Sapphire II PRO
Sapphire II PRO US Clinical Study Protocol ∅1.0mm and 1.25mm
[NCT# NCT03052530]

Phase: US Investigational Device Exemption (IDE #G170007)

Date: February 16, 2017

Version: 1.0

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Protocol Signature Page

Sapphire II PRO US Clinical Study Protocol Ø1.0mm and 1.25mm
Protocol Number: VP-0714

Sponsor: OrbusNeich Medical

Date: February 16, 2017

Version: 1.0

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

Stephen M Powell

Sponsor Representative

23 FEBRUARY 2017

Date

DE Kandzari MD

Principal Investigator

22 February 2017

Date

Jeffrey J Popma, MD

Core Laboratory Director

3/Mar/2017

Date

PROTOCOL VERSION AND AMENDMENT TRACKING

Version	Approval Date
1.0 Initial Release	16 Feb 2017

Protocol Summary

Study Design and Rationale

A prospective, open label, multi-center, single arm, observational study designed to evaluate the acute safety and device procedural success of the Sapphire II PRO ∅1.0 and 1.25 mm PTCA dilatation catheters in subjects with stenotic coronary arteries or bypass grafts during percutaneous coronary intervention.

Sixty (60) subjects will be treated at up to 5 U.S. sites with the Sapphire II PRO ∅1.0 and 1.25 mm PTCA dilatation catheters to pre-dilate coronary arteries or bypass grafts during their index procedure. All subjects will be screened according to the protocol inclusion and exclusion criteria and will be followed through hospital discharge.

Study Summary

Name of Company	OrbusNeich Medical, Inc.
Product	Sapphire II PRO ∅1.0, 1.25 mm PTCA dilatation catheters
Protocol Number	VP-0714
Protocol Title	**Sapphire II- Pro** A prospective, open label, multi-center, single arm, observational study designed to evaluate the acute safety and device procedural success of the Sapphire II PRO ∅1.0 and 1.25 mm PTCA dilatation catheters in subjects with stenotic coronary arteries or bypass grafts during percutaneous coronary intervention.
Planned Number of Subjects and Sites	Sixty (60) subjects will be enrolled at up to 5 U.S. sites.
Primary Endpoint	Device procedural success consisting of the following: • Successful delivery, inflation, deflation and withdrawal of the study balloon • No evidence of vessel perforation, flow limiting dissection (grade C or higher) or reduction in TIMI flow from baseline related to the study balloon • Final TIMI flow grade of 3 at the conclusion of the PCI procedure
Secondary Endpoints	The following clinical endpoints will be measured through hospital discharge: 1. In-hospital Major Adverse Cardiac Events (MACE) -- All death (cardiac and non-cardiac) -- Myocardial infarction (MI) -- Target Lesion Revascularization (TLR) 2. In-hospital stent thrombosis (ST) within the target vessel 3. Clinically significant arrhythmias (requiring intervention)
	Peri-procedural endpoints: • Balloon rupture • Improvement in Minimum Lumen Diameter (MLD) following pre-dilatation with Sapphire II PRO 1.0 and 1.25 mm PTCA dilatation catheters (measured by QCA)
Randomization	Not Applicable

Follow-Up Schedule	Subjects will be followed through hospital discharge.
Required Medication Therapy	Anti-platelet medications should be prescribed according to the standard of care at each investigational site.
Clinical Inclusion Criteria	1. Subject is ≥ 18 years of age. 2. Subject or a legally authorized representative must provide written informed consent prior to any study related procedures. 3. Subject must agree not to participate in any other clinical study during hospitalization for the index procedure that would interfere with the endpoints of this study. 4. Subjects must have a single or double vessel coronary artery disease and clinical evidence of ischemic heart disease, such as stable / unstable angina or silent ischemia.
Angiographic Inclusion Criteria	5. Subject must have de novo or restenotic lesion(s) in native coronary arteries or bypass grafts that are suitable for percutaneous coronary intervention. An embolic protection device must be used in all Saphenous venous grafts (SVG) interventions performed during the index procedure. 6. A maximum of two lesions, including at least one target lesion, in up to two coronary arteries. 7. Target and non-target lesions must be located in different coronary arteries or bypass grafts. 8. Target lesion(s) must have a diameter stenosis of ≥70% by visual estimation and may include chronic total occlusions (CTO) 9. Treatment of non-target lesion, if any, must be completed prior to treatment of target lesion and must be deemed a clinical angiographic success by visual assessment.
Clinical Exclusion Criteria	1. Subject with a known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, anti-platelet medications, or sensitivity to contrast media which cannot be adequately pre-medicated. 2. Subject with known diagnosis of an acute myocardial infarction (AMI) within 72 hours prior to index procedure. 3. Subject with known pregnancy or is nursing. Women of child- bearing potential should have a documented negative pregnancy test within 7 days before index procedure. 4. Planned or actual target lesion treatment with an unapproved device, atherectomy, laser, cutting balloon or thrombectomy during the index procedure. 5. A serum creatinine level > 2.0 mg/dl within seven days prior to index procedure. 6. Cerebrovascular accident (CVA) within the past 6 months. 7. Active peptic ulcer or active gastrointestinal (GI) bleeding within the past 6 months.

	8. Subject has a known left ventricular ejection fraction (LVEF) <30% (LVEF may be obtained at the time of the index procedure if the value is unknown, if necessary)
Angiographic Exclusion Criteria	9. More than two lesions requiring treatment. 10. Unprotected left main coronary artery disease.(Greater than 50% diameter stenosis) 11. Coronary artery spasm of the target vessel in the absence of a significant stenosis. 12. Target lesion with angiographic presence of probable or definite thrombus. 13. Target lesion involves a bifurcation requiring treatment with more than one stent or pre-dilatation of a side branch >2.0 mm in diameter. 14. Non-target lesion to be treated during the index procedure meets any of the following criteria: • Located within a bypass graft (venous or arterial) • Left main location • Chronic total occlusion • Involves a bifurcation (e.g., bifurcations requiring treatment with more than 1 stent) • Treatment not deemed a clinical angiographic success

A maximum of two lesions, including at least one target lesion, may be treated during the index procedure.

Non-target lesion should be treated first and deemed a clinical angiographic success by visual assessment prior to treatment of the target lesion
The lesion identified as the Target lesion is intended to be dilated first during the index procedure with a Sapphire II PRO 1.0 or 1.25 coronary dilatation catheter

Non-Target Lesion

- A maximum of one non-target lesion (in addition to one target lesion in a target vessel) may be treated in a non-target vessel with a commercial treatment during the index procedure and must occur prior to treatment of target lesion.
- Treatment of non-target lesion must be deemed a clinical angiographic success for subjects to be eligible for enrollment into the study.
- Target and non-target lesions must be located in different coronary arteries or bypass grafts.

Target Lesion

- Lesion that is to be treated with the study device during the index procedure.
- Target lesions may be located in the same or different coronary arteries or bypass grafts.
- Target lesion composed of multiple focal lesions that can be covered with one stent will be considered as a single lesion.
- One Sapphire II PRO PTCA dilatation catheter may be used for treatment of two separate target lesions located in the same vessel. It is recommended that

treatment of the distal lesion occurs prior to treatment of a more proximal lesion. *Note:* A separate Sapphire II PRO PTCA dilatation catheter must be used for treatment of each target lesion if located in separate target vessels.

Statistical Methods

Enrollment definition	A subject is considered enrolled in the study following provision of informed consent and upon insertion of the investigational device into a guide catheter.
Follow-up Schedule	Subjects will be followed through hospital discharge
Primary Statistical Hypothesis	Not applicable as the study is observational. Descriptive statistics only.
Sample Size	A sample size of sixty (60) subjects has been chosen in order to characterize the performance of the device. All enrolled subjects will be analyzed on an intent-to-treat (ITT) basis as well as per protocol criteria.

Investigator Statement

I have read the Protocol and Appendices and agree that it contains all necessary details for me and my staff to conduct this study as described. I will provide copies of this Protocol and all pertinent information to the study to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the study devices and the conduct of the study. I will make all reasonable efforts to adhere to the study Protocol.

I will conduct the study in accordance with the Protocol, Good Clinical Practice [GCP] guidelines, as well as local regulations, and I accept respective revisions of the Protocol approved by authorized personnel of the Sponsor and by regulatory authorities. I am aware that, before beginning this study, the institutional review board responsible for such matters in the clinical facility where it will be conducted must approve this Protocol.

I agree to provide all subjects with Informed Consent forms, as required by government regulations and GCP guidelines. I further agree to report to the Sponsor any Adverse Events in accordance with the terms of the Protocol and U.S. Food and drug Administration regulation 21 Code of Federal Regulations 812.150(a)(1).

_____
Site Principal Investigator Name (*print*)

_____
Signature

_____
Date

Table of Contents

Abbreviations

AE	adverse event
CEC	Clinical Events Committee
EC	Ethics Committee
CRF	case report form
FDA	Food and Drug Administration
ICF	informed consent form
ICH	International Committee of Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MI	myocardial infarction
PCI	percutaneous coronary intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
QCA	quantitative coronary angiography
SAE	serious adverse event
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 event

1. General Information

1.1. Principal Investigator

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1.4. Angiographic Core Laboratory

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1.5. Sponsor

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2. Background Information

2.1. Description of Investigational Device

The Sapphire® II PRO Coronary Dilatation Catheter is a percutaneous transluminal coronary angioplasty (PTCA) balloon catheter with a working length of 140cm. The proximal shaft is a PTFE coated stainless steel hypotube. Hydrophilic lubricious coatings are applied to the distal section. The semi-compliant balloons are made of Nylon 12, available in diameters from 1.0 and 1.25 mm and lengths from 5-15mm, and can be inflated by injecting dilute contrast media solution through the trailing hub of the catheter. The nominal inflation pressure is 6 ATM and the rated burst pressure is 14 ATM. One radiopaque platinum marker bands is centrally located within the balloon segment. The catheter is compatible with 5F or larger guiding catheters. The internal lumen of the catheter accepts a standard 0.014 inch PTCA guidewire. The proximal portion of the guidewire enters the catheter tip and advances coaxially out the catheter proximal port, thereby allowing both coaxial guidance and rapid exchange of catheters with a single standard length guidewire. Two marked sections are located on the hypotube shaft to indicate catheter position relative to the tip of either a brachial or femoral guiding catheter. The design of this dilatation catheter does not incorporate a lumen for distal dye injections or distal pressure measurements.

Sapphire II PRO Coronary Dilatation Catheter Size Matrix ∅1.0, 1.25mm:

Balloon Diameter (mm)	Balloon Length (mm)			
	5	**8**	**10**	**15**
1.00	X	X	X	X
1.25	X	X	X	X

2.2. Summary of Findings from Non-Clinical Studies

In Vitro bench testing and characterization of the ∅1.0,1.25mm Sapphire II PRO Coronary Dilatation Catheter has been undertaken according to the requirements of the *Guidance of Industry and FDA Staff – Class II Special Controls Guidance document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters, September 8, 2010*. Likewise, biocompatibility testing was undertaken according to the recommendations found in the aforementioned PTCA guidance and *ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: evaluation and testing*.

2.3. Summary of Known and Potential Risks and Benefits

2.3.1. Potential Risks

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures and it is expected that the surgical and procedural risks will not be significantly different in this clinical trial. The Food and Drug Administration has recently downgraded balloon angioplasty catheters from class III (high risk) to class II (special controls) medical devices.[1] However, since there were not predicate devices for low-profile, small diameter balloon angioplasty catheters, then it was specified that a clinical evaluation for these small diameter devices be conducted under an Investigational Device Exemption is appropriate.[2]

The Sapphire II PRO ∅ 1.0 and 1.25 mm Coronary Dilatation Catheters received CE mark approval in the European Union on 03 FEB 2015 and market approval in Japan on 09 SEP 2014. These catheters have been commercially available outside the US since FEB 2015. An on-going, prospective post-market surveillance program continues to show these devices to be safe and effective.

2.3.2. Risk Management

The investigational plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators and adherence to the pre-determined time points to assess subject clinical status and regular clinical monitoring visits by Sponsor appointed monitoring personnel.

2.3.3. Potential Benefit

Predilatation of complex, highly stenosed lesions with low profile small diameter balloons to optimize lesion preparation prior to stent placement may facilitate procedural success. The Sapphire II PRO ∅ 1.0 and 1.25 mm Coronary Dilatation Catheters have been designed for this purpose with a hydrophilically-coated tapered distal tip, optimal balloon folding for a low crossing profile, and a low-friction inner body to reduce guidewire resistance.

2.4. Statement of Trial Conduct

This study is intended to be conducted according to Good Clinical Practice (GCP) guidelines [3], local regulatory requirements, and subject ethical treatment must be in accordance with the World Medical Association Declaration of Helsinki: Ethical Considerations for Medical Research Involving Human Subjects.[4]

2.5. Study Population

The target study population is subjects with evidence of ischemia and clinically indicated for one- or two-vessel revascularization procedures by percutaneous coronary intervention.

2.6. Summary of Relevant Literature

Three previous trials of small diameter PTCA catheters have been reported in the literature and on ClinicalTrials.gov using a similar assessment method as proposed in this study. These studies are summarized in the following table:

Study Device	Primary endpoint	Subjects	Reference
Emerge™ 1.20mm PTCA Dilatation Catheter; Boston Scientific	Device Procedural Success: (1) Successful delivery, inflation, and withdrawal of study balloon (2) No evidence of vessel perforation, flow limiting dissection, or reduction in flow from baseline from study balloon (3) Final TIMI flow grade of 3 at conclusion of PCI	60	NCT01635881[5] K130391
Mini Trek Rx 1.20mm Dilatation Catheter; Abbott Vascular	Procedural Success (1) Successful balloon delivery and cross lesion (2) Successful balloon inflation and withdrawal (3) No vessel perforation, flow-limiting dissection, reduction in TIMI flow from baseline, and no significant arrhythmias after study balloon (4) Achieve final TIMI 3 flow after PCI	71	CROSS[6] NCT 01186198 K110617
Sprinter Legend Balloon Catheter; Medtronic Vascular	Procedural Success: (1) Delivery of the balloon to the target lesion (2) No evidence of perforation or dissection (3) Restoration of normal blood flow at the end of the procedure	51	NCT00961311[7] K103095

All three small diameter angioplasty catheters were found to be associated with favorable acute safety and efficacy as Predilatation devices in balloon angioplasty procedures.

3. Trial Objectives and Purpose

To assess the acute safety and device procedural success of the 1.0 and 1.25mm diameter Sapphire II PRO dilatation catheter in its intended use for the initial dilatation of coronary artery or by-pass graft stenosis (>70% diameter stenosis).

4. Trial Design

A prospective, open label, multi-center, single arm, observational study designed to evaluate the acute safety and device procedural success of the Sapphire II PRO ∅1.0 and 1.25 mm PTCA dilatation catheters in subjects with stenotic coronary arteries or bypass grafts during percutaneous coronary intervention.

Sixty (60) subjects will be treated at up to 5 U.S. sites with the Sapphire II PRO ∅1.0 and 1.25 mm PTCA dilatation catheters to pre-dilate coronary arteries or bypass grafts during their index procedure. All subjects will be screened according to the protocol inclusion and exclusion criteria and will be followed through hospital discharge.

4.1 Selection and Withdrawal of Subjects

Once the subjects have signed the Institutional Review Board (IRB) approved study informed consent form (ICF) and research authorization forms (RA/HIPAA) and have met all general inclusion and exclusion criteria, the subjects will be considered eligible to be enrolled in the study to receive treatment with the either the 1.0 or 1.25 mm diameter Sapphire II PRO dilatation catheter. A subject is considered enrolled in the study upon insertion of the investigational device into a guide catheter. Upon enrollment, a subject identification number will be assigned to each subject in a consecutive manner within each clinical site.

4.2 Inclusion Criteria

4.2.1 Clinical Inclusion Criteria

- Subject is ≥ 18 years of age.
- Subject or a legally authorized representative must provide written informed consent prior to any study related procedures.
- Subject must agree not to participate in any other clinical study during hospitalization for the index procedure that would interfere with the endpoints of this study.
- Subjects must have a single or double vessel coronary artery disease and clinical evidence of ischemic heart disease, such as symptomatic CAD, stable / unstable angina or silent ischemia.

4.2.2 Angiographic Inclusion Criteria

- Subject must have *de novo* or restenotic lesion(s) in native coronary arteries or bypass grafts that are suitable for percutaneous coronary intervention. An embolic protection device must be used in all Saphenous venous grafts (SVG) interventions performed during the index procedure.
- A maximum of two lesions, including at least one target lesion, in up to two coronary arteries.
- Target and non-target lesions must be located in different coronary arteries or bypass grafts.
- Target lesion(s) must have a diameter stenosis of ≥70% by visual estimation and may include chronic total occlusions (CTO)
- Treatment of non-target lesion, if any, must be completed prior to treatment of target lesion and must be deemed a clinical angiographic success as visually assessed by the physician.

4.3 Exclusion Criteria

4.3.1 Clinical Exclusion Criteria

- Subject with a known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, anti-platelet medications, or sensitivity to contrast media, which cannot be adequately pre-medicated.
- Subject with known diagnosis of an acute myocardial infarction (AMI) within 72 hours prior to index procedure.
- Subject with known pregnancy or is nursing. Women of child- bearing potential should have a documented negative pregnancy test within 7 days before index procedure.
- Planned or actual target lesion treatment with an unapproved device, atherectomy, laser, cutting balloon or thrombectomy during the index procedure.
- A serum creatinine level > 2.0 mg/dl within seven days prior to index procedure.
- Cerebrovascular accident (CVA) within the past 6 months.
- Active peptic ulcer or active gastrointestinal (GI) bleeding within the past 6 months.
- Subject has a known left ventricular ejection fraction (LVEF) <30% (LVEF may be obtained at the time of the index procedure if the value is unknown, if necessary)

4.3.2 Angiographic Exclusion Criteria

- More than two lesions requiring treatment.
- Unprotected left main coronary artery disease. (Greater than 50% diameter stenosis)
- Coronary artery spasm of the target vessel in the absence of a significant stenosis.
- Target lesion with angiographic presence of probable or definite thrombus.
- Target lesion involves a bifurcation requiring treatment with more than one stent or pre-dilatation of a side branch >2.0 mm in diameter.

- Non-target lesion to be treated during the index procedure meets any of the following criteria:
  - Located within a bypass graft (venous or arterial)
  - Left main location
  - Chronic total occlusion
  - Involves a bifurcation (e.g., bifurcations requiring treatment with more than 1 stent)
  - Treatment not deemed a clinical angiographic success.

4.4 Subject Withdrawal Criteria

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 patient 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 CRF and source documents. The Primary Investigators must also report all subject discontinuations to their IRB, MEC, or HREC as defined by their Institution's procedure.

5 Treatment of Subjects

A maximum of two lesions, including at least one target lesion, may be treated during the index procedure.

Non-target lesion should be treated first and deemed a clinical angiographic success by visual assessment prior to treatment of the target lesion.

The lesion identified as the Target lesion is intended to be dilated first during the index procedure with a Sapphire II PRO 1.0 or 1.25 coronary dilatation catheter.

5.1 Non-Target Lesion

- A maximum of one non-target lesion (in addition to one target lesion in a target vessel) may be treated in a non-target vessel with a commercial treatment during the index procedure and must be completed prior to treatment of target lesion.
- Treatment of non-target lesion must be deemed a clinical angiographic success as visually assessed by the physician for subjects to be eligible for enrollment into the study.
- Target and non-target lesions must be located in different coronary arteries or bypass grafts.

5.2 Target Lesion

- Lesion that is to be treated with the study device during the index procedure.
- Target lesions may be located in the same or different coronary arteries or bypass grafts.
- Target lesion composed of multiple focal lesions that can be covered with one stent will be considered as a single lesion.
- One Sapphire II PRO PTCA dilatation catheter may be used for treatment of two separate target lesions located in the same vessel. It is recommended that treatment of the distal lesion occurs prior to treatment of a more proximal lesion.
    - *Note:* A separate Sapphire II PRO PTCA dilatation catheter must be used for treatment of each target lesion if located in separate target vessels.

Table 1.0 Schedule of Procedures

	Screening and Pre-Enrollment	Enrollment and / Pre-dilatation Procedure	Postprocedure	Discharge
Study Eligibility	X			
Informed consent	X			
Medical history	X			
Physical assessment, including vital signs	X			X
Angina class	X		X	X
12-lead ECG	X		X	
Medication review	X			X
Pregnancy test (women only)	X			
Laboratory Tests				
Serum Creatinine	X			
CBC with platelets	X			
CK Total/ CK-MB		X[a]	X[b]	X
Heart catheterization	X	X		
Pre-dilatation procedure		X		
Angiographic Assessment			X	
Review of Adverse medical events and device-related events		X	X	X

a. All subjects must have CK/CK-MB drawn within 24 hours before the procedure to determine eligibility; however, if the results are not available, eligibility may be based upon troponin values.

b. For three CK-MB draws. The first draw should be performed immediately after the procedure, the second draw should be performed 6-12 hours post–procedure and the third draw should be performed 18-24 hours post-procedure. If the subject is discharged prior to 18 hours post procedure, the third CK-MB draw should be obtained at the time of discharge

5.3 Study procedures

5.3.1 Written Informed Consent

Written informed consent must be obtained prior to initiation of any study-related procedures that are performed solely for the purpose of determining eligibility to participate in the study. Once the subjects have signed the Institutional Review Board (IRB) approved study informed consent form (ICF) and research authorization forms (RA/HIPAA) and have met all general inclusion and exclusion criteria, the subjects will be considered eligible to be enrolled in the study to receive treatment with the either the 1.0 or 1.25 mm diameter Sapphire II PRO dilatation catheter. A subject is considered enrolled in the study upon insertion of the investigational device into a guide catheter. Upon enrollment, a subject identification number will be assigned to each subject in a consecutive manner within each clinical site.

5.3.2 Within 24 hours Prior to Index Procedure

The following pre-procedure data must be collected within 24 hours prior to the index procedure for all subjects:

- Current antiplatelet, anti-thrombotic and cardiac medications
- 12-lead electrocardiogram (ECG)
- Laboratory tests:
  - Cardiac enzymes: CK Total and, if CK Total is abnormal (>1x ULN), CK-MB must be performed.
  - If CK/CK-MB results are not available; eligibility may be based upon troponin values.

5.3.3 Index Procedure

The start of the index procedure is defined as the time of sheath insertion. If a previously placed sheath is used (i.e., from an earlier diagnostic procedure), index procedure start time is defined as the time of guide catheter insertion into sheath for wiring the target lesion. During cardiac catheterization, the following procedures and assessments must be completed.

- Perform angiography according to the Angiographic Core Laboratory procedure guidelines.
- Confirm angiographic eligibility criteria.
- Treat the non-target lesion, if any, prior to treatment of the target lesion as described in Section 6.1.
- If treatment of non-target lesion was successful, continue with enrolling the subject in the study.

- Pre-dilate each target lesion, if more than one, with Sapphire II PRO dilatation catheter, and perform an angiogram during inflation of the study balloon to define the point of pre-dilatation during the index procedure.

5.3.4 Completion of Index Procedure

The completion of the Index Procedure is defined as the time the guide catheter is removed, post final angiography. The following information should be collected:

- Document procedural information, including non-target lesion (if applicable), target lesion, pre-dilatation with a study balloon, stent (if applicable) and post-dilatation (if applicable) on the appropriate CRFs.
- Record cardiac medications
- Record antithrombotic and antiplatelet medications.
- If an AE should occur, Complete AE assessment and source document collection
- Record any device deficiencies that might have occurred before or during the procedure as described in Section 8.

5.3.5 Hospital Discharge/ End of Study

The following information must be collected post index procedure:

- Clinical Status assessment including Angina assessment/Ischemia classification.
- 12-lead ECG within 24 hours after the index procedure or prior to hospital discharge, whichever occurs first.
- CK-MB: CK-MB draws must be obtained within 24 hours post-procedure. The first draw should be performed immediately after the procedure, the second draw should be performed 6-12 hours post–procedure and the third draw should be performed 18-24 hours post-procedure.
- ***Note:*** If the subject is discharged prior to 18 hours-post procedure, the third CKMB draw must be obtained at the time of discharge (it is recommended that in these cases the third CK-MB draw occurs no earlier than 16 hours post-procedure).
- Record cardiac medications including antiplatelet and anti-thrombotic therapy
- If an AE should occur, Complete AE assessment and source document collection

6 Assessment of Safety and Efficacy

Clinical events and procedural device success will be assessed per patient.

6.1 Primary end-point

The study primary end-point shall be defined as Device Procedural Success consisting of a composite of the following parameters:

- Successful delivery, inflation, deflation and withdrawal of the study balloon
- No evidence of vessel perforation, flow limiting dissection (grade C or higher) or reduction in TIMI flow from baseline related to the study balloon
- Final TIMI flow grade of 3 at the conclusion of the PCI procedure

6.2 Secondary end-points

6.2.1 Procedure-Related

The following peri-procedural end-points of study device effectiveness will be determined:

- Successful delivery, inflation, deflation, and withdrawal of the study balloon
- Absence of vessel perforation, flow limiting dissection (grade C or higher, or reduction in TIMI flow from baseline related to the study balloon
- Absence of balloon rupture of the study balloon
- Improvement in Minimum Lumen Diameter (MLD) following pre-dilatation with Sapphire II PRO ∅1.0 and 1.25 mm PTCA dilatation catheters (measured by QCA)
- And Lesion Success defined as successful PCI in the absence of vessel perforation, flow limiting dissection (grade C or higher, reduction in TIMI flow from baseline related to the study balloon, or clinically significant arrhythmias

6.2.2 In-hospital Clinical Safety and Efficacy

The following end-points will be measured through hospital discharge:

- In-hospital Major Adverse Cardiac Events (MACE), a composite of:
  - All death (cardiac and non-cardiac)
  - Myocardial infarction (MI)
  - Target Lesion Revascularization (TLR), clinically indicated
- Individual components of the MACE composite end-point
- In-hospital Target Lesion Failure (TLF) a composite of:
  - Cardiac death
  - Target vessel MI
  - TLR, clinically indicated
- In-hospital stent thrombosis (ST) within the target vessel
- Clinically significant arrhythmias (requiring intervention)

Both MI and ST are to be determined by the Academic Research Consortium (ARC) classification criteria.[8] MI to be classified into various types and include the 99th percentile upper reference limit (URL) decision limits for biomarkers employed.[9]

Myocardial Infarction will be defined as:

- Q-Wave MI: Development of new (i.e., not present on the subject's ECG before allocation) pathological Q-waves in 2 or more leads lasting 0.04 seconds with post-procedure CK-MB levels elevated above normal.
- Non–Q-Wave MI: Elevation of post-procedure CK-MB levels to >3.0 times ULN without new Q-waves.

For subjects undergoing bypass surgery, a peri-operative MI will be defined as follows:

a) Total CK-MB >5× ULN.
or
b) Presence of new pathologic Q-waves as defined above.

6.3 Angiographic Core Laboratory

Angiographic results will be submitted to an independent Core Laboratory for review and quantification of angiographic parameters (Beth Israel Deaconess Medical Center Imaging Laboratory, Boston, MA).

6.4 Clinical Events Adjudication

All clinical end-points are to be adjudicated by an independent clinical events committee using definitions consistent with the investigational plan. The CEC will develop a prospective CEC charter before any study data is adjudicated.

7 Adverse Events

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.

Death itself should not be recorded as an AE, but should only be reflected as an outcome of another specific AE. Any AE experienced by the study subjects after enrollment and up until index procedure hospital discharge must be recorded in the CRF.

7.1 Serious Adverse Events

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:
    - Planned hospitalizations for a pre-existing condition.

7.2 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, 2.3 or the device IFU.

7.3 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.

8 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 deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate CRF per the study CRF Completion Guidelines. If an AE results from a device deficiency or other device issue, the AE should be reported on the appropriate CRF.

9 Statistics

This study is designed as a single-arm observational trial. The study sample size is based upon treatment of a reasonable number of subjects with the study device to provide a reliable and meaningful assessment of device performance, rather than based upon any statistical hypothesis of an endpoint.

All statistical analyses will be performed on an intent-to-treat basis. The baseline demographic and lesion characteristics and angiographic and clinical outcomes will be evaluated by descriptive statistics. These calculations will be performed under the assumption that the data are in a normal distribution. All enrolled subjects will be analyzed on an intent-to-treat (ITT) basis as well as per protocol criteria.

10 Direct Access to Source Data/Documents

10.1 The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB review and regulatory inspections.

10.2 Subjects providing informed consent agree to allow Sponsor or designee access and copying rights to pertinent information in their medical records concerning their participation in this study. The Investigator will obtain, as part of the informed consent, permission for study monitors or regulatory authorities to review in confidence any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the patient's personal and private information.

11 Quality Control and Quality Assurance

11.1 Selection of Clinical Sites and Investigator

The sponsor will select Investigators who are qualified by training and experience, and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based upon review of a recent site assessment and the qualifications of the Primary Investigator at the site.

11.2 Protocol and Informed Consent Approval

11.2.1 Protocol/Subject Informed Consent Initial Approval

Institutional Review Board (IRB) approval for the protocol, informed consent form and other study related documents will be obtained by the Primary Investigator at each investigational site prior to participation in this trial. The approval letter must be signed by the IRB chairperson or authorized representative prior to the start of this trial and a copy must be provided to the Sponsor. In addition, the Investigator or designee will provide the Sponsor with all required documentation necessary for initial and ongoing study approval at their site.

In accordance with the investigational site IRB requirements, the Investigator will (a) advise the IRB of the progress of this trial on a regular basis until study completion; (b) obtain written IRB approval at predetermined time points to continue the trial; and (c) submit any amendments to the protocol as well as associated informed consent form changes and obtain written IRB approval obtained prior to implementation.

No investigative procedures other than those defined in this protocol will be undertaken on the enrolled subjects without the written agreement of the IRB and Sponsor.

11.2.2 Protocol/Subject Informed Consent Approval of Amendments

If the protocol and/or the subject informed consent need an amendment, the Sponsor is required to submit such amendment to the Regulatory Agencies and/or other regulating body in each participating country for approval. Approved protocol amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Primary Investigator is responsible for notifying the IRB of the protocol amendment (administrative changes) or obtaining IRB approval of the protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the protocol amendment.

Acknowledgement/approval by the IRB of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must also be provided to the Sponsor.

11.3 Protocol Deviations

It is the Investigator's responsibility to ensure that there are no deviations from the protocol in full compliance with all established procedures of the IRB/MEC/HREC. The Investigator will not deviate from the protocol for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical wellbeing of the subject. All deviations must be reported to the Sponsor. The occurrence of protocol deviations will be monitored by the Sponsor or designee. Investigators will inform their IRB/MEC/HREC of all protocol deviations in accordance with their specific IRB/MEC/HREC reporting policies and procedures.

In the event that an Investigator does not comply with the Investigator Agreement or protocol, the Sponsor will notify the Investigator of the site’s non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor’s SOP.

11.4 Training

11.4.1 Site Training

All Investigators and study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone training will take place as required. Training of Investigators and study personnel will include, but is not limited to, the investigational plan, investigational device usage, protocol requirements, randomization instructions, case report form completion and study personnel responsibilities. All Investigators and study personnel who are trained must sign a training log (or an equivalent) upon completion of the training.

Investigator and study personnel must not perform any study-related procedures prior to being trained. All Investigators must be trained to the protocol and study procedures prior to enrolling subjects.

11.4.2 Training of Sponsor's Monitors

The Sponsor's monitors or designee will be trained to the investigational plan, protocol, randomization instructions, case report forms and investigational device usage. The Sponsor or designee is responsible for the training. Training may be conducted in accordance with the OrbusNeich or their designee's SOP.

11.5 Good Clinical Practice Compliance

The trial will be conducted in compliance with the protocol, Good Clinical Practice guidelines[3], ISO 14155 (Clinical investigation of medical devices for human subjects), as well as local regulations, and applicable regulatory requirements.

11.6 Monitoring

Monitoring of the clinical study will be conducted in a detailed and orderly manner in accordance with established principles of GCP and applicable regulations. A Sponsor 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 IRB has approved protocol changes as required, confirm that appropriate subjects have been enrolled with adequate documented consent, complete records are being maintained, confirm that there is complete follow up of the safety and efficacy endpoint data appropriate and timely reports have been made to Sponsor or their delegate and the IRB, the 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, 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.

11.7 Quality Assurance Assessments

The Sponsor and/or designee may conduct periodic compliance assessments (on-site audits) at various study sites. A Sponsor representative or designee may request access to all trial records, including source documentation, for inspection and duplication during a compliance assessment. The Investigator and research coordinator must be

available to respond to reasonable requests and queries made during the compliance assessment process.

11.8 Regulatory Agency Inspection

In the event that an Investigator is contacted by a Regulatory Agency in relation to this study, the Investigator will notify the Sponsor immediately. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study. The Sponsor will provide any needed assistance in response to regulatory inspections.

11.9 Executive Committee

The Executive Committee is comprised of the Principal Investigator, Core Laboratory Director, and the Sponsor Vice-President of Clinical and Regulatory Affairs, or their designees. This committee will oversee general aspects of the study. This oversight includes review of the final protocol, ongoing monitoring of the general data collection, and review and consideration of implementation or operational issues that may arise and warrant a protocol amendment or other corrective action. The Executive Committee will also approve policy regarding presentations and/or publications.

12 Ethics

All subjects must provide written informed consent in accordance with the Site's IRB, using an IRB-approved informed consent form. The final eligibility for the trial will be the final pre-intervention angiographic qualification.

Study-specific procedures must not be performed until a signed informed consent has been obtained. The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions from the patient.

All subjects are to be fully informed and study conduct must be in accordance with the World Medical Association Declaration of Helsinki: Ethical Considerations for Medical Research Involving Human Subjects.[2]

13 Data Handling and Record Keeping

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

This study will use a CRF to collect study specific data. Before initiation of the trial, the investigator's site staff members who will be entering data will receive training on the completion of the CRF.

During monitoring visits, the site will ensure that access is available to the patient EMR for the clinical research associate (CRA), so that the CRA may verify the data entries in the CRF against source documentation.

13.1 Source Documentation

Source documents are defined as original documents, data and records. Regulations require that the Investigator maintain source documents in the subject's medical records, which confirm the data entered on the case report forms.

13.2 Case Report Form (CRF) Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the protocol and CRF completion. The Sponsor or designee will provide clinical monitoring as specified in Section 11.6 Monitoring.

13.3 Record Retention

The Investigator/Site will maintain all records pertaining to this study for three years following study completion, or as otherwise instructed by the Sponsor, or per local requirements whichever is longer. ICH guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor, or (2) providing an opportunity for the Sponsor to archive the records. The investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated as required during this study, including any data clarification forms (DCFs) received from the Sponsor or its designees. Such documentation is subject to inspection by the Sponsor or its agents, the IRB, or other regulatory agencies.

The Investigator will be notified by the Sponsor of the date of marketing approval or discontinuation of the study. The Investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any study records.

13.4 Investigational Device Management

13.4.1 Investigational Device Accountability

The Sponsor will ship the investigational device (SAPPHIRE II PRO) to the Primary Investigator (or designee) only at each site. The Primary Investigator will maintain adequate records of the receipt and disposition of the investigational device on the device inventory log or case report form (CRF), including part number, device serial number, date implanted, subject identification number and

implanting Investigator. When the enrollment phase of the study is complete, any unused investigational devices will be returned to the Sponsor and a completed Inventory Accountability Report will be generated for the site. The Inventory Accountability Report must document the disposition of all investigational devices including those that have been returned to the Sponsor. Use of any investigational device outside of the protocol (e.g. compassionate use) is strictly forbidden and may constitute grounds for removal of the Investigator/Site from the study.

13.4.2 Investigational Device Return

All unused investigational devices must be returned to the Sponsor when enrollment is complete according to the returned goods process. Investigators will be notified in writing of enrollment completion. All investigational devices or any remaining components that are associated with a device malfunction must be returned to the Sponsor.

13.5 Close-Out Visit

The close out visit will be conducted as a final review of the study and the data gathered by the site, and provide confirmation of the study record retention requirements. The Sponsor study monitor or their delegate will verify that the site's records are in order, in anticipation of a regulatory authority/Sponsor audit. Scheduling of the Close-Out Visit (COV) will be based on site enrollment, anticipated completion dates or status of the trial.

Any outstanding regulatory or monitoring issues will be reviewed. Any missing documents will be retrieved at the visit or sent in prior to the close out visit. All queries should be resolved prior to the visit or during the visit. In addition, the site will also be reminded of the following to submit a final report to the IRB prior to the close-out visit. If the site has not done so by the time of the close-out visit, it will be the responsibility of the monitor/CRA to follow-up with the site until the final report is received, or otherwise agreed upon by OrbusNeich.

14 Insurance

The study is covered under the Sponsor’s liability insurance policy. A certificate of insurance containing essential information about the insurance coverage can be provided to the study Sites upon request.

15 Publication Policy

The Sponsor of this study, recognizing the seminal importance of this investigation, is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results and tertiary analyses. At the conclusion of the study, a multicenter abstract reporting the primary results will be prepared by the Principal Investigators (in collaboration with the Executive Committee, directors of the core laboratories, clinical events committee, and Primary Investigators from high enrolling sites) and presented at

an annual scientific meeting (e.g., Transcatheter Cardiovascular Therapeutics, EuroPCR, the American Heart Association, or the American College of Cardiology). A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until both the preparation and publication of the multicenter results.

Following analysis and presentation of the primary endpoint results, active participation of all committee members, Investigators from high enrolling sites, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the Principal Investigators after review by the Executive Committee.

16 Bibliography

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[3] ICH Harmonized Guideline E6(R2) Good Clinical Practice; dated 11 June 2015

[4] WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013

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[8] Cutlip DE, Windecker S, Mehran R, et al. Clinical endpoints in coronary stent trials: A case for standardized definitions. Circulation 2007; 115:2344-2351.

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