will be referred to the investigator or authorized designee for screening. These subjects will then undergo a screening process, during which subjects will have multiple opportunities to ask questions. The investigator or authorized designee will provide a detailed discussion of the protocol and answer any remaining questions. The subject will be given time to consider study participation. No coercion or undue influence on this decision will be used. Only those subjects who give written informed consent and complete enrollment testing before the date of planned study device implantation will be considered for participation in the study.

## 14.7 Institutional Review Board/Ethics Committee Review

The appropriate EC/IRB must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. The investigator will provide OrbusNeich Medical or their delegate with documentation that the EC/IRB has approved the study *before* the study may begin.

In addition, the investigator must provide the following documentation to OrbusNeich Medical or their delegate:

- EC/IRB annual continuing review and reapproval of the protocol, per current regulations (Title 21 CFR 812.150 [a][3]), J-GCP guidelines, and 1997 ICH guidelines.
- EC/IRB approval of revisions to the informed consent documents or any amendments to the protocol. Any revisions to the protocol that may increase subject risk exposure must be approved before implementation. Administrative changes (such as a change in address or phone number) must be sent to ECs/IRBs but do not require their approval. The investigator will provide OrbusNeich Medical or their delegate with documentation of all approvals.

## 14.8 Financial Disclosure

In compliance with 21 CFR 812.110(d), any listed or identified investigator or subinvestigator (including the spouse and any dependent children of said individuals) directly involved in the treatment or evaluation of research subjects will disclose the following information for the time period during which the investigator is participating in the study and for 1 year following completion of the study:

1. Any financial arrangement entered into between OrbusNeich Medical and the investigator, whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study.
2. Any significant payments of other sorts made by OrbusNeich Medical to the investigator (or their institution) to support the activities of the investigator that totals more than $25,000, exclusive of the costs of conducting this or other clinical studies.
3. Any proprietary interest held by the investigator in the product being evaluated.
4. Any significant equity interest in OrbusNeich Medical, including any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (eg, nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000.

## 15. REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *European Heart Journal*. 2012;33(20):2551–2567. doi:10.1093/eurheartj/ehs184.

2. Mehran R, Dangas GD, Kobayashi Y, et al. Short- and long-term results after multivessel stenting in diabetic patients. *J Am Coll Cardiol*. 2004;43(8):1348–1354. doi:10.1016/j.jacc.2003.04.004.

3. Rodriguez A, Bernardi V, Navia J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. *J Am Coll Cardiol*. 2001;37(1):51–58.

4. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344(15):1117–1124. doi:10.1056/NEJM200104123441502.

5. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet*. 2002;360(9338):965–970. doi:10.1016/S0140-6736(02)11078-6.

6. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 229 patients. *J Am Coll Cardiol*. 1988;12(3):616–623.

7. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331(8):496–501. doi:10.1056/NEJM199408253310802.

8. Sousa JE, Costa MA, Abizaid AC, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation*. 2001;104(17):2007–2011.

9. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation*. 2001;103(2):192–195.

10. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346(23):1773–1780. doi:10.1056/NEJMoa012843.

11. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation*. 2004;109(16):1942–1947. doi:10.1161/01.CIR.0000127110.49192.72.

12. Morice M-C, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346(23):1773–1780. doi:10.1056/NEJMoa012843.

13. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350(3):221–231. doi:10.1056/NEJMoa032441.

14. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48(1):193–202. doi:10.1016/j.jacc.2006.03.042.

15. Mauri L, Hsieh W, Massaro JM, Ho KKL, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356(10):1020–1029. doi:10.1056/NEJMoa067731.

16. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115(18):2435–2441. doi:10.1161/CIRCULATIONAHA.107.693739.

17. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol*. 2007;27(7):1500–1510. doi:10.1161/ATVBAHA.107.144220.

18. Ong ATL, McFadden EP, Regar E, de Jaegere PPT, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005;45(12):2088–2092. doi:10.1016/j.jacc.2005.02.086.

19. Chevalier B, Silber S, Park S-J, et al. Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberté paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the NOBORI 1 trial--Phase 2. *Circ Cardiovasc Interv*. 2009;2(3):188–195. doi:10.1161/CIRCINTERVENTIONS.108.823443.

20. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA*. 2008;299(16):1903–1913. doi:10.1001/jama.299.16.1903.

21. Leon MB, Mauri L, Popma JJ, et al. A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in de novo native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. *J Am Coll Cardiol*. 2010;55(6):543–554. doi:10.1016/j.jacc.2009.08.067.

22. Fajadet J, Wijns W, Laarman G-J, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation*. 2006;114(8):798–806. doi:10.1161/CIRCULATIONAHA.105.591206.

23. Kandzari DE, Mauri L, Popma JJ, et al. Late-term clinical outcomes with zotarolimus- and sirolimus-eluting stents. 5-year follow-up of the ENDEAVOR III (A Randomized Controlled Trial

of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv*. 2011;4(5):543–550. doi:10.1016/j.jcin.2010.12.014.

24. Saito S, Prpic R, Popma JJ, Alexander J, Krucoff MW. The clinical evaluation of the Endeavor zotarolimus-eluting coronary stent in Japanese patients with de novo native coronary artery lesions: primary results and 3-year follow-up of the Endeavor Japan study. *Cardiovasc Revasc Med*. 2011;12(5):273–279. doi:10.1016/j.carrev.2010.12.007.

25. Planer D, Smits PC, Kereiakes DJ, et al. Comparison of everolimus- and paclitaxel-eluting stents in patients with acute and stable coronary syndromes: pooled results from the SPIRIT (A Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) and COMPARE (A Trial of Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice) Trials. *JACC Cardiovasc Interv*. 2011;4(10):1104–1115. doi:10.1016/j.jcin.2011.06.018.

26. Kereiakes DJ, Sudhir K, Hermiller JB, et al. Comparison of everolimus-eluting and paclitaxel-eluting coronary stents in patients undergoing multilesion and multivessel intervention: the SPIRIT III (A Clinical Evaluation of the Investigational Device XIENCE V Everolimus Eluting Coronary Stent System [EECSS] in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) and SPIRIT IV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions) randomized trials. *JACC Cardiovasc Interv*. 2010;3(12):1229–1239. doi:10.1016/j.jcin.2010.09.014.

27. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med*. 2010;362(18):1663–1674. doi:10.1056/NEJMoa0910496.

28. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science*. 1997;275(5302):964–967.

29. Hill JM, Zalos G, Halcox JPJ, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*. 2003;348(7):593–600. doi:10.1056/NEJMoa022287.

30. Novel anti-restenosis therapies. *The American Journal of Cardiology*. 2003;92(6, Supplement 1):94–97. doi:10.1016/S0002-9149(03)00922-6.

31. Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. *J Am Coll Cardiol*. 2005;45(10):1574–1579. doi:10.1016/j.jacc.2005.01.048.

32. Duckers HJ, Silber S, de Winter R, et al. Circulating endothelial progenitor cells predict angiographic and intravascular ultrasound outcome following percutaneous coronary interventions

in the HEALING-II trial: evaluation of an endothelial progenitor cell capturing stent. *EuroIntervention*. 2007;3(1):67–75.

33. Klomp M, Beijk MAM, Tijssen JGP, de Winter RJ. One-year clinical outcome in an unselected patient population treated with the Genous™ endothelial progenitor cell capturing stent. *Catheter Cardiovasc Interv*. 2011;77(6):809–817. doi:10.1002/ccd.22795.

34. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367(11):991–1001. doi:10.1056/NEJMoa1205361.

35. Sharkawi T, Cornhill F, Lafont A, Sabaria P, Vert M. Intravascular bioresorbable polymeric stents: a potential alternative to current drug eluting metal stents. *J Pharm Sci*. 2007;96(11):2829–2837. doi:10.1002/jps.20957.

36. Grube E, Buellesfeld L. BioMatrix Biolimus A9-eluting coronary stent: a next-generation drug-eluting stent for coronary artery disease. *Expert Rev Med Devices*. 2006;3(6):731–741. doi:10.1586/17434440.3.6.731.

37. Di Mario C, Ferrante G. Biodegradable drug-eluting stents: promises and pitfalls. *Lancet*. 2008;371(9616):873–874. doi:10.1016/S0140-6736(08)60389-X.

38. Guan J, Sacks MS, Beckman EJ, Wagner WR. Synthesis, characterization, and cytocompatibility of elastomeric, biodegradable poly(ester-urethane)ureas based on poly(caprolactone) and putrescine. *J Biomed Mater Res*. 2002;61(3):493–503. doi:10.1002/jbm.10204.

39. Guan J, Sacks MS, Beckman EJ, Wagner WR. Biodegradable poly(ether ester urethane)urea elastomers based on poly(ether ester) triblock copolymers and putrescine: synthesis, characterization and cytocompatibility. *Biomaterials*. 2004;25(1):85–96.

40. Asplund B, Aulin C, Bowden T, et al. In vitro degradation and in vivo biocompatibility study of a new linear poly(urethane urea). *J Biomed Mater Res Part B Appl Biomater*. 2008;86(1):45–55. doi:10.1002/jbm.b.30986.

41. Van Minnen B, van Leeuwen MBM, Kors G, Zuidema J, van Kooten TG, Bos RRM. In vivo resorption of a biodegradable polyurethane foam, based on 1,4-butanediisocyanate: a three-year subcutaneous implantation study. *J Biomed Mater Res A*. 2008;85(4):972–982. doi:10.1002/jbm.a.31574.

42. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367(11):991–1001. doi:10.1056/NEJMoa1205361.

43. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for

Cardiovascular Angiography and Interventions. *Circulation*. 2011;124(23):e574–e651. doi:10.1161/CIR.0b013e31823ba622.

44. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2009;53(6):530–553. doi:10.1016/j.jacc.2008.10.005.

45. Novel anti-restenosis therapies. *The American Journal of Cardiology*. 2003;92(6, Supplement 1):94–97. doi:10.1016/S0002-9149(03)00922-6.

46. Haude M, Lee SWL, Worthley SG, et al. The REMEDEE trial: a randomized comparison of a combination sirolimus-eluting endothelial progenitor cell capture stent with a paclitaxel-eluting stent. *JACC Cardiovasc Interv*. 2013;6(4):334–343. doi:10.1016/j.jcin.2012.10.018.

47. Kim J-S, Afari ME, Ha J, et al. Neointimal patterns obtained by optical coherence tomography correlate with specific histological components and neointimal proliferation in a swine model of restenosis. *Eur Heart J Cardiovasc Imaging*. 2013:jet162. doi:10.1093/ehjci/jet162.

48. Pocock SJ, Lansky AJ, Mehran R, et al. Angiographic surrogate end points in drug-eluting stent trials: a systematic evaluation based on individual patient data from 11 randomized, controlled trials. *J Am Coll Cardiol*. 2008;51(1):23–32. doi:10.1016/j.jacc.2007.07.084.

49. Hwang WYK, Foote J. Immunogenicity of engineered antibodies. *Methods*. 2005;36(1):3–10. doi:10.1016/j.ymeth.2005.01.001.

50. DeNardo GL, Bradt BM, Mirick GR, DeNardo SJ. Human antiglobulin response to foreign antibodies: therapeutic benefit? *Cancer Immunol Immunother*. 2003;52(5):309–316. doi:10.1007/s00262-002-0350-y.

51. Mirick GR, Bradt BM, Denardo SJ, Denardo GL. A review of human anti-globulin antibody (HAGA, HAMA, HACA, HAHA) responses to monoclonal antibodies. Not four letter words. *Q J Nucl Med Mol Imaging*. 2004;48(4):251–257.

52. Hwang WYK, Foote J. Immunogenicity of engineered antibodies. *Methods*. 2005;36(1):3–10. doi:10.1016/j.ymeth.2005.01.001.

53. Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial. *J Am Coll Cardiol*. 2011;57(16):1700–1708. doi:10.1016/j.jacc.2011.02.016.

54. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010;363(2):136–146. doi:10.1056/NEJMoa1004130.

55. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372(9644):1163–1173. doi:10.1016/S0140-6736(08)61244-1.

56. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105–3124. doi:10.1002/sim.1875.

57. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med*. 2002;21(16):2313–2324. doi:10.1002/sim.1201.

58. Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. *Journal of Computational and Graphical Statistics*. 1998;7(4):434–455. doi:10.1080/10618600.1998.10474787.

59. Kadota K, Muramatsu T, Iwabuchi M, et al. Randomized comparison of the Nobori biolimus A9-eluting stent with the sirolimus-eluting stent in patients with stenosis in native coronary arteries. *Catheter Cardiovasc Interv*. 2012;80(5):789–796. doi:10.1002/ccd.23280.

60. Eddy DM, Hasselblad V, Shachter RD. *Meta-analysis by the confidence profile method: the statistical synthesis of evidence*. Boston: Academic Press; 1991.

61. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50(6):683–691.

62. Fisher LD. Active control trials: what about a placebo? A method illustrated with clopidogrel, aspirin and placebo. *Journal of the American College of Cardiology*. 1998;31, Supplement 1:49. doi:10.1016/S0735-1097(98)80866-8.

63. Hauck WW, Anderson S. Some Issues in the Design and Analysis of Equivalence Trials. *Drug Information Journal*. 1999;33(1):109–118. doi:10.1177/009286159903300114.

64. Hasselblad V, Kong, DF. Statistical methods for comparison to placebo in active-control trials. *Drug Information Journal*. 2001;35:435–449.

65. Simon R. Bayesian Design and Analysis of Active Control Clinical Trials. *Biometrics*. 1999;55(2):484–487. doi:10.1111/j.0006-341X.1999.00484.x.

66. Hedges LV, Olkin I. *Statistical methods for meta-analysis*. Orlando: Academic Press; 1985.

67. Eddy DM, Hasselblad V. *FAST*PRO: Software for meta-analysis by the confidence profile method*. Boston: Academic Press; 1992.

68. TAXUS™ Express 2™ Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire) - P030025. Available at:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/pma/pma.cfm?num=P030025. Accessed March 4, 2013.

# 16. APPENDIX 1: OPTICAL COHERENCE TOMOGRAPHY IMAGE ANALYSIS PARAMETERS

Neointimal Quantification

- Neointimal thickness: Strut level analysis of the neointimal thickness will be performed by the measuring the distance from the center of the stent blooming to the lumen centromere. This measurement will take into consideration every strut available in a cross-section image at every 0.6-mm longitudinal interval.
- Neointimal area and neointimal volume ($mm^2$ and $mm^3$, respectively) will be obtained at 0.6-mm interval.
- Binary strut coverage (%) obtained at 0.6-mm interval.

Stent Apposition

- Malapposition and how prevalent along the stent (defined as space greater than the strut thickness between stent strut and vessel wall)
- Malapposition length (mm): Malapposition length is defined as the longitudinal length of the OCT pullback with consecutive cross sectional frame with at least 1 malapposed strut in every frame. (Every frame interval is 0.2 mm.)
- Longest malapposition distance (mm): Longest malapposition distance is defined as the longest distance from lumen contour to malapposed strut in each malapposition length.
- Identification of the occurrence of segments with malapposition greater than 20 microns in length (%).

Lumen Quantification

- Lumen area ($mm^2$): Lumen area is defined as an inside area of luminal surface in cross sectional frame within stented segment. Lumen area of all analyzable cross sectional frames is measured. Maximum, minimum, and mean lumen area are collected in each pullback.
    - Stented segment is defined as the segment from distal stent edge to proximal stent edge.
    - Distal stent edge is defined as the first frame with stent struts visible in 3 out of 4 quadrants.
    - Proximal stent edge is defined as the last frame with stent struts visible in 3 out of 4 quadrants.
- Lumen diameter (mm): Lumen diameter is defined a diameter of the lumen area. Lumen diameter of all analyzable cross sectional frames in stented segments is measured. Maximum, minimum, and mean lumen diameter are collected in each pullback.

- Lumen volume ($mm^3$): Lumen volume is defined as inside volume of luminal surface within stented segment. Lumen volume is calculated from lumen area and length of stented segment in each pullback.
- Reference area ($mm^2$): Reference area is defined as an inside area of luminal surface in cross sectional frame within reference segment.
    - Distal reference segment is defined as the segment of 5.0 mm distal from distal stent edge.
    - Proximal reference segment is defined as the segment of 5.0 mm proximal from proximal stent edge.
    - Reference area of all analyzable cross sectional frames in distal and proximal reference segment is measured. Maximum, minimum, and mean reference area are collected in each pullback.
- Reference diameter (mm)
    - Reference diameter is defined as a diameter of the reference area.
    - Reference diameter of all analyzable cross sectional frames in distal and proximal reference segment is measured.
    - Maximum, minimum, and mean reference diameter are collected in each pullback.
- Reference volume ($mm^3$)
    - Reference volume is defined as inside volume of luminal surface within reference segment.
    - Reference volume is calculated from reference area and length of reference segment in each pullback.

Stent Expansion

- Stent expansion (%) vs reference vessel diameters. Optimal stent expansion is defined based on established intravascular ultrasound criteria of optimal stent expansion (in-stent minimal lumen area ≥ 90% of the average reference lumen area or ≥ 100 % of lumen area of the reference segment with the lowest lumen area).

Intrastent Residual Stenosis

- Maximal stenosis within the stent. The region of interest/reference will be defined between the proximal and distal stent edges, and the minimal cross-section area will be automatically detected.

Minimal Lumen Area

- Identification of cases with minimal lumen area < 4 $mm^2$.

Stent Length

- Imaged stent length (mm): Imaged stent length is defined as the length from distal stent edge to proximal stent edge in the OCT pullback.

Edge Dissection

- Edge dissection: Edge dissection is defined as a disruption of the luminal vessel surface in the distal or proximal reference segment.
- Any dissection on adjacent stent edge is documented in each pullback.
- Dissection length (mm): Dissection length is defined as longitudinal length with dissection on adjacent stent edge.

Thrombus

- Presence of thrombus: Thrombus is defined as intraluminal mass ≥ 200 µm, with no direct continuity with the surface of the vessel wall or a highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing.

Stent Deformation/Gap

- Stent elongation or compression will be evaluated primarily by comparing the longitudinal stent length vs the nominal size. 3D reconstructions may be informative as well as detail angiographic review.
- Stent gap will be defined as the presence of any cross-section with at least 2 quadrants without any stent strut in a region of supposed overlap.

Presence of Neoatherosclerosis (Figure 15)

- Qualitative analysis of the intrastent material will be performed in order to differentiate between homogeneous predominantly fibrotic tissue (neointima) vs the presence of neoatherosclerosis, defined as tissue with characteristics suggestive of lipid and/or calcium.

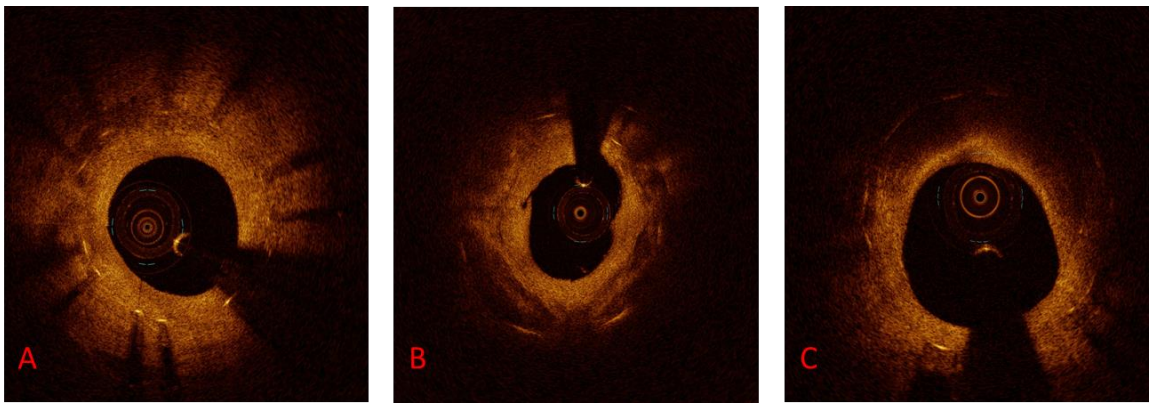



**Figure 15. Presence of Neoatherosclerosis**

A=NIH; B=neoatherosclerosis with predominantly calcified tissue, C=neoatherosclerosis with predominantly lipid tissue.

Presence of Fibrin (Figure 16)

- Semi-quantitative approach for detecting fibrin by measuring the optical density (OD) of the tissue will be applied in representative frames of the proximal, mid, and distal thirds of the stent. Values of OD < 0.6 will be considered as positive for the presence of fibrin.

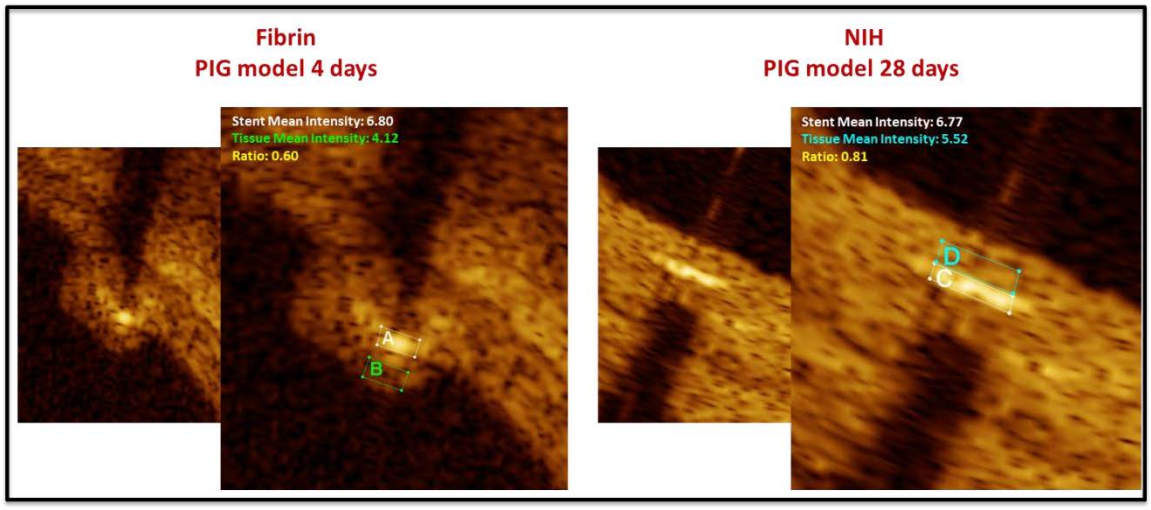



**Figure 16. Presence of Fibrin**

Optical density (pixel intensity) of the tissue covering the stent struts normalized for the optical density of the stent struts. Optical density $=PI_{tissue}/PI_{strut}$ blooming.

# 17. APPENDIX 2: INSTRUCTIONS FOR USE/INVESTIGATOR BROCHURE

Combo™ Bio-engineered Sirolimus Eluting Stent™ (Combo Stent) Instructions for Use ENGLISH

**Not available for sale in the U.S.A.**

Sterile. Sterilized with ethylene oxide gas. Non-pyrogenic. Do not use if package is open or damaged. Use prior to the "Use By" date (UBD) specified on the package. Store device in a dry, dark, cool area. Store below 25°C (77°F); excursions permitted to 40°C (104°F) maximum.

**DEVICE DESCRIPTION**

The Combo Stent™ is a coronary balloon expandable vascular prosthesis. The Combo Stent consists of a 316L stainless steel alloy coated with a biocompatible, biodegradable polymer containing sirolimus (also known as rapamycin). Covalently attached to this matrix is a layer of murine, monoclonal, anti-human CD34 antibody. The antibody specifically targets CD34+ cells in circulation. Endothelial progenitor cells (EPCs) are CD34+. This stent is supplied premounted on a delivery catheter.

**DELIVERY SYSTEM DESCRIPTION**

The Combo Stent is mounted on a low-profile rapid exchange percutaneous transluminal coronary stent delivery catheter with a working length of 138 cm. The balloon is inflated and the stent is deployed by injecting diluted contrast medium solution through the trailing hub of the catheter. The guidewire lumen is accessed through the guidewire exit port, which is located nominally 25cm proximal to the leading tip of the catheter. A guidewire with a maximum diameter of 0.014" may be inserted through the guidewire exit port. The delivery catheter has two shaft markers (90 and 100 cm from the distal tip) that indicate the relative position of the delivery catheter to the guiding catheter. The delivery system has two radiopaque marker bands; the inside edges delimit the working length of the balloon. The stent is mounted on the balloon between the marker bands.

**INDICATIONS**

The Combo Stent is indicated for use in a group of selected patients eligible for balloon angioplasty with symptomatic ischemic heart disease due to de novo and/or restenotic coronary artery lesions. The Combo Stent is indicated for treatment of atherosclerotic or restenotic lesions with a length less than the nominal stent length in coronary arteries having reference vessel diameters of the Combo Stent expanded diameter following primary inflation.

**CONTRAINDICATIONS**

The Combo Stent is contraindicated for use in the following patient types:

- Patients with allergies to required procedural medications, stainless steel alloy and/or sirolimus.
- Patients who have previously received murine therapeutic antibodies and exhibited sensitization through the production of Human Anti-Murine Antibodies (HAMA).
- Patients in whom anti-platelet and/or anticoagulant therapy is contraindicated.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

**WARNINGS**

Use of this type of device is known to be associated with the following risks:

- Coronary or stent thrombosis.
- Increased vascular and/or bleeding complications (due to anticoagulation).
- Increased length of hospital stay relative to length of stay for coronary balloon angioplasty alone. Judicious selection of patients to receive this device rather than balloon angioplasty alone is strongly advised.
- Infection secondary to contamination of the stent which may lead to thrombosis, pseudoaneurysm, or vessel rupture.
- Implantation of the stent may cause spasm, thrombosis, and/or distal embolization. The stent could migrate from the site of implantation down the arterial lumen.
- Excessive stretching of the artery may cause rupture and life-threatening bleeding.
- Stents can be partially deployed in particularly resistant lesions.
- Stent dislodgment from the balloon surface during deployment and/or migration from the target site post-deployment can occur.

- Patients with an unknown hypersensitivity to stainless steel alloy may suffer an allergic reaction to this implant.
- Use of this product may be associated with sensitization towards murine antibodies.
- Long term clinical outcome for this permanent implant is unknown at present.
- This device is designed and intended for single use only. DO NOT reprocess, resterilize and/or reuse. Reuse of single-use devices creates a potential risk of patient or user infections. Reuse may lead to impairment of functional performance. Infections and/or limited performance of the device may lead to injury, illness or death of the patient.

**DRUG INFORMATION**

Sirolimus (Rapamycin), the active ingredient in Rapamune® (Wyeth), has been tested extensively. The following is a summary of data available. See FDA.gov for complete drug safety information.

**MECHANISM OF ACTION**

Sirolimus inhibits T-cell activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. Sirolimus binds to the immunophilin known as intracellular FK-binding protein (FKBP) 12. The rapamycin-FKBP complex binds to and inhibits activation of the mammalian Target of Rapamycin (mTOR), resulting in cell cycle arrest in the late G1-phase and preventing progression to the S-phase.

**PHARMACOKINETICS OF THE COMBO STENT**

The pharmacokinetics of sirolimus when released from the Combo Stent were studied in a porcine model. Each animal had n=5 stents per time point implanted. Whole blood sirolimus PK parameters for this study are outlined below. Pre-clinical studies show that an equivalent amount of drug is delivered to blood vessels compared to commercially available sirolimus-eluting stents. However, the Combo Stent releases less drug into the blood and downstream organs.

**Table 1. Pharmacokinetic Analysis**

| **Pharmacokinetics Analysis for the Combo Stent** | | | |
|---|---|---|---|
| **$r_2$** | **0.994** | **$K_{el}$** (1/h) | **0.0028** |
| **$t_{1/2}$** (h) | **247.0** | **$t_{max}$** (h) | **1.00** |
| **$C_{max}$** (ng/mL) | **3.98** | **$t_{last}$** (h) | **672** |
| **$C_{last}$** (ng/mL) | **0.39** | **$AUC_{last}$** (mg/mL*h) | **827.4** |
| **MRT** (h) | **220.1** | | |
| **Abbreviations: $r_2$** – correlation coefficient of fit of the concentrations during the elimination phase based on a semi-log plot; **$K_{el}$** – elimination constant; **$t_{1/2}$** – terminal half-life ; **$t_{max}$** – time to maximum concentration; **$C_{max}$** – maximum concentration; **$t_{last}$** - time to last quantifiable sirolimus concentration (<10 pg/mL); **$C_{last}$** – last quantifiable sirolimus concentration; **$AUC_{last}$** – observed area-under-the-time-concentration curve; **MRT**- mean residence time | | | |

**DRUG INTERACTIONS**

Drug interaction studies have not been conducted with the Combo Stent. Sirolimus is known to be a substrate for cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations.

It is known from studies of oral sirolimus administration that the following drugs and foods that may interact with sirolimus:

Cyclosporine

Strong Inducers of CYP3A4 and P-gp

- Rifampin
- Rifabutin

Strong Inhibitors of CYP3A4 and P-gp

- Ketoconazole
- Voriconazole
- Itraconazole
- Erythromycin
- Telithromycin
- Clarithromycin

Inducers of CYP3A4 and P-gp

- Carbamazepine
- Phenobarbital

- Phenytoin
- St. John's Wort (Hypericum perforatum)
- Rifapentine

Inhibitors CYP3A4 and P-gp

- Bromocriptine
- Cisapride
- Danazol
- Fluconazole
- Metoclopramide
- Troleandomycin
- Grapefruit Juice
- Cimetidine
- Clotrimazole
- Diltiazem
- HIV-protease inhibitors (e.g., ritonavir, indinavir)
- Nicardipine
- Verapamil

**MUTAGENESIS, CARCINOGENICITY AND REPRODUCTIVE TOXICITY**

Oral sirolimus has been tested extensively (see labeling for Rapamune, Wyeth). Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at sirolimus doses 30 to 120 times higher than the 2mg daily clinical dose (adjusted for body surface area), there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface area), hepatocellular adenoma and carcinoma in males were considered sirolimus related. In the 104-week rat study, at dosages equal to or lower than the clinical dose of 2mg daily (adjusted for body surface area), there were no significant findings.

Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay.

Fertility was diminished slightly in both male and female rats following oral administration of sirolimus at doses approximately 10 times or 2 times, respectively, the clinical dose of 2mg daily (adjusted for body surface area). In male rats, atrophy of testes, epididymides, prostate, seminiferous tubules and/or reduction in sperm counts were observed. Reduction of sperm count in male rats was reversible upon cessation of dosing in one study. Testicular tubular degeneration was also seen in a 4-week intravenous study of sirolimus in monkeys at doses that were approximately equal to the clinical dose (adjusted for body surface area).

**PREGNANCY**

Pregnancy Category C: There are no adequate sirolimus or Combo Stent related studies in pregnant women. Effective contraception should be initiated before implanting a Combo Stent and continued for 1 year after implantation.

**LACTATION**

It is unknown whether sirolimus is excreted in human milk. A decision should be made whether to continue nursing or implant the Combo Stent.

**PRECAUTIONS**

- Only physicians who have received appropriate training should perform implantation of the stent.
- Use of this product should be limited to hospitals where emergency coronary artery bypass graft surgery can be quickly performed in the event of a potentially injurious or life-threatening complication.
- The Combo Stent is intended for single use only. Under no circumstances should a Combo Stent or any part thereof be resterilized or reused.
- All equipment required for the implantation of this stent must be carefully examined prior to use to verify proper function.
- Do not remove the stent from its delivery catheter as removal may damage the stent and/or lead to stent dislodgement. The Combo Stent and its delivery catheter are designed for use as a single unit. The Combo Stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through rotating hemostasis valve and guiding catheter hub.

- When the delivery catheter is exposed to the vascular system, it should be manipulated only while under high-quality fluoroscopic observation. If resistance is met during manipulation, determine the cause of the resistance before proceeding. Excessive manipulation of the stent delivery system may cause dislodgment of the stent from the delivery catheter. Do not re-straighten a kinked hypotube; straightening a kinked hypotube may result in breakage.
- An unexpanded stent should be introduced into the coronary arteries one time only. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the unexpanded stent back into the guiding catheter.
- For deployment of the stent, use a mixture of low viscosity contrast media and sterile saline. Do not inflate the delivery system with air or any gaseous media.
- Balloon pressure should not exceed the rated burst pressure of the delivery catheter. Use of a pressure monitoring device is required to prevent over-pressurization.
- Do not attempt to reposition a partially deployed stent. Attempted repositioning may result in severe vessel damage.
- When re-crossing a recently implanted stent, care should be taken to assure the guidewire is placed within the lumen and not between the stent and the vessel wall. Otherwise, inadvertent dislodgement of the stent may result, leading to faulty positioning.
- When stents from various manufacturers are chosen to complete the treatment of a single vessel, only stent materials of similar composition should be used.
- Whenever possible, when more than one stent is deployed in sequential lesions in a single coronary artery, the most distal stent should be deployed first.
- Do not use oil-based contrast medium, organic solvents or alcohols; there is a possibility of catheter leak, damage, or loss of lubrication.
- The safety and effectiveness of the use of the Combo Stent has not been established in the following patient populations:
    - Patients with other Drug Eluting Stents
    - Women who are pregnant or who are of childbearing potential who do not use adequate contraception.
    - Patients with unresolved thrombus at the lesion site.
    - Patients with coronary artery reference vessel diameter <2.5 mm or > 4.0 mm.
    - Patients with lesions located in saphenous vein grafts, ostial target lesions, chronic total occlusions, or lesions in the unprotected left main coronary artery.
    - Patients with diffuse disease or poor flow distal to the identified lesions.
    - Patients with tortuous vessels in the region of the obstruction or proximal to the lesion.
    - Patients with a recent acute myocardial infarction where there is evidence of thrombus or poor flow.


**MAGNETIC RESONANCE IMAGING**

Non-clinical testing has demonstrated that the Combo Stent is MR Conditional for single and overlapping lengths up to 61 mm. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 and 3.0 Tesla only.
- Maximum spatial gradient magnetic field of 720 gauss/cm (7.2 T/m) or less.
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode).

Under the scan conditions defined above, the Combo Stent is expected to produce a maximum temperature rise of 5.3 °C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 11 mm from the Combo Stent when imaged with a gradient echo pulse sequence and a 3.0 Tesla MRI system. The artifact does obscure the device lumen.

**POTENTIAL COMPLICATIONS AND ADVERSE EFFECTS**

Potential complications and adverse effects (in alphabetical order) which may be associated with percutaneous coronary treatment procedures including use of this product include, but are not limited to, the following:

- Acute or subacute closure of the coronary artery
- Allergic reactions to stainless steel alloy or contrast medium
- Aneurysm/pseudoaneurysm
- Arrhythmias, including ventricular fibrillation
- Arteriovenous fistula
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent thrombosis
- Coronary vessel dissection, perforation, rupture or injury
- Death
- Distal embolization of stent
- Drug reactions, including to antiplatelet agents, anticoagulation agents or contrast media
- Emergent coronary artery bypass surgery
- Failure to deliver the stent
- Fever
- Hemorrhage or bleeding complications which may require transfusion
- Hypotension/hypertension
- Immunologic reaction to murine antibodies
- Infection
- Myocardial ischemia/infarction
- Peripheral ischemia
- Renal failure
- Restenosis of stented segment
- Shock/pulmonary edema
- Stable or unstable angina
- Stent migration
- Stroke/cerebrovascular accident
- Target vessel and/or lesion revascularization
- Total occlusion of the coronary artery
- Vascular complications including hematoma, pseudoaneurysm or hemorrhage at the insertion site, which may require vessel repair

**INDIVIDUALIZATION OF TREATMENT**

The risks and benefits described above should be considered for each patient before using the Combo Stent. Patient selection factors to be assessed should include judgment regarding risk of antiplatelet therapy.

Antiplatelet drugs should be used in combination with the Combo Stent. Physicians should use the information from the REMEDEE clinical trials, coupled with the recent literature on current medical practice on coronary stent procedures, including drug eluting stents, and balloon dilatation, such as the practice guidelines published by the European Society of Cardiology, American College of Cardiology, and the American Heart Association and the specific needs of individual patients to determine the specific antiplatelet/anticoagulation regimen to be used for their patients in general practice.

It is very important that the patient is compliant with the post-procedure antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medications could result in a higher risk of thrombosis, myocardial infarction or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a drug eluting stent and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with premature discontinuation of antiplatelet therapy. Patients, who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding, should be monitored carefully for

cardiac events and, once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physician.

**RECOMMENDED ADDITIONAL MATERIALS**

- Low-viscosity contrast media diluted 1:1 with sterile saline
- Appropriate vascular sheath introducer and dilator set
- Guiding catheter of appropriate size, tip shape and length (I.D. of at least 0.057" is recommended for 2.5 – 3.5 mm diameters and 0.068" for 4.0 mm diameter devices)
- Guidewire with maximum diameter of 0.014"
- Rotating Hemostasis Valve (I.D. of at least 0.096" is recommended)
- Inflation device with manometer readings from 0 to 20 atm in 1 atm increments
- Appropriately sized PTCA pre-dilatation catheter
- Flushing tool
- 20cc syringe
- Sterile normal saline

**INSPECTION PRIOR TO USE**

Carefully inspect the sterile package before opening. Do not use the product after the "Use By" date (UBD). Do not use if any defects are noted.

**CLINICAL PROCEDURE**

Use of a coronary stent and delivery system requires advanced angioplasty skills. The following instructions provide technical guidance but do not obviate the need for the physician to have undergone formal training in the use of coronary stents and delivery systems.

1. Remove the inner pouch from the outer foil pouch. **Note**: The foil pouch is not a sterile barrier. The outside surface of the inner pouch is NOT sterile.
2. In a sterile environment, slowly remove the Combo Stent from the inner pouch and place on a sterile surface. Note: Use caution not to damage product when removing it from the hoop dispenser.
3. Prior to use of the Combo Stent, all equipment should be carefully examined for defects. Examine the Combo Stent for kinks or bends in the catheter and damage to the stent. Do not use any defective equipment.
   **Caution: Do not roll the stent between fingers and do not wipe down the mounted stent or balloon as this may cause dislodgement/damage to the stent and/or coating.**
4. Utilize standard techniques and the manufacturer's instructions to place the vascular sheath, guiding catheter, and guidewire.
5. Stent Delivery System Preparation:
   a. Visually inspect the crimped stent for uniformity, protruding struts and position of the stent ends relative to the balloon marker bands. **Note:** The stent should be centered between the marker bands. Do not use defective product.
   b. Evacuate air from the balloon segment by performing the following steps:
      i. Fill the 20cc syringe or the inflation device with approximately 4cc of the recommended contrast media and attach the syringe to the catheter hub. Orient the catheter with the leading tip and the balloon pointing in a downward vertical position.
      ii. Apply negative pressure and aspirate for 15 seconds. Do not flick the balloon as this may cause damage to the stent. **Note:** If the delivery catheter does not maintain negative pressure, check all connections. If connections are secure and the catheter still does not maintain negative pressure, do not use.
      iii. Slowly release the vacuum to neutral, allowing contrast media to fill the shaft of the delivery catheter.
      iv. Disconnect the syringe or inflation device from the inflation port of the delivery catheter.
      v. Remove all air from the syringe or inflation device barrel.
      vi. Reconnect the syringe or inflation device to the port of the dilatation catheter. Maintain negative pressure on the balloon until air no longer returns to device.
      vii. Slowly release the device pressure to neutral.

c. Disconnect the 20cc syringe (if used) and connect the inflation device to the inflation port of the balloon catheter without introducing air into the system.
d. **Note:** All air must be removed from the balloon and displaced with contrast media prior to inserting into the body, otherwise complications may occur. Repeat steps 5b as necessary.
e. Remove the protective mandrel from the guidewire lumen by pulling on the looped end of the mandrel.
f. Flush guidewire by attaching a syringe filled with sterile heparinized normal saline to a flushing tool.
g. Insert the flushing tool into the distal end of the balloon catheter and inject the saline into the guidewire lumen. Flushed solution should be seen coming out of the guidewire exit port located approximately 25cm from the leading tip of the balloon.

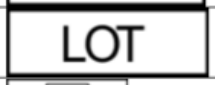
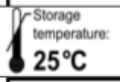
**USE OF THE COMBO STENT**

1. Soak the entire stent in sterile heparinized normal saline for 30 seconds with light agitation. **Note:** Do not wipe the balloon/stent assembly as this may cause dislodgment/damage to the stent and/or coating.
2. Ensure hemostasis valve is properly opened and advance the Combo Stent over the guidewire to the treatment site.
3. Position the stent across the lesion using the radiopaque markers on the balloon. The stent is centered between the two radiopaque markers. **Caution: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system, the entire system (SDS, guiding catheter, and guidewire if necessary) should be removed as a single unit.**
4. Inflate the delivery catheter balloon (see product labeling for compliance table), expanding the stent to optimize strut apposition against the arterial wall. If necessary, the delivery catheter can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. Do not exceed the rated burst pressure of the balloon. **Caution: Under-expansion of the stent may result in under-deployment and subsequent stent movement. Care must be taken to properly size the stent to ensure complete apposition of the stent to the artery wall following balloon deflation.**
5. After stent deployment, deflate the balloon catheter and withdraw the SDS while maintaining the position of the guidewire and negative pressure on the balloon. **Caution: Do not begin withdrawal of the SDS until the balloon is fully deflated. Incomplete deflation may cause increased balloon catheter withdrawal forces. Using fluoroscopy, observe the withdrawal of the SDS to ensure that the catheter does not catch on to the stent. If resistance is encountered, carefully move the SDS forward, rotate, and then gently withdraw the SDS.**
6. Using angiography, with or without intravascular ultrasound, confirm the position of the stent within the artery and its proper apposition against the arterial wall. **Note:** Implantation requires that the stent be in full contact with the vessel wall, covering the lesion. In addition, the optimum diameter should be 100 to 110% of that of the reference vessel segment.
7. If the deployed stent size is still inadequate with respect to the reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. Deployed stents should not be left under-dilated. **Caution: Do not dilate the stent beyond the following limits.**

| Nominal Stent Diameter (mm) | Dilatation Limit (mm) |
|---|---|
| 2.5, 2.75 | 3.25 |
| 3.0, 3.5, 4.0 | 4.50 |

8. Following angiographic confirmation of complete and adequate stent expansion, remove the guidewire, guiding catheter, and introducer sheath using the technique of choice. **Caution: Should unusual resistance be felt at any time during removal of the SDS, the entire system (SDS, guiding catheter, and guidewire if necessary) should be removed as a single unit.**
9. Discard all disposable devices used during this procedure per local requirements for medical device waste disposal.

**EXPLANATION OF SYMBOLS**

| | |
|---|---|
| Balloon Diameter |   |
| Stent Length |   |
| Catalog Number |   |
| Lot Number |   |
| Use By |  |
| Contents (numeral represents quantity of units inside) |   |
| Outer Packaging is Not Sterile Barrier |  |
| Guiding Catheter |  |
| Storage Temperature Below 25 °C |   |
| Sterilized Using Ethylene Oxide |   |
| Do Not Reuse |   |
| Read Instructions (IFU) Prior to Use |   |
| Do Not Resterilize |   |
| MR Conditional (static magnetic field strength of 1.5 or 3.0 Tesla) |   |

References:

The physician should consult recent literature on current medical practice on coronary stent procedures and balloon dilatation, such as the practice guidelines published by the European Society of Cardiology, American College of Cardiology, and the American Heart Association.

© 2014 OrbusNeich Medical, Inc. All rights reserved. OrbusNeich Medical, Combo, Combo Stent, and Bio-engineered Sirolimus Eluting Stent are registered trademarks of OrbusNeich Medical, Inc.