INVESTIGATIONAL PLAN

PROSPECT II and PROSPECT ABSORB
An integrated natural history study and randomized trial

Providing Regional Observations to Study Predictors of Events in the Coronary Tree

A multicenter prospective natural history study using multimodality imaging in patients with acute coronary syndromes - PROSPECT II (Natural History Study), combined with a randomized, controlled, intervention study - PROSPECT ABSORB (Randomized Trial)

Project Identification:	**PROSPECT II and PROSPECT ABSORB**
Study Plan version:	**Version 4; 28 APR 2020**
Study Medical Devices:	**I:** TVC Imaging system by InfraReDx, Burlington, MA, USA **II:** Absorb™ Bioresorbable Vascular Scaffold by Abbott Vascular, Santa Clara, CA, USA
Study Chairs:	**David Erlinge, MD, PhD** Professor of Cardiology Department of Cardiology, Lund University Skane University Hospital SE-22185 Lund, Sweden Tel. +46 733 746165 Email: david.erlinge@gmail.com **Gregg W. Stone, MD** Professor of Medicine Director of Academic Affairs for the Mount Sinai Heart Health System Professor of Medicine (Cardiology) Professor of Population Health Sciences and Policy The Zena and Michael A. Wiener Cardiovascular Institute Icahn School of Medicine at Mount Sinai, New York, NYCo-Director of Medical Research and Education Cardiovascular Research Foundation New York, NY, USA Tel. +1-646-434-4134 Email: gregg.stone@mountsinai.org

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Coordinating Principal Investigator of PROSPECT ABSORB:	**Gregg W. Stone, MD**
Sponsor and Coordinating Academic Research Organization Representative	**Uppsala Clinical Research Center (UCR)** **Lars Wallentin, MD, PhD** Professor of Cardiology Uppsala Science Park, Hubben Dag Hammarskjölds väg 38 751 85 Uppsala universitet Tel: +46 70 631 3566
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PROTOCOL SIGNATURE PAGE

I, the undersigned, have read and understand the Investigational Plan and agree that it contains all necessary information for conducting the study.

I agree to conduct the study according to this Investigational Plan, and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice, EN ISO 14155:2011(E) and the applicable national laws and regulations.

Sponsor and Coordinating Academic Research Organization Representative — **Lars Wallentin, MD, PhD**

Signature and date: Lars Wallentin 28 April 2020

Coordinating Academic Research Organization Representative — **Ori Ben-Yehuda, MD**

Signature and date: _____

Chair and Coordinating Principal Investigator PROSPECT II — **David Erlinge, MD, PhD**

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Chair and Coordinating Principal Investigator PROSPECT ABSORB — **Gregg W. Stone, MD**

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Sponsor and Coordinating Academic Research Organization Representative	**Lars Wallentin, MD, PhD**
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Coordinating Academic Research Organization Representative	**Ori Ben-Yehuda, MD**
Signature and date:	DocuSigned by: Signer Name: Ori Ben-Yehuda Signing Reason: I approve this document Signing Time: 08-May-2020 | 12:56 EDT 6284874FD78D4261A139CA9337FB9BF6
Chair and Coordinating Principal Investigator PROSPECT II	**David Erlinge, MD, PhD**
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Sponsor and Coordinating Academic Research Organization Representative — **Lars Wallentin, MD, PhD**

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Coordinating Academic Research Organization Representative — **Ori Ben-Yehuda, MD**

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Chair and Coordinating Principal Investigator PROSPECT II — **David Erlinge, MD, PhD**

Signature and date: _____ 28 April 2020

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Signature and date: _____

PROTOCOL SIGNATURE PAGE (CONT.)

I, the undersigned, have reviewed this Investigational Plan and approve to the content from a statistical perspective.

Lead statistician Cardiovascular Research Foundation, NY	**Aaron Crowley, MA, Biostatistician**
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Statistician Uppsala Clinical Research Center	**Karin Jensevik Biostatistician**
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I, the undersigned, have reviewed this Investigational Plan and approve to the content from a statistical perspective.

Lead statistician Cardiovascular Research Foundation, NY	**Aaron Crowley, MA, Biostatistician**
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Statistician Uppsala Clinical Research Center	**Karin Jensevik Biostatistician**
Signature and date:	04 May 2020

LOCAL PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Title of the study: A multicenter natural history study using multimodality imaging in patients with unstable atherosclerotic lesions - **PROSPECT II (Natural History Study)**, combined with a randomized, controlled, intervention study **PROSPECT ABSORB (Randomized Trial)**

Local Principal Investigator: _____

Site:

_____

_____

I, the undersigned, have read and understand the Investigational Plan specified above and agree on the contents. The Investigational Plan, the Clinical Study Agreement and additional information given serve as a basis for co-operation in this study.

I agree to conduct the study according to this Investigational Plan and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice, EN ISO 1455:2011(E) and applicable national laws and regulations.

Signature and Date:

_____

_____

Name (Print)

SYNOPSIS

Study identification: PROSPECT II (Natural History Study) and PROSPECT ABSORB (Randomized Trial)
Title of study: A multicenter natural history study using multimodality imaging in patients with acute coronary syndromes - **PROSPECT II (Natural History Study)**, combined with a randomized, controlled, intervention study **PROSPECT ABSORB (Randomized Trial)**
Name of Investigational Products: TVC Imaging system (CE marked), InfraReDx Inc, Burlington, MA, USA Absorb Bioresorbable Vascular Scaffold (CE marked), Abbott Vascular, Santa Clara, CA, USA
Study Chairmen David Erlinge, MD, PhD, Department of Cardiology, Lund University, Lund, Sweden Gregg W. Stone, MD, Columbia University, New York, NY, USA
Coordinating Principal Investigators: PROSPECT II: David Erlinge, MD, PhD, Department of Cardiology, Lund University, Lund, Sweden PROSPECT ABSORB: Gregg W. Stone, MD, Columbia University, New York, NY, USA
Coordinating Academic Research Organizations: Cardiovascular Research Foundation (CRF), New York, NY, USA Uppsala Clinical Research Center (UCR), Uppsala University Hospital, Uppsala, Sweden
Sponsor: Uppsala Clinical Research Center (UCR), Uppsala University Hospital, Uppsala, Sweden
Funding support: InfraReDx Inc, Burlington, MA, USA Abbott Vascular, Santa Clara, CA, USA The Medicines Company, Basel, Switzerland
Study centers: Approximately 16 sites in Sweden, Denmark, and Norway.
Planned study period: 2014-2019 with registry follow-up for an additional 15 years (to 2034)
Objectives: PROSPECT II (Natural History Study): To test the ability of two coronary artery imaging modalities (intravascular ultrasound [IVUS] and near infrared spectroscopy [NIRS]) to identify angiographically non-obstructive high-risk (vulnerable) plaques that are subsequently responsible for unanticipated coronary events. PROSPECT ABSORB (Randomized Trial): To determine whether the Absorb Bioresorbable Vascular Scaffold (BVS) can safely enlarge luminal dimensions as measured approximately 2 years after implantation in high-risk but angiographically non-obstructive lesions with site-determined IVUS plaque burden ≥65%.
Methodology: PROSPECT II: Multicenter, prospective, natural history study of troponin positive patients with acute coronary syndromes (ACS) examined with angiography and intended for PCI for the initial culprit lesion(s). Prior to PCI all target lesions (those lesions for which PCI is planned) will be examined (if possible) by IVUS/NIRS. After successful PCI of all flow-limiting lesions determined angiographically and/or by FFR/iFR intended to be treated (termed "culprit lesions," whether responsible for the original ACS or otherwise flow-limiting and requiring PCI for complete revascularization), intravascular ultrasound (IVUS), and intracoronary near infrared spectroscopy (NIRS) will be performed over a 6-10 cm length in all three coronary arteries with a combined IVUS/NIRS catheter. Clinical and register follow-up will identify all new coronary events, the origin of which will be determined by follow-up angiography when clinically indicated. These lesions will be identified and compared to the baseline examination at a central angiographic and IVUS/NIRS core laboratory, and adjudicated to have arisen from either originally treated culprit lesions or untreated "non-culprit lesions." This will allow determination of the baseline patient-related and lesion-related variables in culprit and non-culprit lesions that increase the risk for future unanticipated cardiovascular events.

PROSPECT ABSORB (Randomized Trial): Patients with angiographically non-obstructive lesions that are not intended to undergo PCI based on the current standard of care, and that are site-assessed by IVUS to have plaque burden of ≥65% (which has previously been shown in the first PROSPECT study to identify lesions at high risk of causing future coronary events despite their non-obstructive angiographic appearance) will be randomized (1:1) to treatment with ABSORB BVS + guideline directed medical therapy (GDMT) versus GDMT alone. All such randomized patients will undergo repeat angiography and IVUS/NIRS after 25 months of follow-up.

Estimated number of subjects:
Approximately 900 patients will be enrolled in the PROSPECT II natural history follow-up study. From these 900 patients the aim is to randomize ~300 patients with a (1:1) treatment allocation to BVS + GDMT or GDMT alone in PROSPECT ABSORB. The enrolled patients who do not fulfill the criteria for PROSPECT ABSORB will be followed in PROSPECT II (~600 patients).

Patient enrollment and procedure overview:
PROSPECT II: Patients with a troponin positive ACS within the prior 4 weeks (STEMI >12 hours or NSTEMI) in whom coronary angiography is planned will be screened and asked to participate in the study. After informed consent has been obtained and prior to PCI, all target lesions (those lesions for which PCI is planned) will be examined (if possible) by IVUS/NIRS. If the patient is successfully treated with PCI of all intended culprit lesions without major procedural complication(s), all three coronary arteries will be examined with IVUS/NIRS. The IVUS results will be visible (unblinded) to the operator, but the NIRS data will be blinded. The patient will be considered formally enrolled in PROSPECT II only after PCI of all intended target culprit lesions has been successfully completed with no major complication(s), and after the study imaging catheter is passed out of the guide catheter into a coronary artery (n = approximately 900 patients). If a staged procedure is required to achieve revascularization of all intended lesions, the patient will not be enrolled until after the staged procedure has been performed without major procedural complication(s). Once enrolled, IVUS and NIRS will be performed over a 6-10 cm length in all three coronary arteries with a combined IVUS/NIRS catheter to assess both the treated culprit lesion(s) and long segments of the untreated coronary tree. Patient enrollment and 3-vessel IVUS and NIRS imaging may be performed either in the same procedure during which the culprit PCI lesion(s) are treated, or during a subsequent angiographic procedure as long as this occurs within 4 weeks of the initial ACS presentation, and after successful and uncomplicated treatment of all target lesions. If the imaging catheter passed into a coronary artery for imaging a non-culprit segment of the coronary tree and no non-culprit segment imaging data is obtained (e.g. the catheter fails and a second catheter is not used), the patient will be disenrolled (discontinued) from the study, and only be followed up for safety purposes for 30 days.

PROSPECT ABSORB: Patients in whom one or more lesions are identified with (a) an angiographically visually estimated diameter stenosis of <70%; (b) a visually estimated reference vessel diameter (RVD) of 2.5 – 4.0 mm; (c) a visually estimated lesion length ≤50 mm; d) a site determined IVUS PB ≥65%; and (e) is located at least 10 mm from a previous stent and at least 10 mm of intervening segment between the previous stent and the non-culprit lesion does not have PB >50% will be enrolled in the PROSPECT ABSORB trial and randomized 1:1 to treatment with ABSORB BVS + GDMT versus GDMT alone (n = approximately 300 patients, 150 patients in each group). For patients with multiple qualifying lesions, a single lesion will be selected for randomization prior to assignment to BVS + GDMT versus GDMT alone.

Inclusion and Exclusion Criteria:

PROSPECT II (Natural History Study) All patients

Clinical inclusion criteria (all must be present):

1. Troponin positive ACS (STEMI >12 hours or NSTEMI) occurring within the prior 4 weeks of enrollment, with symptoms consistent with acute ischemia lasting >10 minutes, intended for angiography and PCI if appropriate.

Clinical exclusion criteria (none must be present):

1. Known estimated creatinine clearance <30 mL/min.

2. Cardiogenic shock, decompensated hypotension, or heart failure requiring intubation, inotropes, intravenous diuretics, or a hemodynamic support device.
3. Patient has a known hypersensitivity, allergy, or contraindication to any of the following: Aspirin, both heparin and bivalirudin, all 3 of clopidogrel, prasugrel, and ticagrelor, or to contrast that cannot be adequately pre-medicated.
4. Refractory ventricular arrhythmias (eg, ventricular tachycardia or fibrillation) requiring either intravenous pharmacologic treatment or defibrillation during the index PCI procedure.
5. Persistent acute conduction system disease requiring temporary pacemaker insertion during the index PCI procedure.
6. Prior CABG at any time or planned CABG.
7. Patient has any medical illness (eg, cancer or severe congestive heart failure) or recent history of substance abuse that may cause non-compliance with the protocol (including follow-up angiography if enrolled in PROSPECT ABSORB), confound the data interpretation or is associated with a life expectancy less than 3 years.
8. Patient is currently enrolled in another investigational use device or drug study that has not reached its primary endpoint. If the patient is enrolled in another study that is not investigational, required visits for that trial must not interfere with the conduct of this study.
9. Prior participation in this study.

Angiographic inclusion criteria (all must be present):

1. Patient must have 1-vessel, 2-vessel, or 3-vessel disease in native coronary arteries requiring PCI.

   Note: Culprit lesions (those responsible for the ACS or which otherwise require PCI) may be either de novo, restenotic, or due to stent thrombosis.

2. Successful PCI without major complications must be performed in all intended culprit lesions, including the lesion(s) responsible for the ACS, and any other angiographically evident flow-limiting lesions that by standard of care require treatment. This may be accomplished either during a single procedure or after a staged procedure, but in the case of staging the patient may not be enrolled until after all stages are successfully completed without major complications, and this must occur within 4 weeks of initial ACS presentation.

   Note: At operator discretion FFR, iFR, or other cath lab techniques to assess physiologic lesion significance may be used to guide the decision whether to intervene on borderline lesions, but IVUS and NIRS should not be used for this purpose.

Angiographic exclusion criteria (none must be present):

1. PCI is required of the left main coronary artery or a left main stenosis is present with a visually estimated angiographic DS of >30%.
2. Angiographic evidence of severe calcification and/or marked tortuosity of the target (culprit) or a non-culprit vessel is present that would preclude the feasibility of safe imaging of at least the proximal 6 cm of all vessels.
3. The presence of a chronic total occlusion of a major epicardial coronary vessel that is not successfully recanalized during the PCI procedure, and thus would preclude intravascular imaging.

   Note: A side branch of a major vessel (eg, a diagonal branch) may be occluded as long as the major epicardial vessel (eg, the left anterior descending artery) is patent and can be imaged.

PROSPECT ABSORB (Randomized Trial):

Angiographic inclusion criteria (all must be present):

After PCI of all intended target culprit lesions, and following successful and uncomplicated imaging of at least one, but preferably all 3 coronary vessels (culprit and non-culprit) in the PROSPECT II natural history phase of the study, the patient is eligible for randomization in the PROSPECT ABSORB Trial if one or more eligible lesions are identified which meet all of the following angiographic criteria:

1. The lesion is a de novo lesion (may be located in either the target or non-target vessel)
2. The lesion has an angiographic diameter stenosis <70%, and is not intended for revascularization based on angiographic criteria and FFR/iFR.

   Note: FFR/iFR should be performed on all noncritical lesions of >40% visually estimated angiographic stenosis that are candidates for the PROSPECT ABSORB substudy.
3. The lesion has a site-determined IVUS plaque burden in at least one frame ≥65%.

   Note: Such a lesion may or may not be angiographically evident, i.e., the visually estimated angiographic diameter stenosis may range from 0% to <70%.
4. The reference vessel diameter of an eligible lesion is ≥2.5 mm to ≤4.0 mm (visually estimated) capable of being treated with a 2.5 mm, 3.0 mm, or 3.5 mm diameter BVS.
5. The lesion length of an eligible lesion is ≤50 mm (visually estimated), capable of being treated by no more than two BVS (maximum length of each BVS 28 mm), allowing for 2 mm BVS overlap and 2 mm of "normal" reference segment treatment at each edge.
6. The lesion must be at least 10 mm from a previously implanted stent/scaffold and an intervening 10 mm segment between the previous stent and the non-culprit lesion must not have plaque burden (PB) >50%
7. A bifurcation lesion may be enrolled only if the side branch is (a) ≤2.5 mm in reference vessel diameter, AND (b) has either no lesion requiring treatment, or atherosclerotic disease limited to within 5 mm of its origin from the parent vessel such that the operator believes that the side branch can be successfully treated with balloon angioplasty only (without a stent). If a stent subsequently becomes necessary, only a metallic drug-eluting stent (DES; Xience [Abbott Vascular, Santa Clara, CA] strongly recommended) may be used to treat the side branch with a T-stent technique.
8. Randomization must occur immediately after the 3-vessel imaging run in the PROSPECT II protocol. If the patient randomizes to BVS, BVS placement must be performed immediately after randomization.

   Note: If 2 or more lesions meeting eligibility criteria are present, only one may be randomized. Priority should be given to an eligible lesion not in a culprit vessel. *In general, the lesion most proximal in the coronary tree and supplying the greatest amount of myocardium should be randomized.* The CASS segment of this lesion will be identified prior to randomization allocation.

Angiographic exclusion criteria (none must be present):

1. The randomized lesion cannot be within 10 mm of a lesion previously treated by PCI.
2. The randomized lesion may not be in the left main coronary artery.
3. The randomized lesion may not be an ostial LAD or ostial LCX lesion (defined as within 3 mm of the left main coronary artery).
4. The randomized lesion may not be an ostial RCA lesion (defined as within 3 mm of the aorto-ostium).
5. Angiographic evidence of severe calcification and/or marked tortuosity of the target vessel and/or lesion intended for randomization is present that would make it unlikely that the BVS could be advanced to or across the lesion or be adequately expanded.

Study follow-up:

PROSPECT II (Natural History Study)

Clinical follow-up:

Patients will be followed in the Scandinavian quality registers (eg, SWEDEHEART). Patients will undergo follow-up through register data collection and by calls by study coordinators at 1 month (30 days), 6 months (180 days), 12 months, and 24 months, assessing MACE and safety parameters. MACE will be followed in all patients throughout the whole study period until last patient has been followed for 24 months. Patients will then undergo follow-up through register data collection at yearly intervals starting at 3 years and through 15 years. Additional phone follow-up to patients may also be performed.

PROSPECT ABSORB (Randomized Trial)

Clinical follow-up:

Patients will be followed in the Scandinavian quality registers (eg, SWEDEHEART). Patients will undergo follow-up through register data collection and by calls by study coordinators at 1 month (30 days), 6 months (180 days), 12 months, and 24 months. MACE will be followed in all patients throughout the whole study period until last patient has been followed for 24 months. Patients will then undergo follow-up through register data collection at yearly intervals starting at 3 years and through 15 years, with additional phone follow-up subject to Executive Committee approval.

Angiographic follow-up:

All patients randomized in PROSPECT-ABSORB will undergo routine angiographic and 3-vessel IVUS/NIRS follow-up at 25 months; ie, 1 month after the 24 month telephone follow-up. The 25 month angiogram may be performed within a window of between 24.5 months and 28 months after enrollment.

> Note: 25-month angiographic follow-up will not be required in PROSPECT-ABSORB randomized patients who either a) have had scaffold thrombosis or in-scaffold restenosis (DS>50% as determined by the angiographic core laboratory) at any time point prior to 25 months, OR b) have had a repeat angiogram ≥12 months after enrollment and in whom IVUS/NIRS of the randomized target lesion was performed.

Primary and Major Secondary Endpoints (Outcome Variables):

PROSPECT II (Natural History Study)

Primary endpoint: Patient-level rate of non-culprit lesion-related major adverse cardiac events (NC-MACE) at the time when the last patient enrolled reaches at least 24-month follow-up defined as an event arising from an originally untreated NCL consisting of the composite of 1) cardiac death, 2) myocardial infarction, 3) unstable angina, or 4) progressive angina or anginal equivalent symptoms either 4a) requiring revascularization by CABG or PCI, and/or 4b) with ACL-confirmed rapid lesion progression.

Major secondary endpoint: Lesion level rate of NC-MACE at the time when the last patient enrolled reaches at least 24-month follow-up.

Primary safety endpoint: major complications of IVUS/NIRS imaging, defined as imaging-related death, or vessel dissection/perforation/spasm or other complication requiring percutaneous or surgical treatment (including pericardiocentesis), as adjudicated by an angiographic core lab.

PROSPECT ABSORB (Randomized Trial)

Primary efficacy endpoint: The minimum luminal area (MLA) at the randomized non-culprit lesion site in patients treated with the ABSORB BVS + GDMT compared to GDMT only measured at 25 months.

Primary safety endpoint: Target lesion failure (cardiac death, target-vessel myocardial infarction, or ischemia-driven target lesion revascularization) up to 24 months (prior to routine imaging follow-up).
Statistical methods: **PROSPECT II (Natural History Study)** Baseline demographic, clinical, angiographic, grayscale IVUS, NIRS, and outcome variables will be summarized for lesions with and without high-risk (vulnerable) plaque defined by both NIRS and IVUS as well as for the overall population. <u>Pre-specified criteria for vulnerable plaque</u>: 1) For NIRS the pre-specified cutoff is defined as the highest quartile (25%) of the maximum lipid core burden index over a 4-mm length ($maxLCBI_{4mm}$). As a secondary sensitivity analysis, a cutoff of ≥400 will be used. 2) For IVUS, plaque burden of ≥70% and/or MLA ≤4.0 mm^2 will be used as pre-specified cutoff values to identify high-risk (vulnerable) plaque, both features having been identified in the first PROSPECT natural history study as independent predictors of future MACE. These analyses will include all untreated non-culprit lesions from the register (n=~600 patients), the GDMT only arm from PROSPECT ABSORB (n=~150 patients), and the untreated non-culprit lesions from the BVS arm of PROSPECT ABSORB (n=~150 patients). Subject-level analyses will also be presented for patients with versus without lesions containing high-risk features (including core lab assessed PB ≥70%, and/or MLA ≤4.0 mm^2, and/or $maxLCBI_{4mm}$ greater than or equal to the upper quartile cutoff). Exploratory analyses at the lesion and subject level may be conducted to identify other high-risk features of vulnerable plaque and patients. **PROSPECT ABSORB (Randomized Trial)** Baseline demographic, clinical, angiographic, grayscale IVUS, NIRS, and outcome variables (including follow-up imaging data) for the randomized cohort (~300 patients) will be summarized for ABSORB BVS + GDMT versus GDMT alone as well as the overall population. Analyses will be conducted for the Safety Analysis Set (SA) and the Full Analysis Set (FAS) for patients in PROSPECT II, and for the Safety Analysis Set (SAA), Full Analysis Set (FASA) and the Per Protocol Set (PPA) for patients in the PROSPECT ABSORB randomized substudy. Note: The Intravascular Imaging (IVI) core lab analysis in the Registry (PROSPECT II) will define high-risk plaque based on PB ≥70%. At the site level, the cutoff for inclusion in PROSPECT ABSORB will be 65% to account for an observed tendency for sites to under-estimate plaque burden during acute treatment of ACS patients.

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1 BACKGROUND INFORMATION AND RATIONALE

Ischemic heart disease is the leading cause of death in the world, causing 12.2% of all worldwide deaths, a total of 7.2 million deaths each year (1). In high income countries, 16.3% of all deaths are caused by ischemic heart disease. More than 3 million people worldwide have ST-segment elevation myocardial infarctions (STEMIs) and 4 million have non–ST-segment elevation myocardial infarctions (NSTEMIs) each year. In total, 7 million acute coronary syndromes (ACS) occur each year (2).

Cholesterol accumulation in the vessel underlies the development of atherosclerosis, the underlying substrate for coronary artery disease. Cholesterol is also one of the most important factors in development of ACS, demonstrated both in large genetic studies and in intervention studies in which cholesterol-lowering therapies reduced the incidence of ACS. In autopsy studies, the most common cause of ACS is rupture and subsequent thrombosis of a thin-cap fibroatheroma (TCFA) in the coronary tree. TCFA is a metabolically active lesion consisting of an inflamed fibrous cap overlying a necrotic core consisting of cholesterol, cholesterol esters, and necrotic cellular debris (3).

The challenge is to be able to identify high-risk (vulnerable)* plaques in living subjects before they cause an ACS and to develop a pre-emptive strategy to stabilize the plaque, protect against ACS, and save lives (4). Identification and stabilization of high-risk plaque may reduce the high incidence of morbidity and mortality caused by coronary artery disease.

The PROSPECT study was a multimodality imaging natural history in 697 patients with ACS undergoing successful PCI. After successful PCI of target culprit lesions, intravascular ultrasound (IVUS) with radiofrequency IVUS (virtual histology – VH-IVUS) was performed in the proximal 6-8 cm of all 3 coronary arteries, after which patients were followed for a median of 3.4 years (5). Plaque burden (PB) ≥70% in untreated non-culprit, non-stenotic lesions was the most important plaque characteristic associated with future coronary events arising from that lesion, with an approximately 5× adjusted risk by multivariable analysis during the 3.4-year median follow-up study period. The non-culprit lesion (NCL)-related event rate in lesions with a PB ≥70% was ~10% over 3 years, despite high compliance with guideline directed medical therapy (GDMT). The importance of PB >70% as a predictor of coronary events has been confirmed in the smaller VIVA (8× increased risk) and PREDICTION trials (6,7). In PROSPECT, TCFA lesion morphology, as defined by VH-IVUS, was the second most important factor predicting NCL-related MACE, with an approximately 3.5-fold adjusted risk. Of note, approximately 23% of lesions in PROSPECT were defined as TCFAs by VH-IVUS, similar to the rate seen in pathologic studies.

Although VH-IVUS was capable of identifying high-risk NCLs in PROSPECT, interpretation of these images is difficult (requiring a core laboratory), and it is difficult with VH-IVUS to distinguish calcium from necrotic core, possibly explaining why the adjusted hazard ratio of a VH-TCFA was “only” 3.5. Intravascular imaging with near-infrared spectroscopy (NIRS) is a CE-marked technology developed for the explicit

*The terms *vulnerable* and *high-risk* are used interchangeably throughout this protocol

purpose of detecting lipids, which are present in most vulnerable plaques. NIRS has been validated in vitro to be highly specific for lipid rich plaque (LRP) detection (8). NIRS has detected LRP in ~85% of lesions responsible for ACS cases (9). More recently, an IVUS/NIRS study evaluating culprit lesions in 20 patients with STEMI found that almost all STEMI culprit lesions are characterized by a large LRP concentrated at the culprit site (9). A NIRS signature of STEMI culprit lesions, defined by a maximum lipid core burden index (LCBI) over a 4-mm length of >400, was found to be both a sensitive and specific marker for identification of the STEMI culprit segments. The maxLCBI >400 signature of a segment causing STEMI has been confirmed in a validation study of 85 STEMI patients (10). These NIRS studies are consistent with post-mortem observations implicating rupture of LRP as the cause of acute myocardial infarction and highlight the role of LRP in culprit lesions across the spectrum of ACS; however, this signature of a vulnerable plaque causing ACS needs to be confirmed in a prospective natural history study.

The Absorb bioresorbable vascular scaffold (BVS; Abbott Vascular, Santa Clara, CA) is a CE-marked, fully bioresorbable, everolimus-eluting, stent-like device manufactured of polylactic acid (PLA). Preliminary experience with this device in >500 patients with lesions more severe than these NCLs in PROSPECT has demonstrated a low rate of 1-year MACE events (<3%), with a low rate of restenosis. Within 12 months of implantation of the Absorb BVS, vasoreactivity has started to return to the vessel. Within 24 months of implantation of the Absorb BVS, only small remnants of the device are visible by sensitive techniques such as optical coherence tomography (OCT). By 3 years, the BVS has completely resorbed, leaving behind a vessel with its native architecture intact. Use of the Absorb BVS to passivate vulnerable plaques is particularly attractive given the potential for this device to be devoid from long-term adverse effects such as very late scaffold thrombosis, restenosis, and neoatherosclerosis. In addition, Absorb BVS implantation may result in a new fibrous cap forming over prior TCFAs (11), and possibly lead to a reduction in plaque burden over time. Treatment of vulnerable plaques with Absorb (especially those with large plaque burden) is thus a promising therapy to prevent death, MI, and ACS in patients at high risk for future events, such as those already presenting with ACS or with diabetes mellitus.

In conclusion, the pathophysiology of plaque rupture and identification of plaques at risk for rupture (vulnerable plaque) is complex and incompletely understood. Pathologic studies have shown that patients presenting with ACS (typically due to thrombosis of a LRP) are likely to have one or more quiescent but high-risk LRPs elsewhere in the coronary tree. In patients with ACS, these plaques tend to progress, over a 12-month period, with an increasing amount of necrotic core and decreasing minimum lumen area (12).

The present study has two components, an overall prospective observational study using multimodality imaging (PROSPECT II) that will examine the natural history of patients with unstable atherosclerotic coronary artery disease with the specific goal to establish the utility of low-risk intracoronary imaging modalities, IVUS and NIRS, to identify plaques prone to future rupture and clinical events. The randomized PROSPECT ABSORB substudy will examine whether treatment of vulnerable plaques

with the Absorb BVS plus GDMT safely increases the MLA at 24 months compared with GDMT alone.

The cutoff for inclusion in PROSPECT ABSORB will be a site-determined PB ≥65% (rather than the 70% cutoff identified in the original PROSPECT analysis (Stone et al., NEJM, 2011(5)) to account for an observed tendency for sites to underestimate plaque burden during acute treatment of ACS patients. Nonetheless, in PROSPECT, a core laboratory determined PB ≥65% was also associated with a high (7.0%) rate of MACE during 3-year follow-up, a rate which may be reduced with a bioresorbable scaffold.

2 STUDY DESIGN

The current protocol is a 2-component integrated clinical study consisting of the main PROSPECT II study (Natural History Study) and the PROSPECT ABSORB substudy (randomized trial).

PROSPECT II is a multicenter, prospective, natural history study of ACS patients undergoing standard of care angiography and PCI for treatment of the initial culprit lesion(s). Participants will be examined with IVUS and NIRS in all three coronary arteries. Clinical follow-up for up to 15 years with a minimum of 24 months for any one patient will identify new coronary events. Angiography as per standard of care is expected to be performed in >85% of patients with events during follow-up. The coronary segment(s) responsible for these events will be identified by angiography and compared to the baseline examination by the core lab. The primary endpoint will be assessed at the 24-month follow-up time period.

The substudy PROSPECT ABSORB is a multicenter, prospective, randomized, open-label study. Patients enrolled in PROSPECT II in whom one or more angiographically non-obstructive lesions are identified by IVUS with a high risk of causing future coronary events (site-determined plaque burden ≥65%) will be randomized (1:1) to treatment with Absorb BVS + GDMT or GDMT alone. Patients in PROSPECT ABSORB will undergo repeat angiography and IVUS/NIRS imaging after 25 months and clinical follow-up for up to 15 years. The primary endpoint will be assessed at the 25-month follow-up time period.

The PROSPECT II study is expected to screen 1500 patients in order to enroll approximately 900 patients. From these 900 patients the aim is to randomize ~300 patients for the PROSPECT ABSORB. The included patients that do not fulfill the criteria for PROSPECT ABSORB will be followed in PROSPECT II (~600 patients). The patients will be enrolled from approximately 16 sites in Sweden, Denmark, and Norway.

3 STUDY TIME TABLE

Subject enrollment is planned to start in Q2 2014 aiming for last patient enrolled in Q4 2017. The primary 24-month follow-up will continue until Q4 2019 or beyond,

depending on the timing of the last patient enrolled. Patients will then be followed for up to an additional 15 years, through approximately Q4 2034.

4 STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVES

PROSPECT II (Natural History Study)

To test the ability of two coronary artery imaging modalities, IVUS and NIRS, to identify angiographically non-obstructive vulnerable plaques that are subsequently responsible for future unanticipated coronary events.

PROSPECT ABSORB (Randomized Trial) Substudy

To determine whether the Absorb Bioresorbable Vascular Scaffold (BVS) can safely enlarge luminal dimensions as measured 25 months after implantation in high-risk, angiographically non-obstructive lesions with site-determined IVUS plaque burden ≥65% (roughly equivalent to core lab assessed lesions with PB 70%).

4.2 SECONDARY OBJECTIVES

PROSPECT II (Natural History Study)

1. To determine in patients with successfully treated ACS the proportion of MACE during follow-up that are attributable to recurrent disease at the originally treated culprit lesion site(s) versus those arising from previously untreated non-culprit lesion (NCL) sites.
2. To examine the association of maxLCBI$_{4mm}$ (upper quartile of all measured values) in untreated NCLs as a signature for high-risk plaques causing future ACS.
3. To examine the association of lipid core burden index (LCBI) and future NCL-related, vessel-related, and patient-related MACE.
4. To examine the association of maxLCBI$_{4mm}$ and LCBI for culprit lesion peri-PCI MACE.
5. To examine the association of maxLCBI$_{4mm}$ and LCBI at the index culprit site with future restenosis and stent thrombosis.
6. To assess the safety and procedural success of 3-vessel IVUS/NIRS imaging during PCI.
7. To identify serologic biomarkers that correlate with findings on angiographic, IVUS, and NIRS imaging and subsequent coronary events.
8. To identify genetic markers that correlate with findings on angiographic, IVUS, and NIRS imaging and subsequent coronary events.

The last two objectives will be analyzed within two separate substudies, and their respective analyses will be detailed in separate SAPs, as appropriate.

PROSPECT ABSORB (Randomized Trial)

1. To determine whether implantation of the Absorb BVS in angiographically non-obstructive lesions with high plaque burden plus GDMT compared to GDMT alone:

    a. Is safe, with a low rate of periprocedural complications.
    b. Results in significant enlargement of luminal dimensions at approximately 2-year follow-up.
    c. Results in significant plaque regression at approximately 2-year follow-up.
    d. Results in the conversion of a high-risk plaque phenotype (large lipid core plaque) to a low-risk phenotype (small or absent lipid core plaque) at approximately 2-year follow-up.
    e. Results in a low 2-year absolute rate of NCL MACE, with fewer NCL MACE than in those patients treated with GDMT only. Although this trial is under-powered for clinical events, the results will serve to inform a large pivotal randomized trial.

5 ENDPOINTS (OUTCOME VARIABLES)

5.1 PRIMARY ENDPOINTS

PROSPECT II (Natural History Study)

Patient-level rate of NCL-related MACE (NC-MACE) evaluated at the longest follow-up available, assessed at the time when the last patient enrolled reaches at least 24 months. NC-MACE is defined as an event arising from an originally untreated NCL consisting of the composite of 1) cardiac death, 2) MI, 3) unstable angina, or 4) progressive angina or anginal equivalent symptoms either 4a) requiring revascularization by CABG or PCI, and/or 4b) with ACL-confirmed rapid lesion progression.

PROSPECT ABSORB (Randomized Trial)

The MLA at the randomized NCL site in patients treated with Absorb BVS + GDMT compared to GDMT only as measured at 25 months.

5.2 SECONDARY ENDPOINTS

PROSPECT II (Natural History Study)

Major secondary endpoint: Lesion level rate of NC-MACE in all patients throughout the whole study period until last patient has been followed for 24 months.

Secondary imaging endpoints: Angiographic diameter stenosis and other qualitative and quantitative angiographic measures (eg, stent thrombosis, plaque rupture), as well as (for patients in whom it is available) plaque burden/regression and remodeling, external elastic membrane (EEM), max$LCBI_{4mm}$, LCBI, and other IVUS

and NIRS endpoints, during follow-up in culprit lesions and NCLs (and their change from baseline to follow-up).

Other secondary clinical endpoints: Total MACE, culprit lesion-related MACE, NC-MACE, indeterminate MACE and their components at the patient level, vessel level ,and lesion level, measured at 48 hours post-procedure, in-hospital, at 1 month (30 days), 6 months, 12 months, 24 months, and yearly through 15 years.

PROSPECT ABSORB (Randomized Trial)

Secondary imaging endpoints: Angiographic diameter stenosis, plaque burden/regression and remodeling, EEM, max$LCBI_{4mm}$, LCBI, NIRS plaque composition and cap thickness, and other angiographic, IVUS, and NIRS measures at 25 months in culprit lesions, NCLs, and the randomized lesions (and their change from baseline to 25-month follow-up).

Secondary clinical endpoints: Total MACE, culprit lesion-related MACE, NC-MACE, randomized lesion-related MACE, indeterminate MACE and their components at the patient level, vessel level, and lesion level measured at 48 hours post-procedure, in-hospital, at 1 month (30 days), 6 months (180 days), 12 months, 24 months, and yearly through 15 years.

5.3 SAFETY ENDPOINTS

PROSPECT II (Natural History Study)

Primary Safety Endpoint: Major complications of IVUS/NIRS imaging defined as imaging-related death or vessel dissection/perforation/spasm or other complication requiring percutaneous or surgical treatment (including pericardiocentesis), as adjudicated by an angiographic core lab**.**

Other Safety endpoints:

- In-hospital (index culprit-lesion PCI-related) MACE

PROSPECT ABSORB (Randomized Trial)

The primary safety endpoint is target lesion failure (TLF) (cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization) up to 24 months (prior to routine imaging follow-up).

- **Other Safety endpoints:** TLF measured at 1 month, 6 months, 12 months, 24 months, and possibly yearly through 15 years
- Periprocedural (Absorb BVS PCI procedure) MACE
- Scaffold thrombosis (definite or probable per ARC definition) as per CEC and Core Lab adjudication measured at 1 month, 6 months, 12 months, 24 months, and possibly yearly through 15 years
    - Temporal classification:
        - All
        - Acute (0 to 24 hours after stent implantation)
        - Subacute (>24 hours to 30 days after stent implantation)
        - Late (>30 days to 1 year after stent implantation)

- Very late (>1 year after stent implantation)

- **Measurements of Interest**

As detailed in the statistics section as well as the statistical analysis plan, multiple measurements will be made and used in the analyses and assessed for their prognostic value. These include but are not limited to:

1. Max LCBI-4mm (upper quartile and ≥400) and LCBI in 10 mm and 30 mm segments and coronary arteries not treated with PCI at inclusion.
2. Total LCBI in all coronary arteries
3. Max LCBI-4mm (upper quartile and ≥400) and LCBI in segments treated with PCI at inclusion.
4. Plaque burden ≥70%, as well as ≥65%, in coronary segments not treated with PCI at inclusion.
5. MLA <4 mm^2 in coronary segments not treated with PCI at inclusion.
6. EEM in coronary segments not treated with PCI at inclusion.
7. Remodeling in coronary segments not treated with PCI at inclusion.
8. IVUS and NIRS measures of fibrous cap thickness
9. Disease angle defined as an angle with plaque thickness>0.5mm and disease arc≥330 degree
10. Angiographic diameter stenosis, minimum luminal diameter, reference vessel diameter, and lesion length.
11. Angiographic measures of plaque rupture, including ulceration and thrombosis.

5.4 TIMEPOINTS

Event rates will be determined at the following periods: In-hospital, 1 month (30 days), 6 months (180 days), 12 months, 24 months, and then yearly (1 year = 365 days). The study follow-up will be terminated according to the decision of the Steering Committee after all patients have achieved a minimum follow-up of 2 years and a maximum of 15 years.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 SUBJECT INCLUSION AND EXCLUSION CRITERIA

6.1.1 PROSPECT II (ALL PATIENTS - NATURAL HISTORY STUDY)

Clinical inclusion criteria (all must be present):

1. Troponin positive ACS (STEMI >12 hours or NSTEMI) occurring within the prior 4 weeks of enrollment, with symptoms consistent with acute ischemia lasting >10 minutes, intended for angiography and PCI, if appropriate.

Clinical exclusion criteria (none must be present):

1. Known estimated creatinine clearance <30 mL/min.

2. Cardiogenic shock, decompensated hypotension or heart failure requiring intubation, inotropes, intravenous diuretics, or a hemodynamic support device.
3. Patient has a known hypersensitivity, allergy, or contraindication to any of the following: Aspirin, both heparin and bivalirudin, all 3 of clopidogrel, prasugrel and ticagrelor, or to contrast that cannot be adequately pre-medicated.
4. Refractory ventricular arrhythmias (eg, ventricular tachycardia or fibrillation) requiring either intravenous pharmacologic treatment or defibrillation during the index PCI procedure.
5. Persistent acute conduction system disease requiring temporary pacemaker insertion during the index PCI procedure.
6. Prior CABG at any time or planned CABG.
7. Any medical illness (eg, cancer or severe congestive heart failure) or recent history of substance abuse that may cause non-compliance with the protocol (including follow-up angiography if enrolled in PROSPECT ABSORB), confound the data interpretation, or is associated with a life expectancy less than 3 years.
8. Patient is currently enrolled in another investigational use device or drug study that has not reached its primary endpoint. If the patient is enrolled in another study that is not investigational, required visits for that trial must not interfere with the conduct of this study.
9. Prior participation in this study.

<u>Angiographic inclusion criteria</u> (all must be present):

1. Patient must have 1-vessel, 2-vessel, or 3-vessel disease in native coronary arteries requiring PCI.

   Note: Culprit lesions (those responsible for the ACS or which otherwise require PCI) may be either de novo, restenotic, or due to stent thrombosis.
2. Successful PCI without major complications must be performed in all treated culprit lesions, including the lesion(s) responsible for the ACS, and any other angiographically evident flow-limiting lesions that by standard of care require treatment. This may be accomplished either during a single procedure or after a staged procedure, but in the case of staging the patient may not be enrolled until after all stages are successfully completed without major complications and this must occur within 4 weeks of initial ACS presentation.

   Note: At operator discretion FFR, iFR, or other cath lab techniques to assess physiologic lesion significance may be used to guide the decision whether to intervene on borderline lesions, but IVUS and NIRS should not be used for this purpose.

<u>Angiographic exclusion criteria</u> (none must be present):

1. PCI is required of the left main coronary artery or a left main stenosis is present with a visually estimated angiographic DS of >30%.

2. Angiographic evidence of severe calcification and/or marked tortuosity of the target (culprit) or a non-culprit vessel is present that would preclude the feasibility of safe imaging of at least the proximal 6 cm of all vessels.
3. The presence of a chronic total occlusion of a major epicardial coronary vessel that is not successfully recanalized during the PCI procedure, and thus would preclude intravascular imaging.

    Note: A side branch of a major vessel (eg, a diagonal branch) may be occluded as long as the major epicardial vessel (eg, the left anterior descending artery) is patent and can be imaged.

6.1.2 PROSPECT ABSORB (RANDOMIZED TRIAL)

Angiographic inclusion criteria (all must be present):

After PCI of all intended target culprit lesions and following successful and uncomplicated imaging of at least one, but preferably all 3 coronary vessels (culprit and non-culprit) in the PROSPECT II natural history phase of the study, the patient is eligible for randomization in the PROSPECT ABSORB study if one or more eligible lesions are identified that meet all of the following angiographic criteria:

1. The lesion is a de novo lesion (may be located in either the target or non-target vessel)
2. The lesion has an angiographic diameter stenosis <70% and is not intended for revascularization based on angiographic criteria and FFR/iFR.

    Note: FFR/iFR should be performed on all non-critical lesions of >40% visually estimated angiographic stenosis that are candidates for the PROSPECT ABSORB substudy.

3. The lesion has a site-determined IVUS plaque burden in at least one frame ≥65%.

    Note: Such a lesion may or may not be angiographically evident, ie, the visually estimated angiographic diameter stenosis may range from 0% to <70%.

4. The reference vessel diameter of an eligible lesion is ≥2.5 mm to ≤4.0 mm (visually estimated) capable of being treated with a 2.5 mm, 3.0 mm, or 3.5 mm diameter BVS.
5. The lesion length of an eligible lesion is ≤50 mm (visually estimated), capable of being treated by no more than two BVS (maximum length of each BVS 28 mm), allowing for 2 mm BVS overlap and 2 mm of "normal" reference segment treatment at each edge.
6. The lesion must be at least 10 mm from a previously implanted stent/scaffold and an intervening 10 mm segment must not have plaque burden (PB) >50%

7. A bifurcation lesion may be enrolled only if the side branch (a) has a reference vessel diameter ≤2.5 mm, and (b) has either no lesion requiring treatment or atherosclerotic disease limited to within 5 mm of its origin from the parent vessel such that the operator believes that the side branch can be successfully treated with balloon angioplasty only (ie, without a stent). If a stent subsequently becomes necessary, only a metallic drug-eluting stent (DES; Xience [Abbott Vascular, Santa Clara, CA] strongly recommended) may be used to treat the side branch with a T-stent technique.
8. Randomization must occur immediately after the 3-vessel imaging run in the PROSPECT II protocol. If the patient randomizes to BVS, BVS placement must be performed immediately after randomization.

    Note: If 2 or more lesions meeting eligibility criteria are present, only one may be randomized. Priority should be given to an eligible lesion not in a culprit vessel. *In general, the lesion most proximal in the coronary tree and supplying the greatest amount of myocardium should be randomized.* The CASS segment of this lesion will be identified prior to randomization allocation.

Angiographic exclusion criteria (none can be present):

1. The eligible lesion cannot be within 10 mm of lesion previously treated by PCI.
2. The randomized lesion may not be in the left main coronary artery.
3. The randomized lesion may not be an ostial LAD or ostial LCX lesion (defined as within 3 mm of the left main coronary artery).
4. The randomized lesion may not be an ostial RCA lesion (defined as within 3 mm of the aorto-ostium).
5. Angiographic evidence of severe calcification and/or marked tortuosity of the target vessel and/or lesion intended for randomization is present that would make it unlikely that the BVS could be advanced to or across the lesion or be adequately expanded.

6.2 WITHDRAWAL OF SUBJECTS

A patient can be withdrawn from the natural history study and/or the randomized trial at any time if it is the wish of the patient or if it is medically necessary, as judged by the Investigator. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. Patients will consent to continued merging of data from the study database (collected up to withdrawal date) with data from the Scandinavian quality registers even if they have withdrawn from the study. If a patient decides to withdraw from the study, and if the patient agrees, he/she will be contacted in order to obtain information about the reason(s) for discontinuation and any experienced endpoint events or serious adverse device effects (see section 10). The date and reason for the withdrawal will be recorded in the case report form (eCRF).

Public databases will be used to ascertain the vital status of subjects withdrawn from the study.

7 DESCRIPTION OF DEVICES

7.1 TVC IMAGING SYSTEM

The InfraReDx TVC Imaging System is a CE-marked diagnostic intravascular imaging catheter intended for NIRS and IVUS examination of coronary arteries in patients undergoing invasive coronary angiography. The system is intended for imaging the lumen and vessel wall structures in addition to the detection of lipid core containing plaques of interest (LCP) within one automated co-registered pullback. See the Instructions For Use/User's Guide Model No. TVC-MC8, IFU0144rC in the Investigator's File.

7.2 ABSORB BIORESORBABLE VASCULAR SCAFFOLD

The Absorb BVS is a CE-marked temporary scaffold indicated for improving coronary luminal diameter that will eventually resorb and facilitate normalization of vessel function in patients with ischemic heart disease due to *de novo* native coronary artery lesions. The Absorb BVS System includes a pre-mounted polymer poly (L-lactide) (PLLA) scaffold coated with a blend of the antiproliferative drug everolimus and polymer poly (D,L-lactide) (PDLLA) in a 1:1 ratio. See latest released/effective Instructions For Use (IFU, BVSS, Absorb, International) in the Investigator's File.

8 RISK ASSESSMENT

8.1 TVC IMAGING SYSTEM

Additional imaging with IVUS may benefit patients enrolled in the study. The knowledge of vessel diameter will help operators choose the correct stent size, which in turn can reduce restenosis and stent thrombosis. There is increased risk associated with IVUS imaging; 3-vessel imaging performed in the previous PROSPECT study resulted in a 0.3% rate of dissection that caused non-fatal procedure-related myocardial infarction. The IVUS/NIRS TVC Imaging System is designed to be similar in mode of use to an IVUS catheter. The safety record of the IVUS/NIRS catheter in the over 3,000 patients in whom it has been used has been similar to that expected with an IVUS catheter. See also the IFU.

Overall the risk/benefit ratio is reasonable for the PROSPECT II study.

8.2 ABSORB BIORESORBABLE VASCULAR SCAFFOLD

In the original PROSPECT study, the per patient 24-month NC-MACE rate attributed to patients with ≥1lesion with a core laboratory-assessed PB ≥70% was 17.7% vs 6.0%

in patients with no lesions with PB ≥70%, and for PB ≥65% was 13.2% vs 5.4% in patients with no lesions with PB ≥65%. It is hypothesized that this risk may be reduced by treatment with Absorb BVS, thereby providing patients with a potential benefit. The Absorb BVS has demonstrated a favorable safety profile with only 0.6% scaffold thrombosis during the first year of placement as shown in pooled analysis of the ABSORB Cohort B and EXTEND trials (13). Overall the risk/benefit ratio is reasonable for the PROSPECT ABSORB substudy.

9 STUDY PROCEDURES (SEE ALSO APPENDIX II: TABLE OF STUDY PROCEDURES)

PROSPECT II: Patients with a troponin positive ACS within the prior 4 weeks (STEMI or NSTEMI) in whom coronary angiography is planned will be screened and asked to participate in the study. It is estimated that approximately 1500 patients will need to be screened to enroll 900 patients. After informed consent has been obtained and prior to PCI, all target lesions (those lesions for which PCI is planned) will be examined (if possible) by IVUS/NIRS. If the patient is successfully treated with PCI of all intended culprit lesions without major procedural complication(s), all three coronary arteries will be examined with IVUS/NIRS. The IVUS results will be visible (unblinded) to the operator, but the NIRS data will be blinded. **The patient will be considered formally enrolled in PROSPECT II only after PCI of all intended target culprit lesions has been successfully completed and after the study imaging catheter is passed out of the guide catheter into a coronary artery (n = approximately 900 patients).** If a staged procedure is required to achieve revascularization of all intended lesions, the patient will not be enrolled until after the staged procedure has been performed without major procedural complication(s). Once enrolled, IVUS and NIRS will be performed over a 6-10 cm length in all three coronary arteries with a combined IVUS/NIRS catheter to assess both the treated culprit lesion(s) and long segments of the untreated coronary tree. Patient enrollment and 3-vessel IVUS and NIRS imaging may be performed either in the same procedure during which the culprit PCI lesion(s) are treated, or during a subsequent angiographic procedure as long as this occurs within 2 weeks of the initial ACS presentation, and after successful and uncomplicated treatment of all target lesions.

All patients in whom a successful IVUS/NIRS of at least one major coronary artery was performed will constitute the analysis population. The angiography and the IVUS/NIRS for all included patients will be sent to the core lab according to Appendix III and the study Manual of Operations. If the imaging catheter passed into a coronary artery for imaging a non-culprit segment of the coronary tree and no non-culprit segment imaging data is obtained (e.g. the catheter fails and a second catheter is not used),, the patient will be disenrolled (discontinued) from the study, and only be followed up for safety purposes for 30 days.

All patients will be followed in the Scandinavian quality registers (eg, SWEDEHEART). Patients will undergo follow-up through register data collection and by calls by study coordinators at 1 month (30 days), 6 months (180 days), 12 months, and 24 months, assessing MACE and safety parameters. Patients will then undergo follow-up through register data collection starting at 3 years and continuing through 15

years. Additional phone follow-up may be performed as needed to obtain more complete follow-up information.

For at least the first 24 months after enrollment, and possibly for up to 15 years, every time patients are examined with coronary angiography during the follow-up period (documented in the register), the study monitor will be informed and will contact the local hospital to make sure copies of charts, lab values, examinations, and a copy of the angiogram and all diagnostic procedures performed (eg, IVUS, NIRS, OCT, FFR, iFR) are forwarded to Uppsala Clinical Research Center (UCR) and the angiographic core lab (ACL) (Cardiovascular Research Foundation [CRF]). The events will be adjudicated by the independent clinical endpoint classification group (CEC) at UCR. In parallel, the ACL will be responsible for reviewing and analyzing all repeat angiograms.

PROSPECT ABSORB: Patients in whom one or more lesions in a non-target (untreated) vessel are identified with (a) an angiographically visually estimated diameter stenosis <70%; (b) a visually estimated reference vessel diameter (RVD) of 2.5-4.0 mm; (c) a visually estimated lesion length ≤50 mm; and (d) a site-determined IVUS plaque burden ≥65% (site reading) will be enrolled in the PROSPECT ABSORB trial and randomized 1:1 to treatment with Absorb BVS + GDMT vs GDMT alone (n = approximately 300 patients; 150 patients in each group). For patients with multiple qualifying lesions, a single lesion will be selected for randomization prior to assignment to BVS + GDMT versus GDMT alone.

Patients who do not fulfill the criteria to be included in PROSPECT ABSORB (Randomized Trial) or who refuse consent for PROSPECT ABSORB will continue as part of the main study PROSPECT II (Natural History Study).

For the patients included in PROSPECT ABSORB (Randomized Trial), coronary angiography with 3-vessel IVUS/NIRS will be performed at 25-month follow-up to evaluate the randomized lesion for vascular changes and the non-randomized coronary segments for atherosclerosis progression. The 25 month angiogram can be performed within a window of between 24.5 months and 28 months after enrollment. A study flowchart and schedule of procedures are presented in Appendix II.

> Note: 25-month angiographic follow-up will not be required in PROSPECT-ABSORB randomized patients who either a) have had scaffold thrombosis or in-scaffold restenosis (DS>50% as determined by the angiographic core laboratory) at any time point prior to 25 months, OR b) have had a repeat angiogram ≥12 months after enrollment and in whom IVUS/NIRS of the randomized target lesion was performed.

Randomization at Site

For patients enrolled in PROSPECT II (Natural History Study) there is no randomization. For the substudy PROSPECT ABSORB (Randomized Trial) randomization is performed 1:1 to treatment with Absorb BVS + GDMT vs GDMT alone stratified for site. When a patient is determined to be eligible for inclusion in the study the patient will be randomized to one of the two treatment arms using sealed, opaque, consecutively numbered envelopes. For patients with multiple qualifying lesions, a single lesion will be selected prior to randomization allocation. The

randomization procedure is described in the study Manual of Operation. If the patient is assigned to BVS, the procedure must be performed immediately after randomization assignment.

Based on findings from PROSPECT I we assume that approximately a third of subjects in PROSPECT II (Natural History Study) will be eligible for randomization in PROSPECT-ABSORB. In order to maintain the power of both parts of the study, if during the conduct of the study the ratio of subjects enrolled in the main PROSPECT II study and the PROSPECT ABSORB substudy is different than the 3:1 anticipated, the Operations Committee will assess whether sufficient power is maintained in the ABSORB substudy and will consider prolonging enrollment (vs. completing the trial with fewer than 300 subjects randomized to PROSPECT ABSORB) and will be responsible for monitoring the enrollment and communicating with the sites (see Section 16.5.4 in Statistical Section for possible power scenarios).

Stenting with ABSORB BVS

Prepare the vessel:

- Avoid very small vessels (QCA RVD <2.25 mm, roughly equivalent to visual estimated 2.5 mm).
- 1:1 balloon-to-artery ratio predilatation (sized with OCT/IVUS etc.)
- The usage of a non-compliant (NC) balloon is recommended
- Enable full expansion of pre-dilatation balloon to facilitate full scaffold expansion
- Achieve a residual stenosis between 20% and 40% after predilatation

Size the vessel appropriately:

- The reference vessel diameter of an eligible lesion is ≥2.5 mm to ≤4.0 mm (visually estimated) capable of being treated with a 2.5 mm, 3.0 mm, or 3.5 mm diameter BVS.
- Use standard dose of intracoronary nitroglycerine prior to determining RVD
- Size the scaffold according to the exact vessel size based on information from vessel preparation and imaging – avoid undersizing!
- Deploy the scaffold slowly, 2 atm increments over 5 seconds, until the scaffold is completely expanded
- Maintain target deployment pressure for 30 sec. or as long as patient can tolerate

Post-dilate the scaffold:

- Obligatory post-dilatation with a NC balloon at high pressure (>16 atm)
- The nominal NC balloon diameter should be equal to or 0.25 mm or 0.5 mm larger than the nominal scaffold diameter; in no case should the nominal NC balloon diameter be >0.5 mm larger than the nominal scaffold diameter
- Ensure <10% final residual stenosis and a complete apposition of the scaffold

9.1 BASELINE ANGIOGRAPHY

Following intracoronary injection of nitroglycerin (at least 100 µg, 200 µg preferred), baseline angiography of all 3 major epicardial coronary arteries will be performed per the ACL guidelines (see Appendix III).

9.2 PROCEDURE FOR ENROLLMENT

Assessment of angiographic eligibility must be done by visual assessment prior to enrollment. Angiograms will be submitted to the ACL for analysis.

Patients are eligible for enrollment if PCI of at least one lesion has been performed and 3-vessel IVUS/NIRS is judged by the investigator to be feasible and capable of being performed safely. There may be situations where the procedure is stopped prior to the imaging device being delivered beyond the guide catheter into a coronary artery (eg, patient becomes clinically unstable, power outage). In these situations, the patient will not be considered enrolled in the study. Once the IVUS/NIRS catheter is advanced out of the guiding catheter, the patient is considered enrolled in the study.

If the imaging catheter passed into a coronary artery for imaging a non-culprit segment of the coronary tree and no non-culprit segment imaging data is obtained (e.g. the catheter fails and a second catheter is not used) the patient will be disenrolled (discontinued) from the study and only be followed up for safety purposes for 30 days.

9.3 PERCUTANEOUS CORONARY INTERVENTION (PCI)

The decision as to which lesions should undergo PCI should be made on the basis of angiography and other clinical factors, as per standard of care. FFR and iFR should be used to assess borderline lesions (angiographic stenosis ≥40%). IVUS/NIRS may not be utilized to determine the suitability of angiographically non-obstructive lesions for revascularization.

Once the target lesion(s) have been identified, IVUS/NIRS of all target lesions will be performed prior to PCI. The IVUS images are unblinded, and may be used to guide the interventional procedure as per standard of care. The NIRS images will be blinded.

The interventional procedure will be performed per the institutional standard of care. Eligible patients may then be enrolled into PROSPECT II if PCI of all attempted target culprit lesions was successful and uncomplicated.

Definition of successful PCI: Successful PCI is defined as a residual diameter stenosis of <50% in all lesions attempted and TIMI 3 flow in the target vessel.

Definition of uncomplicated PCI: PCI will be considered uncomplicated if all of the following occur: (a) the patient has had no intra-procedural chest pain lasting >10 minutes; (b) the patient has had no intra-procedural ST-segment changes lasting >10 minutes; (c) there is no angiographic evidence of sustained vessel closure, slow or no

reflow, side branch loss, distal embolization, perforation, or residual dissection (>type B); (d) the patient has not required cardiopulmonary resuscitation; (e) the patient has not had ventricular arrhythmias requiring cardioversion or intravenous medication or conduction system disease requiring temporary pacemaker insertion; (f) the patient has not had hypotension, heart failure, or respiratory failure requiring any of the following: Intubation, intra-aortic balloon insertion, or other hemodynamic support device use or requirement for intravenous pressors; (g) the patient has not had other situations that in the judgment of the investigator may result in a MACE within 30 days, including the likely diagnosis of periprocedural MI (SCAI criteria, see CEC Charter,). Successful PCI of all attempted target culprit lesion(s) must be completed before patient enrollment, and no major complications can have occurred for the patient to be enrolled in the study. If staged procedures are required for revascularization, the patient may only be enrolled after the last stage is successfully completed and as long as there were no procedural complications in either stage and the final stage is completed within 4 weeks of patient presentation with the ACS.

9.4 IMAGING FOLLOWING PERCUTANEOUS INTERVENTION

Once the patient is formally enrolled in PROSPECT II, 3-vessel IVUS/NIRS imaging must be performed in the culprit vessel(s) and all non-culprit vessel(s), including the LAD, the LCX, and the RCA. IVUS/NIRS is initially performed in the culprit vessel(s) after successful, uncomplicated intervention. Following successful PCI of the culprit vessel(s), and after injection of intracoronary nitroglycerin (at least 100 μg, 200 μg preferred), the proximal 6-10 cm of the culprit vessel (in addition to the left main coronary segment of the left coronary artery) will be imaged and recorded with the IVUS/NIRS system using automated pullback. If possible, a distal fiduciary branch should be identified as the starting point to serve as an anatomic locator. If IVUS of the culprit lesion(s) indicates that stent deployment is not optimal, additional post-dilatation may be performed at operator discretion after which a final IVUS/NIRS imaging run should be performed to document the final result.

Following final imaging and intervention in the culprit vessel(s), the proximal 6-10 cm of the non-culprit vessel(s) should be imaged with IVUS/NIRS. If the culprit lesion was in the LAD, the LCX and RCA should be imaged as the non-culprit vessel(s). If the culprit lesion was in a LCX, the LAD and RCA should be imaged as the non-culprit vessels. (In these cases imaging should progress from left to right.) If the culprit lesion was in the RCA, the LAD and LCX should be imaged as the non-culprit vessels (typically the LAD and left main coronary artery first). These additional imaging procedures should never unduly jeopardize patient safety. Note that if one of the major vessels (LAD, LCX, or RCA) has a very large side branch supplying the left ventricle (eg, a diagonal or obtuse marginal which by visual estimation is ≥3.0 mm in diameter), it is desirable to perform IVUS/NIRS imaging of a long segment of this large branch as well.

All image data (angiography and IVUS/NIRS) must be submitted to the core laboratory as detailed in Appendix III and in the study Manual of Operations.

For patients returning to the enrolling institution during the 24-month follow-up period with a cardiac event that requires cardiac catheterization, 3-vessel angiography is mandatory, and 3-vessel IVUS/NIRS imaging is strongly recommended. These images must be submitted to the core laboratory for analysis. These additional procedures should never unduly jeopardize patient safety.

9.5 CONCOMITANT MEDICATIONS

All prescribed medications will be at the discretion of the investigator taking into consideration patient safety and institutional standards of care and guidelines. Data regarding prescribed cardiac and diabetes medications will be recorded at the time of admission, during the catheterization and hospitalization, at discharge, and at the time of regularly scheduled follow-up periods. Use of the following classes of cardiac medications will be collected: Aspirin, glycoprotein IIb/IIIa inhibitors, pre- and intra-procedural anti-thrombin agents, clopidogrel, ticlopidine, prasugrel, ticagrelor, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta blockers, vitamin K antagonists, statins, and other lipid-lowering agents. GDMT (including dual antiplatelet therapy and lipid-lowering therapy) should be applied based on the appropriate ACC/AHA and ESC guidelines (eg, ACC/AHA Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease [2011 update] and ESC Management of Dyslipidemia Guidelines). In addition, guidelines for the management of patients with STEMI and ACS should be followed, including the choice of antiplatelet therapies (presently ticagrelor and prasugrel preferred to clopidogrel as P2Y12 inhibitor).

Investigational Device Accountability
The use of catheters for the InfraReDx TVC imaging system and the Abbott BVS will be documented in an accountability log and kept in the Investigator's File at each study site.

9.6 CLINICAL AND LABORATORY PROCEDURES

9.6.1 LABORATORY ASSESSMENTS

Laboratory analysis should be performed according to local clinical practice. Local measurement results of hemoglobin, creatinine, HbA1c, cholesterol, LDL, HDL, triglyceride levels, p-glucose, white blood cell count, platelet count, hs-Troponin (before and after PCI) and hs-CRP will be reported in the eCRF according to instructions.

9.6.2 BIOMARKER/GENETICS EVALUATION AND BIOBANK

Blood samples for analyses of possible biomarkers for cardiovascular disease will be obtained from all patients.

An arterial blood sample (maximum 100 mL) will be collected at baseline. The blood sample should be taken from the arterial sheath after the diagnostic angiogram to ensure all inclusion and exclusion criteria are met, but before PCI is performed.

The samples must be centrifuged and frozen in aliquots at -20°C for a maximum period of one month and then transferred to a -70°C freezer and shipped to the Core Biomarker Lab (UCR Laboratory) in Uppsala, Sweden at regular intervals. If the site does not have a -70°C freezer, samples must be shipped within the first month to the UCR Laboratory. Sampling material and a detailed sampling handling instructions will be provided by the UCR Laboratory at the study initiation visit.

A biobank will be created for explorative analysis of biomarkers possibly linked to cardiovascular disease in the circulating blood and genetic analysis will be performed also in relation to cardiovascular disease. Proteomic, lipidomic, transcriptomic, and metabolomic analysis will be performed.

9.6.3 POST-PROCEDURE AND DISCHARGE

The care of the patient in the post-procedure period and the timing of discharge will be at the discretion of the investigator. Medications at discharge will also be at the discretion of the investigator according to guidelines and local routines. GDMT is strongly recommended.

9.6.4 ONE MONTH (30-DAY) FOLLOW-UP

Telephone follow-up at 30 days (± 7 days) including:
• Data regarding any endpoint events or serious adverse device effects (see section 10), including repeat hospitalization and coronary angiography
• Use of cardiac medications (see section 9.6.)

9.6.5 6 MONTHS (180 DAYS) FOLLOW-UP

Telephone follow-up at 6 months (180 days) (±14 days) including:
• Data regarding any endpoint events or serious adverse device effects (see section 10), including repeat hospitalization and coronary angiography
• Use of cardiac medications (see section 9.6.)

9.6.6 12-MONTHS (1-YEAR) FOLLOW-UP

Telephone follow-up at 12 months (±30 days) including:
• Data regarding any endpoint events or serious adverse device effects (see section 10), including repeat hospitalization and coronary angiography
• Use of cardiac medications (see section 9.6.)

9.6.7 24-MONTHS (2-YEARS) FOLLOW-UP

Telephone or hospital visit at 24 months (±14 days) including:
• Data regarding any endpoint events or serious adverse device effects (see Section 10), including repeat hospitalization and coronary angiography
• Use of cardiac medications (see Section 9.6).

9.6.8 SWEEP FOLLOW-UP

At the time the last patient enrolled reaches 24 month follow-up, an additional registry (or medical record review) sweep will be performed in all patients.
• Data regarding any MACE events including coronary angiography will be collected

9.6.9 25 MONTHS IMAGING FOLLOW UP - PROSPECT ABSORB (RANDOMIZED TRIAL)

Three-vessel angiography and 3-vessel IVUS/NIRS should be performed at 25 months (window from 24.5 months to 28 months) in all patients after the 24-month (±2 weeks) clinical follow-up has been performed and documented.

> **Note:** 25-month angiographic follow-up will not be required in PROSPECT-ABSORB randomized patients who either a) have had scaffold thrombosis or in-scaffold restenosis (DS>50% as determined by the angiographic core laboratory) at any time point prior to 25 months, OR b) have had a repeat angiogram ≥12 months after enrollment and in whom IVUS/NIRS of the randomized target lesion was performed.

Additional follow-up visits

Any patient who develops cardiac symptoms or a MACE during the follow-up period should be evaluated by the investigator by telephone contact or clinic visit as deemed appropriate. Requisite data are listed:
• Data regarding any endpoint events or serious adverse device effects (see Section 10), including repeat hospitalization and coronary angiography
• Use of medications

For any occurrence during follow-up of an adverse cardiac event, detailed records of that event, including but not limited to hospitalization records (admission record, discharge summary, catheterization and operative reports, and other supporting data as required) must be collected and sent to the CEC for adjudication. Any repeat coronary angiographic and IVUS/NIRS imaging procedures must be collected and sent to the core laboratory, whether performed at the enrolling hospital or a non-enrolling hospital. Further details can be found in the Study Manual of Operations.

Additional phone follow-up may be performed as needed to obtain more complete follow-up information.

9.6.10 ANNUAL CLINICAL FOLLOW-UP AT 3 YEARS THROUGH 15 YEARS

Clinical follow-up by telephone may be extended at yearly intervals from 3 years (±1 month) up to 15 years (±1 month). Based on the findings of the study at 24 months, the Executive Committee will determine whether follow-up will be extended and for how long, and sites will be notified. Such visits will assess:

• Data regarding any endpoint events including repeat hospitalization and coronary angiography
• Use of cardiac medications (see Section 9.6.)

9.6.11 EVENT-DRIVEN IMAGING IN PROSPECT II (NATURAL HISTORY STUDY)

For patients returning to the enrolling institution with a subsequent cardiac event that requires catheterization, it is strongly recommended that 3-vessel IVUS/NIRS follow-up be conducted at the time of the catheterization. A 3-vessel angiogram should also be performed. These images will be sent to their respective core laboratories for analysis. As patients may have multiple events during follow-up period, all efforts should be made to image the first event.

10 ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the procedure or device.

10.1 ADVERSE DEVICE EFFECT (ADE)

An adverse device effect is defined as any untoward and unintended response to a medical device/imaging tool/scaffold. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use. It also includes any event that is a result of a user error. Observed and potential adverse device effects for the InfraReDx TVC Imaging System and the Absorb BVS can be found in the respective IFU/User's Guide in the Investigator's File.

10.2 SERIOUS ADVERSE EVENT (SAE)

An SAE is defined as an adverse event that:
- Led to death.
- Led to a serious deterioration in the health of the subject that:
    - Resulted in a life-threatening illness or injury
    - Resulted in a permanent impairment of a body structure or a body function
    - Required in patient hospitalization or prolongation of existing hospitalization
    - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect

10.3 SERIOUS ADVERSE DEVICE EFFECT (SADE)

An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. A list of serious adverse events, which may result from the use of the device/imaging tool or occur as a result of the

imaging procedure, is described in the TVC Imaging system and the Absorb BVS Instructions For Use (IFU).

10.4 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

A USADE is defined as any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, the device if that effect, problem, or death was not identified in nature, severity, or degree of incidence in the current risk analysis report, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of the subjects. (Significant device failure may constitute an adverse event if an undesirable experience occurs.) This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device or any event that is a result of a user error.

10.5 RECORDING AND REPORTING OF NON-SERIOUS AND SERIOUS ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS.

Any adverse event, whether device related or not, occurring at the baseline visit and at the 25-month visit (PROSPECT ABSORB) will be collected.

Any event the investigator deems to be serious MUST be reported to the Sponsor within one business day from the knowledge and determination of the event. The SAEs will be monitored until they are adequately resolved or explained.

Between visits, up to 24 months of follow-up (or 25 months in the case of subjects in the PROSPECT ABSORB substudy), only endpoint events, as defined below and in Section 11, and SADEs will be collected.

Death, myocardial infarction, hospitalization for unstable or progressive angina, symptom-driven revascularization, and scaffold thrombosis are defined as potential endpoints and will be reported to the CEC group for central adjudication (see Section 11). The events will be collected for all patients throughout the study after the patient is enrolled. These adjudicated events will not be reported to health authorities as SAEs as they are considered part of the natural history of the condition under investigation and will be monitored regularly by an independent DSMB throughout the study.

SADEs, endpoint related or not, will be collected throughout the study up to 25 months follow-up (PROSPECT ABSORB). The Investigator shall report all SADEs to the Sponsor within one business day from the knowledge and determination of the event and to the reviewing IEC/IRB as soon as possible (per the overseeing policy of the IEC/IRB) after the Investigator first learns of the effect. The Sponsor will report USADEs to the manufacturer within 24 hours from the knowledge and determination of the event and will report SADEs and USADEs to the National Competent Authority according to local regulations.

All events listed above should be documented in the patient eCRF including time of onset, a complete description of the event, severity, duration, actions taken, and event outcome.

10.6 SAFETY MONITORING

All events associated with the baseline imaging and/or scaffold deployment procedure will be reported to the Data and Safety Monitoring Board (DSMB) and reviewed on a regular basis. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend to the Executive Committee to stop or otherwise modify the study. After weighing the recommendation of the DSMB, the Executive Committee will make the final decision whether the study should be stopped, modified, or continued without change. The DSMB procedures will be described in the DSMB Charter.

11 ADJUDICATION OF EVENTS

All suspected major adverse cardiac events (NC-MACE) will be adjudicated by the independent CEC group at UCR. The CEC Charter defines the specific criteria and definitions for each study endpoint (both primary and secondary) as detailed below, and will be approved by the Executive Committee. The details of the adjudication process are described in the CEC Charter.

In parallel, the ACL at Cardiovascular Research Foundation, will be responsible for reviewing and analyzing all repeat angiograms to determine lesion progression and if an event was related to the culprit lesion or NCL or the randomized BVS lesion and if revascularization was performed. Regular meetings will be held by the CEC group with the ACL and, if needed, the intravascular core lab to accurately adjudicate lesion assignment. The ACL will use a work process defined in a separate work process plan.

The result of the angiographic review will determine if the event (adjudicated by the CEC group) will finally be classified and analyzed as a culprit lesion or an NCL.

The following endpoints will be adjudicated by the CEC group:

- Death
- Myocardial infarction
- Unstable angina
- Progressive angina or anginal equivalent symptoms
- Symptom-driven revascularization
- Stent/Scaffold thrombosis

On the basis of the findings from the ACL, each event will be attributed to either the culprit lesion/vessel, non-culprit lesion/vessel, randomized lesion (PROSPECT ABSORB substudy – considered an untreated NCL if randomized to control or a treated [non–ACS-related] culprit lesion if randomized to BVS), or indeterminate.

In addition, all IVUS/NIRS related AEs are to be reviewed by CEC and ACL in order to capture any unidentified study endpoints, as listed above.

12 DATA HANDLING AND RECORD KEEPING

12.1 QUALITY REGISTRY DATA

Data from the Scandinavian quality registers for included patients in the study will be used for clinical follow-up at all pre-specified periods. In addition, telephone follow-up will be performed at all intervals up to 24 months and optionally after 24 months through 15 years. Study-specific data up to 24-month follow-up (or 25 months in the case of subjects in the PROSPECT ABSORB substudy) will be accurately recorded by authorized personnel on electronic CRFs (eCRF). eCRFs will be completed in a timely manner.

12.2 MEDICAL RECORD/SOURCE DOCUMENTATION

All digital or paper hospital records regarding the treatment of the patient included in the study, whether obtained at the enrollment hospital or another treating hospital, are considered source data. In order to comply with these regulatory requirements, at a minimum, the following is a list of information that should be maintained*:*

- Clinical study identification
- Subject identification
- Date when patient information was given and when signed informed consent was obtained
- Diagnosis
- Fulfillment of inclusion criteria
- Specification of visit dates, concomitant medication, and any AEs
- Specification of the subject's cessation in the study (eg, completion or premature withdrawal)
- Specification of the subject's outcome in the study

In addition, the raw (digital) data from all angiograms and intravascular imaging studies, whether obtained at the enrollment hospital or another treating hospital, are considered source data and must be collected and sent to the core laboratory.

12.3 RECORD RETENTION

To enable audits and evaluations by the Sponsor and inspections by regulatory authorities, the Investigator shall keep records (essential documents) of the study for 15 years following study completion unless otherwise instructed by regulatory agencies. This includes any original source data related to the study, the subject identification list (with subject numbers, full names and addresses), the original signed informed consent forms, copies of all case report forms, and detailed records of investigational/device products disposition. The investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any study records.

13 SELECTION OF CLINICAL SITES AND INVESTIGATORS

The Sponsor is responsible for selecting qualified investigators, obtaining a signed investigators' agreement, and providing the investigators with the information needed to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring the protection of human patients enrolled in the study, and identifying and distributing significant new information relevant to the investigation to the investigators. The Sponsor will evaluate circumstances where an investigator deviates from the Investigational Plan, and will retain the right to remove either the investigator or the investigational site from the study.

The Sponsor and study management will select investigators qualified by training and experience to participate in this observational study. The sites will be selected based upon review of a recent site assessment, proficiency with the use of IVUS, and the qualifications of the primary investigator at the site. Investigators may be selected to participate in the study only after submitting recent curriculum vitae.

The Investigators should provide a curriculum vitae or equivalent documentation of suitability to be responsible for the study, and should sign a financial disclosure on conflict of interests. All Investigators and other responsible personnel should be listed together with their function in the study on the signature and delegation list to be filed in the Investigators File.

The study sites may also be subject to quality assurance audits by the sponsor or its designee as well as inspection by a regulatory authority. The Investigator and other responsible personnel must be available during the monitoring visits, audits, and inspections and should devote sufficient time to these processes.

13.1 SITE TRAINING

All investigators are required to attend Sponsor training sessions including training sessions by InfraReDx and Abbott Vascular as appropriate, which may be conducted at an investigator's meeting, a site initiation visit, or other appropriate training sessions. Training will include, but not be limited to, the Investigational Plan with manuals and instructions, imaging device usage, scaffold usage, quality registry completion, eCRF completion, and study personnel responsibilities. All Investigators/study personnel that are trained must sign a training log. No Investigator/study personnel will perform any study-related procedures prior to signing a signature and delegation log and training log as appropriate.

A minimum of five (5) BVS implantations on non-study patients need to have been performed by each interventionalist who will be implanting the BVS prior to participation in the PROSPECT II study. A site will only be activated after there has been at least one such trained interventionalist at the site.

At the initiation of the study, the study monitor or designee will visit each site where the study is conducted. The study monitor will ensure that clinical study site personnel are informed about and understand the study requirements.

13.2 INVESTIGATOR RESPONSIBILITIES

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice. The Investigator will provide copies of the Investigational Plan to all co-investigators or other staff responsible for study conduct. The Investigator and representative will provide the Sponsor with notification of relocation to another institution. The Investigator shall ensure also that the data entry will be done in a timely manner.

14 IRB/EC APPROVAL OF THE INVESTIGATIONAL PLAN AND INFORMED CONSENT

The Investigator prior to participation in this study will obtain institutional review board or independent ethics committee (IRB/IEC) approval for the Investigational Plan and informed consent form. The approval letter must be signed by the IRB/IEC chairman or authorized representative prior to the start of this study and must be provided to the Sponsor. No changes will be made to the Investigational Plan or informed consent form without Sponsor and IRB/EC approval.

14.1 PATIENT INFORMED CONSENT

A copy of the template consent form from each site must be forwarded to the Sponsor for review and approval prior to implementation. All patients must provide written informed consent in accordance with the local IRB/IEC. Patients must be consented using an IRB/IEC-approved informed consent form. The approved consent form must clearly reflect the Investigational Plan version number. The Investigator or representative must be available to answer all of the patient's study-related questions during the consent process.

It should be clearly stated that the data will not identify any subject taking part in the study, in accordance with the European Union Data Protection Directive (95/46/EU) and any local law on personal data, compare Personuppgiftslagen, (PuL), SFS 1998:204, in Sweden.

A copy of the patient information and the signed Informed Consent form should be given to the patient. The Investigator (or the designated representative) who gave the verbal and written information to the subject shall sign the informed consent form. The Investigator should file the signed informed consent forms in the Investigator's File for possible future audits and inspections.

14.2 INVESTIGATIONAL PLAN AMENDMENTS

Approved Investigational Plan amendments will be provided to the Investigators by the Regulatory Sponsor prior to implementing the amendment. The Investigator will be responsible for notifying the IRB/IEC of the Investigational Plan amendment (administrative changes) or obtaining IRB/IEC approval of the Investigational Plan

amendment (changes in patient care or safety), according to the instructions provided by the Sponsor.

14.3 INVESTIGATIONAL PLAN DEVIATIONS

It is the responsibility of the Investigator to ensure that there are no deviations from the Investigational Plan without notification and approval of the Sponsor and full compliance with all established procedures of the IRB/IEC. The investigator will not deviate from the Investigational Plan for any reason without prior written approval from the Sponsor, except in cases of medical emergencies, when the deviation is necessary to eliminate an apparent immediate hazard to the patient. In that event, the investigator will notify the Sponsor and the IRB/IEC.

15 DATA MANAGEMENT

An eCRF will be used in this study covering all study specific data up to the 24-month follow-up (or 25 months in the case of subjects in the PROSPECT ABSORB substudy). For all follow-up coronary events the patients chart, angiograms and intravascular imaging studies will be source data. Data management will be conducted by the Sponsor, according to the study-specific Data Management Plan (DMP). The investigator is responsible for ensuring the accuracy, completeness, and legibility of the data reported in the eCRF. The monitor will check in accordance with the monitoring plan the accuracy, completeness, and legibility of the data reported in the eCRFs before the database is locked. The transfer of laboratory data (biomarker, NIRS, IVUS, and ACL data) will be done according to the study specific DMP and in accordance with the Sponsor standard operating procedures (SOPs).

15.1 DATA VALIDATION AND CODING

The eCRF/study database will be subject to both logical computerized checks and manual validation checks against listings in accordance with the study-specific Data Validation Plan (DVP). All inconsistencies detected during these procedures will be resolved through Data Clarification Forms (DCF's) as specified in the DVP.

Adverse Events will be coded by the Sponsor according to appropriate version of the Medical Dictionary for Regulatory Activities (MedDRA). The correctness of the codes used will verified by medical expertise.

15.2 QUALITY CONTROL AND CLEAN FILE

When all data entered into the database, including all coding, are deemed final, a clean file procedure will be initiated, including a quality control process preceding the actual Clean File meeting. Post clean file procedure, the database will be locked and the data will be prepared for the final analysis for the primary endpoint and other efficacy and safety parameters. The clean file process will be defined in more detail in the DMP. Export of final data to involved parties in accordance with respective agreement will be performed as specified within the DMP. Data management and the data handling process will be conducted in accordance with Good Clinical Practice (GCP), Good Clinical Management Practice (GCMP), and EN ISO 14155:2011.

16 STATISTICAL ANALYSIS

16.1 DESIGN OF THE STUDY

PROSPECT II (Natural History Study) is a multicenter, prospective, observational, 900-patient study of troponin-positive ACS patients designed to test the hypothesis that angiographically non-obstructive lesions with large plaque burden and small minimum luminal area as identified by grayscale IVUS and large lipid content as identified by intracoronary NIRS are associated with an increased risk for future acute coronary events.

This study also includes a substudy, PROSPECT ABSORB (Randomized Trial) randomizing 300 patients with one or more lesions with plaque burden ≥65% as assessed at the site by IVUS in a 1:1 fashion to Absorb BVS + GDMT or GDMT alone designed to determine whether the Absorb BVS in such large plaque burden lesions safely increases luminal dimensions at 25-month follow-up.

16.1.1 HYPOTHESES TESTED

The primary analysis will test the ability of the two coronary artery imaging modalities (IVUS and NIRS) to identify angiographically non-obstructive vulnerable plaques that are subsequently responsible for future unanticipated coronary events, in particular to distinguish lesions pre-specified as high-risk: lesion with/without PB ≥70% by IVUS Core Lab assessment and lesions with/without $maxLCBI_{4mm}$ greater than or equal to the upper quartile (25%) of all measured values.

A Cox proportional hazards regression model will be run, assuming that the hazard function $\lambda(t)$ for time to NC-MACE given a single binary predictor X1 has the following regression form:

$$\log[\lambda(t|X1)/\lambda 0(t)] = \beta 0 + \beta 1 X1$$

where $\lambda 0(t)$ is the baseline hazard, and X1 is the imaging measure as an indicator variable (patients with and without the high-risk imaging characteristic).

The null and alternative hypotheses in Cox regression model are:

H_0: $\beta 1 = 0$

H_a: $\beta 1 = B \neq 0$,

where $\beta 1$ (the log hazard ratio of the two groups) is the regression slope coefficient for X1.

16.2 GENERAL METHODS

All statistical analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, NC) or other widely accepted statistical or graphical software. Subject

data listings and tabular and graphical presentations of results will be provided. Unless otherwise indicated, all statistical tests will be performed at the 2-sided $\alpha = 0.05$ significance level.

Baseline demographic, clinical, angiographic, grayscale IVUS, NIRS, and outcome variables will be analyzed.

The primary endpoint analysis will be adjusted for covariates, chosen *a priori* and partly based on the results of the original PROSPECT study: age, sex, diabetes mellitus (none, medically-treated without insulin, insulin-treated); hypertension, prior PCI, clinical presentation (STEMI versus NSTEMI), high-dose statin (atorvastatin ≥40 mg or rosuvastatin ≥20 mg) and/or any PCSK9 inhibitor (evolocumab or alirocumab) use as a time-dependent variable (updated at baseline, discharge, and each subsequent follow-up visit), and total imaged NIRS-IVUS length (mm). An unadjusted analysis will also be conducted, as well as a covariate analyses that will also include LCBI as a continuous variable. Adjusted analyses may also be performed using continuous data for all non-binary variables.

For continuous variables, descriptive statistics such as the N, mean, median, standard deviation, and range will be presented. For discrete variables, counts and percentages will be presented. Where formal statistical hypothesis testing is to be performed, the details will be presented in the Statistical Analysis Plan (SAP). A survival analysis will be used to analyze time-to-event variables such as time to NC-MACE. Survival curves will be constructed using Kaplan-Meier estimation.

The analysis of 2-year imaging (angiographic, IVUS, NIRS) endpoints will be performed separately for PROSPECT ABSORB randomized patients and non-PROSPECT ABSORB patients, as all of the PROSPECT ABSORB randomized patients are scheduled to have imaging assessments done at 25 months, while for the rest of the PROSPECT II patients, repeat imaging will be performed only in patients with an unexpected visit.

16.3 ANALYSIS POPULATIONS

16.3.1 PROSPECT II (NATURAL HISTORY STUDY)

1. Full Analysis Set (FAS): All patients in whom NIRS imaging of at least one major coronary artery was successful. This is the primary analysis dataset for the PROSPECT II natural history study.

2. Safety Analysis set (SA): All patients in whom an IVUS/NIRS catheter exited the guide catheter and entered a coronary artery after successful and uncomplicated target lesion PCI. All patient-level outcome variables/safety analyses will be performed in this analysis set.

16.3.2 PROSPECT ABSORB (RANDOMIZED TRIAL)

1. Intention to Treat Set - PROSPECT ABSORB (ITT): All patients who were randomized into the PROSPECT ABSORB substudy. The ITT set is the primary analysis dataset for the PROSPECT ABSORB randomized trial.

2. Per Protocol – PROSPECT ABSORB (PPA): All patients randomized into the PROSPECT ABSORB substudy who meet all inclusion criteria and none of the exclusion criteria, and are treated according to the randomized assignment, with no major protocol violations.

3. Safety Analysis set – PROSPECT ABSORB (SAA): All patients randomized into PROSPECT ABSORB, excluding those randomized to Absorb BVS arm in whom the Absorb BVS did not exit the guide catheter, whether implanted or not.

16.4 RANDOMIZATION

Randomization into the PROSPECT ABSORB (Randomized Trial) will be conducted via block randomization with random block size, stratified by site, in a 1:1 fashion (BVS + GDMT to GDMT alone). The randomization list is generated by computer in a permuted block fashion and transferred to a sequence of sealed, opaque, consecutively numbered envelopes before the start of the study. When a patient has consented and is found eligible for the study, randomization is performed by opening the next envelope in sequence. For patients with multiple qualifying lesions, a single lesion will be selected and declared prior to randomization allocation.

16.5 DETERMINATION OF SAMPLE SIZE

16.5.1 POWER ANALYSIS AND SAMPLE SIZE ESTIMATE FOR PROSPECT II (NATURAL HISTORY STUDY)

PASS 2008 Software (NCSS LLC, Kaysville, UT), for a Cox Regression model, was used to calculate the sample size for the primary endpoint.

The sample size estimation is based on the results for plaque burden reported in the original PROSPECT study and considers all patients with untreated lesions and all untreated lesions. That is, NCLs (those not treated in the index PCI), as well as IVUS-defined lesions that are not treated as part of the randomized substudy are taken into consideration both at patient-level and lesion-level

The power of PROSPECT II (Natural History Study) is calculated based on testing the ability of the two coronary artery imaging modalities (intravascular ultrasound [IVUS] and near infrared spectroscopy [NIRS]) to identify patients with angiographically non-obstructive vulnerable plaques which are subsequently responsible for future unanticipated coronary events. In particular, lesions with core laboratory-assessed PB $\geq$70% or MLA $\leq$4.0 mm^2 by IVUS and lesions with $maxLCBI_{4mm}$ greater than or equal to the upper quartile (25%) of all measured values are pre-specified as high-risk plaques.

Additional assumptions used in the power calculations are as follows:

- Two-tailed test $\alpha = 0.05$
- R-squared of high-risk lesions with other variables in the model is 0.1 for adjusted analyses (conservatively estimated from PROSPECT)
- Proportional hazards

16.5.2 PATIENT-LEVEL ANALYSIS

In the original PROSPECT study, by grayscale IVUS, 220 patients were identified among 660 patients with at least 1 lesion with PB ≥70%. Among these 220 patients, 288 observed lesions had PB ≥70%, which equates to 1.3 high-risk lesions per patient. For the purpose of the sample size calculation, all 600 patients in PROSPECT II who are entered directly into the natural history study are assumed to have no lesions with PB ≥70%. In the randomized substudy approximately 300 patients will have a mean of 1.3 lesions per patients with PB ≥70%. 150 of these patients are randomized to GDMT alone. 150 of these patients will have 1 PB ≥70% lesion treated by BVS and thus will have mean 0.3 untreated lesions per patient with PB ≥70%, equivalent to 45 patients with 1 untreated PB ≥70%.

Therefore, it is estimated that approximately 195 of 900 patients (22%) would be considered high-risk according to the criteria of having one or more untreated lesions with plaque burden ≥70%.

In the original PROSPECT study, the per patient 24-month NC-MACE rate attributed to patients with ≥1 lesion with PB ≥70% was 17.7% vs 6.0% in patients with no lesions with PB ≥70%. Thus, the assumed overall per patient 2-year NC-MACE rate given the calculations above is 8.5%.

The primary analysis will be adjusted for covariates, chosen *a priori* and partly based on the results of the original PROSPECT study. The list of covariates includes: age, sex, diabetes mellitus (none, medically-treated without insulin, insulin-treated); hypertension, prior PCI, clinical presentation (STEMI versus NSTEMI), high-dose statin (atorvastatin ≥40 mg or rosuvastatin ≥20 mg) and/or any PCSK9 inhibitor (evolocumab or alirocumab) use as a time-dependent variable (updated at baseline, discharge, and each subsequent follow-up visit), and total imaged NIRS-IVUS length (mm). An unadjusted analysis will also be conducted. The power analysis will be presented under both conditions.

In an adjusted analysis for PB ≥70%, assuming an overall event rate of 8.5%, an adjusted hazard ratio of 2.5 and 900 patients (of which 22% are high-risk), there would be 88.3% power to detect the relationship between high-risk patients and NC-MACE. The adjusted hazard ratio of 2.5 is based on the results for PB ≥70% in the original PROSPECT study. It is expected that a similar or higher rate of high-risk patients will be detected based on $\text{maxLCBI}_{4\text{mm}}$ greater than or equal to the upper quartile of observed values. Based on the VH-TCFA data from PROSPECT (in which 23% of lesions were classified as TCFAs according to VH-IVUS, and 51% of patients had ≥1 TCFA), it is assumed that approximately 50% of patients will be categorized as high-risk, defined as those with at least one lesion with $\text{maxLCBI}_{4\text{mm}}$ greater than or equal

to the upper quartile of observed values. Therefore, assuming a prevalence of 50% high-risk patients, the overall effect on a patient level will be similar for plaque burden and $maxLCBI_{4mm}$ (that is, that the hazard ratio is similar for these two modalities) and an overall event rate remaining constant at 8.5%, there will be 96.7% power to detect an adjusted hazard ratio of 2.5. Note that in the original PROSPECT study, the adjusted patient-level HR for VH-TCFA was 1.7. For the patient-level analysis in PROSPECT II (Natural History Study), it is assumed that the HR for $maxLCBI_{4mm}$ will be similar to the HR for PB, thus the adjusted hazard ratio of 2.5 is based on the results for PB ≥70% in the original PROSPECT study.

In an unadjusted analysis for plaque burden, assuming an overall event rate of 8.5%, an unadjusted HR of 3.0 and 900 patients (of which 22% are high risk), there would be 97.8% power to detect the relationship between high-risk patients (those with at least one lesion with PB ≥70%) and NC-MACE. The unadjusted HR of 3.0 is based on the results for PB in the original PROSPECT study.

Assuming the prevalence of high-risk patients will be 50% based on $maxLCBI_{4mm}$ > the upper quartile of observed values and an overall event rate remaining constant at 8.5%, the register will have >99% power to detect an unadjusted HR of 3.0 on a patient-level analysis. In the patient-level analysis, it is again assumed that the HR for $maxLCBI_{4mm}$ will be similar to the HR for PB, and thus the unadjusted HR of 3.0 is based on the results for PB in the original PROSPECT study.

16.5.3 LESION-LEVEL ANALYSIS

In the original PROSPECT study, by VH and grayscale IVUS, 2880 NCL were identified in 609 patients or 4.7 lesions per patient. Thus, it is estimated that in the 600 patients in the register having no NCL with PB <70% there will be 2820 NCL detected. Based on grayscale IVUS in the original PROSPECT study, 288 lesions with PB ≥70% were identified in 220 patients, or approximately 1.3 lesions per patient. Thus, in the 300 patients randomized into PROSPECT ABSORB (Randomized Trial), it is estimated that 1020 untreated NCL with PB <70% and 240 untreated NCL with PB ≥70% will be detected. This includes 195 untreated NCL with PB ≥70% and 510 untreated NCL with PB <70% in the 150 patients from the control arm of the PROSPECT ABSORB (Randomized Trial), and 45 untreated NCL with PB ≥70% and 510 untreated NCL with PB <70% in the 150 patients from the BVS arm of PROSPECT ABSORB (Randomized Trial). Assuming 2% of the images will be unable to be read leaves a total of 3763 untreated NCL with PB <70% and 235 untreated NCL with PB ≥70%.

Thus, 5.9% of all untreated NCL would be considered high-risk according to the criteria of plaque burden ≥70% (as compared to 9% of lesions in the PROSPECT study). The reduction occurs because approximately 150 lesions with PB ≥70% as assessed by the site and treated with BVS are excluded from the analysis, thus reducing the overall prevalence.

In the original PROSPECT study, the per-lesion 2-year event rate attributed to lesions with PB ≥70% was 8.7% vs 0.8% in lesions with PB <70%. Thus, the assumed overall per-lesion event rate given the number of lesions calculated above is 1.3%.

Additional assumptions used in the power calculations are as follows:

- Two-tailed test $\alpha = 0.05$
- R-squared of high-risk lesions with other variables in the model is 0.1 for adjusted analyses (conservatively estimated from PROSPECT)
- Proportional hazards

The primary analysis will be adjusted for covariates, chosen *a priori* and partly based on the results of the original PROSPECT study. The preliminary list of covariates includes: age, sex, diabetes mellitus (none, medically-treated without insulin, insulin-treated); hypertension, prior PCI, clinical presentation (STEMI versus NSTEMI), high-dose statin (atorvastatin ≥40 mg or rosuvastatin ≥20 mg) and/or any PCSK9 inhibitor (evolocumab or alirocumab) use as a time-dependent variable (updated at baseline, discharge, and each subsequent follow-up visit), and total imaged NIRS-IVUS length (mm). An unadjusted analysis will also be conducted. The power analysis will be presented under both conditions.

Given the above assumptions and using a Cox regression of time to NC-MACE on the binary independent variable (positive versus negative observation), the power for various scenarios are shown below.

In an adjusted analysis for PB, assuming an overall event rate of 1.3%, an adjusted HR of 5.0 and 3998 lesions (of which 5.9% are high-risk lesions), there would be 73.4% power to detect the relationship between high-risk NCL and NC-MACE. The adjusted HR of 5.0 is based on the results for PB ≥70% in the original PROSPECT study.

With NIRS, it is expected that a similar or higher rate of high-risk lesions will be detected based on $\text{maxLCBI}_{4\text{mm}}$ greater than or equal to the upper quartile of observed values compared with PB. Based on the VH-TCFA data from PROSPECT, it is assumed that the prevalence of high-risk lesions based on $\text{maxLCBI}_{4\text{mm}}$ greater than or equal to the upper quartile of observed values will be approximately 19%. Given the overall event rate remaining constant at 1.3%, there will be 91.9% power to detect an adjusted HR of 3.5. The adjusted HR of 3.5 is conservatively based on the results for VH-TCFA in the original PROSPECT study, although it is expected that analysis for $\text{maxLCBI}_{4\text{mm}}$ will result in a stronger association.

In an unadjusted analysis for PB, assuming an overall event rate of 1.3%, an unadjusted HR of 8.0 and 3998 lesions (of which 5.9% are high-risk lesions), there would be 94.2% power to detect the relationship between high-risk NCL and NC-MACE. The unadjusted HR of 8.0 is based on the results for PB in the original PROSPECT study.

Assuming again that the prevalence of high-risk lesions based on $\text{maxLCBI}_{4\text{mm}}$ greater than or equal to the upper quartile of observed values will be approximately 19% and an overall event rate remaining constant at 1.3%, there will be 97.5% power to detect an unadjusted HR of 4.0. The unadjusted HR of 4.0 is conservatively based on the results for VH-TCFA in the original PROSPECT study, although it is expected that analysis for $\text{maxLCBI}_{4\text{mm}}$ will result in a stronger association.

16.5.4 POWER ANALYSIS AND SAMPLE SIZE ESTIMATE FOR PROSPECT-ABSORB (RANDOMIZED TRIAL)

Patients are entered into the randomized trial with lesions with site-determined PB ≥65%, which should be equivalent to core laboratory assessed PB ≥70%. Assuming a mean MLA at baseline of 4.41 ± 1.60 mm^2 in each group at baseline (data from PROSPECT in NCL with PB ≥70%), and assuming the MLA at 25 months will decrease in the control group to 4.01 ± 1.60 mm2 versus an increase to 5.16 mm^2 in the Absorb BVS arm (an absolute 1.15 mm^2 difference between the groups), and assuming the same standard deviation in each group, then evaluating 140 patients (each with 1 randomized lesion with PB ≥70%) 1:1 to Absorb BVS + GDMT versus GDMT alone yields 99% power to demonstrate this difference with a 2-sided $\alpha = 0.05$. Assuming ~75% angiographic and IVUS follow-up, a minimum of 187 subjects would need to be randomized. With 196 subjects randomized and 75% angiographic follow up, Prospect-Absorb would also have 80% power to detect a smaller absolute difference of 0.75 mm^2. The trial would also have 80% power to detect an absolute difference of 1.15 mm^2 with 64 evaluable subjects (86 subjects randomized assuming 75% angiographic and IVUS follow-up).

For patients with multiple lesions with PB ≥70%, only 1 lesion will be randomized, generally the lesion in the most proximal non-target vessel supplying the largest amount of myocardium. This lesion will be declared to the IVRS system prior to randomization.

16.6 STATISTICAL ANALYSIS FOR PROSPECT II (NATURAL HISTORY STUDY)

Baseline demographic, clinical, angiographic, grayscale IVUS, NIRS, and outcome variables will be summarized for lesions with and without vulnerable plaque defined by both NIRS and IVUS as well as the overall population. For NIRS, the cutoff is defined as $maxLCBI_{4mm}$ greater than or equal to the upper quartile of observed values. Additional cutoffs of (1) $maxLCBI_{4mm}$ ≥400 (2) ≥lower quartile vs <lower quartile, and (2) ≥400 vs ≥100 and <400 vs <100 (definition of lipid-rich plaque (LRP) category) will also be examined. For IVUS, PB ≥70% and MLA ≤4.0 mm^2 will be used as pre-specified cutoff values (both features having been identified in PROSPECT as independent predictors of future AEs). These analyses will include all untreated lesions from the PROSPECT II natural history study (n=600 patients), the GDMT-only arm from the PROSPECT ABSORB randomized trial (n=150 patients), and the untreated NCL from the BVS arm of the PROSPECT ABSORB randomized trial (n=150 patients). Subject-level analyses will also be presented for patients with versus without lesions containing high-risk features (including PB ≥70%, and/or $maxLCBI_{4mm}$ greater than or equal to the upper quartile of observed values (and ≥400), and/or MLA ≤4.0 mm^2, and/or other characteristics as identified by univariate and multivariate analysis.

16.6.1 PRIMARY ENDPOINT ANALYSIS

The primary endpoint in PROSPECT II is rate of NC-MACE in all patients throughout the whole study period assessed when the last patient has been followed for 24 months on a patient level. Cox proportional hazards model will be used to test the relationship between vulnerable plaque patients and NC-MACE. Overall event rates will be

presented as well as the HRs and 95% confidence intervals. Patients will be censored based on the last known follow-up. The assumption of proportional hazards will first be tested by plotting the log-negative-log survival curves vs the log of survival time for each level of treatment group. If it is determined that the proportional hazard assumption is violated, then a logistic regression will be performed adjusting for time of follow-up in each group. The primary analysis set for this analysis is the FAS analysis set.

Both unadjusted and covariate adjusted analyses will be performed. The primary analysis is specified as the adjusted analysis.

16.6.2 MAJOR SECONDARY ENDPOINT ANALYSIS

The major secondary endpoint in PROSPECT II is NC-MACE on a lesion level. Cox proportional hazards model will be used to test the relationship between high-risk lesion characteristics and NC-MACE. Lesions will be censored based on the last known follow-up for the patient. Other analysis details are as described above.

For this secondary analysis, the Wei-Lin-Weissfeld method will be used. A robust sandwich covariance matrix estimate will be used to account for the within-patient dependencies (correlations of lesions within each patient).

16.6.3 SENSITIVITY ANALYSIS

Sensitivity analyses for the primary endpoint and major secondary endpoints will be described in the Statistical Analysis Plan.

16.6.4 ADDITIONAL SECONDARY ANALYSES

Secondary endpoints including clinical and imaging, will be analyzed in a similar way as the primary and major secondary endpoints above, or, as applicable, as described in the General Methods section. The univariate and multivariate analyses will be performed, in general, for all study time points at patient level, vessel level, and lesion level, as applicable and detailed in the SAP.

An additional analysis of the primary endpoint will be performed removing the patients who had a single vulnerable plaque treated by Absorb BVS and who had no other vulnerable plaque lesions.

PB, max$LCBI_{4mm}$, MLA, and other covariates will also be analyzed as continuous variables in the Cox regression model.

MACE will also be analyzed (culprit-lesion related, NC-MACE, or indeterminate) in univariate and multivariate analyses, performed for all study time points at the patient level, vessel level, and lesion level.

The correlation of the PB, max$LCBI_{4mm}$, MLA, and other continuous variables will be explored and reported.

An ROC analysis will be conducted to additionally report the "optimal" cutoff for PB, max$LCBI_{4mm}$, MLA and other continuous variables based on the current data.

16.6.5 SAFETY ANALYSIS

The analysis set for this analysis is the SA analysis set.

The primary safety endpoint in PROSPECT II is major complications of IVUS/NIRS imaging of 3 vessels, defined as imaging-related death, or vessel dissection/perforation/spasm or other complication requiring percutaneous or surgical treatment (including pericardiocentesis), during the hospitalization in which the imaging was performed, as assessed by the ACL . The number and percent of complications will be presented on a patient level for the entire study, not broken down by imaging risk group.

Other safety endpoint analyses:

- In-hospital (index culprit-lesion PCI-related) MACE

Note: For patients who undergo planned staged procedures, adverse events from both procedures will add to the categorical measurement of imaging-related and culprit-lesion PCI-related in-hospital event rates. All other event rates are determined in time-to-first event analyses from the time of enrollment.

16.6.7 ANALYSIS WINDOW

Clinical follow-up for the primary endpoints should occur at 24 months ± 14 days, prior to the imaging follow-up for those patients in the PROSPECT ABSORB cohort. For clinical endpoints, a year is defined as 365 days. Analyses up to 24 months will include all data/events occurring up to and including 730 days.

16.6.8 HANDLING OF DROPOUTS AND MISSING DATA

For the primary safety endpoint of NC-MACE all available data will be used and dropouts will be censored at their last known status time.

16.7 STATISTICAL ANALYSIS FOR PROSPECT ABSORB (RANDOMIZED TRIAL)

Baseline demographic, clinical, angiographic, grayscale IVUS, and outcome variables (including follow-up imaging data) for the randomized cohort (300 patients) will be summarized for Absorb BVS + GDMT versus GDMT alone as well as the overall population. These analyses will be conducted in the FASA and PPA analysis sets. Safety analyses will be conducted on SAA.

16.7.1 PRIMARY EFFICACY ENDPOINT ANALYSIS

The primary efficacy endpoint is the IVUS MLA at 25 months in the randomized lesions. The mean MLA in each group will be presented along with the difference between groups and 95% confidence intervals and compared via analysis of covariance, adjusted for baseline MLA.

The analysis set for the primary endpoint is the ITT analysis set. Imaging results will be reported from the IVUS analysis set.

16.7.2 SENSITIVITY ANALYSIS

As a sensitivity analysis, the primary analysis of the primary efficacy endpoint, will be conducted including images obtained outside the pre-defined window.

To assess the impact of missing values from patients with insufficient follow-up on the primary study endpoint, the primary analysis of the primary efficacy endpoint will be repeated where, in the FAS, patients with insufficient follow-up will have their data imputed via multiple imputation by the MCMC algorithm. The resulting estimates and confidence intervals will be presented

16.7.3 SECONDARY EFFICACY ENDPOINTS ANALYSIS

Secondary endpoints including clinical and imaging, will be analyzed in a similar way as the primary and major secondary efficacy endpoints above. The univariate and multivariate analyses will be performed, in general, for all study time points at patient level, vessel level, and lesion level, as applicable and detailed in the SAP.

Study lesion (randomized)-level endpoints and patient-level endpoints related to the randomized lesion and vessel will be analyzed between the treatment groups, stratified by severity of LRP (NIRS) at baseline (by $maxLCBI_{4mm}$ and LCBI in separate models).

A NC-MACE bivariate analysis will be performed by treatment for all PROSPECT II covariates, at study time points, and at patient level, vessel level, and lesion level.

16.7.4 SAFETY ENDPOINT ANALYSIS

The analysis set for the safety endpoints is the Safety Analysis set (SAA).

The primary safety endpoint is TLF (cardiac death, target-vessel myocardial infarction, or ischemia-driven TLR) up to 24 months (prior to routine imaging follow-up). Patients will be censored at the time of their 24-month clinical follow-up, or if this did not occur, just prior to the time of the routine imaging follow-up, or at their last known status time.

Other safety endpoint analyses:

- TLF measured at 1 month, 6 months, 12 months, 24 months, and possibly yearly through 15 years will be analyzed in the same way as for the primary TLF time point.

- Periprocedural (Absorb BVS procedure-related) MACE will be analyzed in a Cox proportional hazards model, by treatment, with only max$LCBI_{4mm}$ and, respectively, LCBI as covariates, at lesion level, vessel level, and patient level.
- Scaffold thrombosis (definite or probable per ARC definition) as per CEC and Core Lab adjudication measured at 1 month, 6 months, 12 months, 24 months, and possibly yearly through 15 years
    - Temporal classification:
    - All
    - Acute (0 to 24 hours after stent implantation)
    - Subacute (>24 hours to 30 days after stent implantation)
    - Late (>30 days to 1 year after stent implantation)
    - Very late (>1 year after stent implantation)
- Complications of IVUS/NIRS imaging during PCI will be analyzed in a similar way with the primary safety endpoint:
    - Core lab assessed and adjudicated
    - Site assessed

16.7.5 ANALYSIS WINDOW

Imaging follow-up for patients in PROSPECT ABOSRB should occur at 25 months (**from 24.5 months to28 months**); 25-month angiographic follow-up will not be required in PROSPECT-ABSORB randomized patients who either a) have had scaffold thrombosis or in-scaffold restenosis (DS>50% as determined by the angiographic core laboratory) at any time point prior to 25 months, OR b) have had a repeat angiogram ≥12 months after enrollment and in whom IVUS/NIRS of the randomized target lesion was performed. The imaging data from such patients will be included in the primary analysis dataset.

These exceptions notwithstanding, a sensitivity analysis will be conducted including images obtained outside the window for the primary efficacy endpoint.

Clinical follow-up for the primary safety endpoint should occur at 24 months ± 2 weeks, prior to the imaging follow-up. For clinical endpoints, a year is defined as 365 days. Analyses up to 24 months will include all data/events occurring up to and including 730 days.

See Study Flow Chart in Appendix II.

16.7.6 HANDLING OF DROPOUTS AND MISSING DATA

For the primary safety endpoint of NC-MACE all available data will be used and dropouts will be censored at their last known status time.

For the primary efficacy endpoint of MLA, all available data will be used. In addition, as a sensitivity analysis in the FAS group, in order to assess the impact of missing values from patients with insufficient follow-up on the primary study endpoint, patients with insufficient follow-up will have their data imputed via multiple imputation by the MCMC algorithm. The resulting estimates and confidence intervals will be presented.

For all other analyses, only available data will be analyzed.

16.8 SUBGROUP ANALYSIS

For PROSPECT II, subgroup analysis will be performed for the primary and major secondary endpoints by age, sex, the presence of medically treated or insulin-treated diabetes mellitus, metabolic syndrome status, prior history of MI, prior PCI, clinical presentation (STEMI versus NSTEMI), maxLCBI$_{4mm}$ (cutoffs defined as: the upper quartile of observed NCL values, median of observed NCL values, ≥400 versus <400, categorized into 3 groups: ≥ upper quartile versus < upper quartile and ≥ lower quartile versus < lower quartile, and categorized into 3 groups: ≥400 versus ≥100 and <400 versus <100), plaque burden (cutoffs defined as: ≥70% versus <70%, <40% versus ≥40% to <50% versus ≥50% to 60% versus ≥60% to 70% versus ≥70% to <80% versus >80%, and median of observed NCL values), MLA (cutoff defined as: ≤4 versus >4 mm^2, and median of observed NCL values), remodeling index (positive remodeling is defined as remodeling index >1.0, negative remodeling is defined as remodeling index <0.88, intermediate remodeling is defined as remodeling index ≥0.88 and ≤1.0), lesion length by IVUS (cutoff defined as the median of observed NCL values), distance from ostium to the MLA by IVUS (cutoff defined as the median of observed NCL values), renal insufficiency (calculated creatinine clearance <60 versus ≥60 mL/min), white blood cell count (cutoff defined as the median of observed values, use of aggressive lipid lowering agents at baseline, and baseline levels of LDL, HDL, and hs-CRP (cutoffs defined as the median of observed values). Other subgroups and endpoints may be analyzed. Forest plots for all primary endpoints will be constructed. Periprocedural (Absorb BVS PCI procedure) MACE will be analyzed by levels of maxLCBI$_{4mm}$ (cutoff defined as the upper quartile of observed values).

For PROSPECT ABSORB, the major subgroup of interest will be for the safety results (patient level) and efficacy results (lesion level), for the primary endpoint of MLA at 25-month IVUS follow-up, according to whether the baseline maxLCBI$_{4mm}$ was greater than or equal to versus less than the upper quartile of observed values; greater than or equal to versus less than the median of observed values; or greater than or equal to versus less than 400. Additional subgroups and endpoints, as in the PROSPECT II analysis, may also be analyzed, including using PB and MLA as covariates. Other covariates for the primary endpoint will be reference vessel area by IVUS (cutoff defined as the median of observed values), the presence of calcification by IVUS (cutoff defined as <180 versus ≥180 degrees)).

16.9 DEVIATIONS FROM PROTOCOL ANALYSIS PLAN

Details of the statistical analysis will be outlined in a study-specific SAP. Any changes to analyses planned in the final version of the protocol will be described and justified in the SAP and noted in the final study report.

16.10 INTERIM ANALYSIS AND STOPPING RULES

There are no planned formal interim analyses in this study. If the pooled event rate is lower than expected, and/or the 24-month clinical results are of sufficient interest and import to warrant additional follow-up, patient follow-up in PROSPECT

II/PROSPECT ABSORB may be extended beyond 2 years to a maximum of 15 years to collect additional events.

There will be an independent DSMB assigned to review data during the course of the study. Details and any potential stopping rules suggested by this committee will be described in the DSMB Charter. See also section 10.6.

17 MONITORING PLAN

Monitoring will be performed by the Sponsor or its designee in accordance with the principles of International Conference on Harmonisation (ICH) GCP, the EN ISO 14155, and Sponsor SOPs. During the study, the monitor will have regular contacts with the study sites, including visits, where necessary, to ensure that the study is conducted and documented properly.

The extent of monitoring will be described in the monitoring plan prepared by the Sponsor. The monitor will ensure that accountability of investigational products is performed and will review source documents for verification of consistency (source data verification) with the data recorded in the eCRFs. The monitor will also provide information and support to the investigator sites.

18 CRITERIA FOR TERMINATION OF THE STUDY

The Executive Committee reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all delivered unused study device and other study-related materials must be collected without delay and eCRFs must be completed as far as possible.

The study could be prematurely discontinued in the following cases (examples):

- New findings about the study device(s) that changes the benefit/risk ratio.
- Investigational plan is difficult to cope with.
- Recruitment of eligible subjects is far too low.
- Unacceptable low Investigator, Academic Sponsor or subject compliance.
- Critical change in personnel, administrative, or scientific standards at either the coordinating academic research organizations or at the study site(s).

19 QUALITY ASSURANCE

The Regulatory Sponsor representative or designee may request access to all study records, including source documentation, for inspection and duplication during a quality assurance audit. In the event that an investigator is contacted by a regulatory agency in relation to this study, the Investigator will notify UCR immediately. The Investigator and Research Coordinator must be available to respond to reasonable

requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study. The Regulatory Sponsor may provide any needed assistance in responding to regulatory audits.

20 CONFIDENTIALITY

Patients providing a signed informed consent are agreeing to allow the Sponsor and/or the coordinating academic research organizations access to pertinent information in their medical records concerning their participation in this study. This information will be shared with regulatory bodies. This Investigational Plan, documentation data, and all other information generated will be held in strict confidence by the Investigator and their representatives. No information concerning the study or the data will be released to any unauthorized third party without prior written approval by the Sponsor.

21 COMPLIANCE TO STANDARDS AND REGULATIONS

The study will be conducted in accordance with the Investigational Plan, applicable regulatory requirements, ICH GCP, EN ISO 14155, and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions.

22 INSURANCE

Study patients are insured by Local Country Patient Insurances of Sweden, Denmark, and Norway. Appropriate product insurances are held by InfraReDx Inc and Abbott Vascular for their respective products in the study.

23 PUBLICATION POLICY

All information not previously published concerning the investigational product, including patent applications, manufacturing processes, basic scientific data, etc, is considered as confidential and should remain the sole property of the manufacturing company. The Investigator agrees to use this information only in connection with this study and will not use it for other purposes without written permission from the Sponsor.

The coordinating academic research organizations will each maintain a copy of the complete final and locked dataset to facilitate joint academic projects. After completion of the study, statistical analyses will be performed by CRF and the Sponsor in collaboration with the Coordinating Principal Investigators, and the results will be presented to the funding manufacturers Based on these data, a clinical study report will be prepared and the data will be presented at one or more major international medical congresses, and at least two manuscripts (PROSPECT II and PROSPECT ABSORB) intended for publication in major medical/scientific journals will be prepared. These

presentations and publications will report the combined results from all centers. No presentations or publications from individual sites are permitted until publication of these two joint manuscripts. Before public presentation or publication of the results, the funding manufacturers will be given the opportunity to review and to provide non-binding comments on the presentations/manuscripts. The publication procedure for the principal and subsequent presentations and publications will be defined in more detail in a Publication Charter.

24 COMMITTEES

24.1 DATA SAFETY MONITORING BOARD (DSMB)

The DSMB will comprise at least three members. The DSMB members will not have any affiliation with CRF, the Sponsor, the Coordinating Principal Investigators, the core labs, or the clinical investigation sites. The DSMB will be responsible for making recommendations to the Executive Committee regarding any potentially significant safety-related observations.

24.2 CLINICAL ENDPOINT CLASSIFICATION (CEC)

The independent CEC group at UCR will be composed of interventional and/or non-interventional cardiologists who are not participants in the study and are independent from the study. The CEC group will review and adjudicate all potential MACE events. In parallel, the ACL at CRF will be responsible for reviewing and analyzing all repeat angiograms to determine lesion progression and if an event was related to the culprit lesion or NCL or the randomized BVS lesion and if revascularization was performed. All details of the CEC and ACL process are specified in the CEC and ACL charter respectively.

24.3 OPERATIONS COMMITTEE (OC)

The Operations Committee (OC) is a Regulatory Sponsor-designated team comprising the Coordinating Principal Investigators, the Sponsor, and CRF representatives and coordinated by the Regulatory Sponsor PM. Representatives from the funding companies are represented as appropriate. The OC will be responsible for the day-to-day administrative management of the study. This OC will monitor patient enrollment, clinical site progress, and Investigational Plan compliance. The OC will provide assistance to the sites with study management issues, including compliance with specific record keeping and reporting requirements.

24.4 STEERING COMMITTEE (SC)

The Steering Committee (SC) is responsible for overseeing the operational progress of the study. The SC comprises the Study Chairs/Coordinating Principal Investigators, the National Coordinators, and representatives of the Sponsor and the coordinating academic research organizations. The funding companies will be represented as appropriate. This SC will meet regularly to discuss patient accrual, the Investigational

Plan and amendments, actions upon recommendations of the DSMB, etc. SC members are listed in a separate document

24.5 EXECUTIVE COMMITTEE (EC)

The Executive Committee (EC) is responsible for overseeing the administrative progress of the investigational plan. The EC comprises the Study Chairs, and representative(s) from the Coordinating Academic Research Organizations. Other representatives may participate in the EC meeting if appropriate. This committee will meet regularly to monitor patient accrual, non-compliance with the Investigational Plan at individual centers, to review and act upon recommendations of the DSMB, and to determine policy regarding any publications arising from data generated from the performance of the study. EC members are listed in a separate document.

25 STUDY ADMINISTRATIVE STRUCTURE

A separate document as part of the Trial Master File/Investigator File will specify the study administrative structure including Sponsor representatives, responsible collaborative parties, the EC, SC, and OC, and the study sites. This document will be updated regularly as needed and distributed as appropriate.

26 REFERENCES

1. Organization WH. The global burden of disease: 2004 update. Geneva, Switzerland: WHO Press, 2008.
2. White HD, Chew DP. Acute myocardial infarction. Lancet 2008;372:570-84.
3. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 2000;20:1262-75.
4. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733-43.
5. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.
6. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. JACC Cardiovasc Imaging 2011;4:894-901.
7. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. Circulation 2012;126:172-81.
8. Gardner CM, Tan H, Hull EL, et al. Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. JACC Cardiovasc Imaging 2008;1:638-48.
9. Madder RD, Goldstein JA, Madden SP, et al. Detection by near-infrared spectroscopy of large lipid core plaques at culprit sites in patients with acute ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2013;6:838-46.
10. Erlinge D, Muller JE, Puri R. Validation of a near-infrared spectroscopic signature of lipid located at culprit lesions in ST-segment elevation myocardial infarction. 81st Congress of the European Atherosclerosis Society. Lyon, France, 2013.
11. Brugaletta S, Radu MD, Garcia-Garcia HM, et al. Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap the plaque? Atherosclerosis 2012;221:106-12.
12. Zhao Z, Witzenbichler B, Mintz GS, et al. Dynamic nature of nonculprit coronary artery lesion morphology in STEMI: a serial IVUS analysis from the HORIZONS-AMI trial. JACC Cardiovasc Imaging 2013;6:86-95.
13. Muramatsu T, Onuma Y, van Geuns RJ, et al. 1-year clinical outcomes of diabetic patients treated with everolimus-eluting bioresorbable vascular scaffolds: a pooled analysis of the ABSORB and the SPIRIT trials. JACC Cardiovasc Interv 2014;7:482-93.

27 LIST OF APPENDICES

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Appendix IV. IVUS/NIRS Guidelines

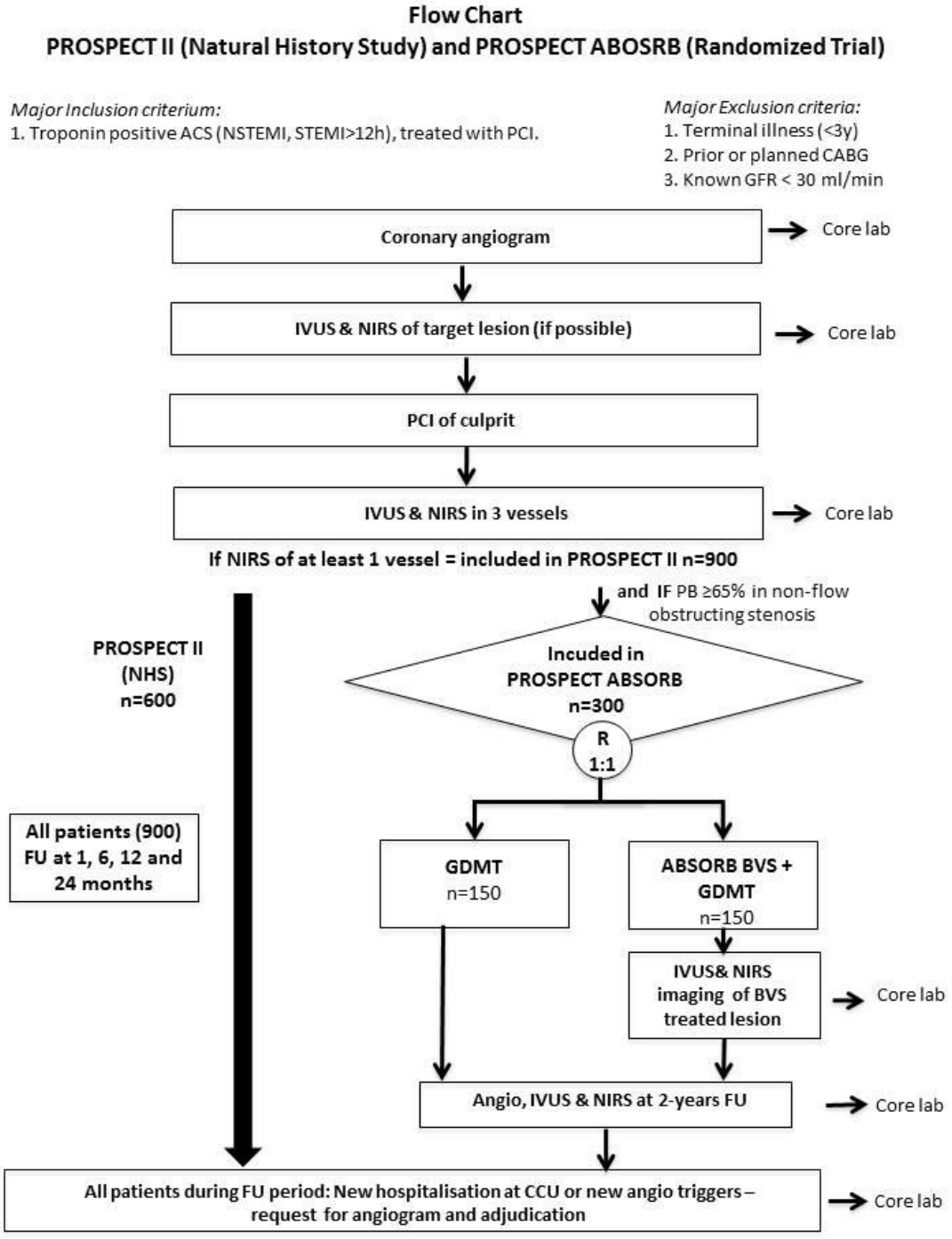
Appendix V: Endpoint Definitions (Copied from CEC Charter)

APPENDIX I ACRONYMS AND ABBREVIATIONS

ACC	American College of Cardiology
ACL	Angiographic Core Laboratory
ACS	Acute Coronary Syndromes
AHA	American Heart Association
BVS	Bioresorbable vascular Scaffold
CABG	Coronary artery bypass graft
CASS	Coronary Artery Surgery Study
CE	Conformité Européenne
CEC	Clinical endpoint classification
CK-MB	Creatine kinase – myocardial band isoenzyme
CRF	Cardiovascular Research Foundation
eCRF	Electronic case report form
DCF	Data clarification form
DES	Drug-eluting stent
DMP	Data management plan
DS	Diameter stenosis
DSMB	Data safety monitoring board
DVP	Data validation plan
EC	Executive committee
ECG	Electrocardiogram
EEM	External elastic membrane
ESC	European Society of Cardiology
FAS	Full analysis set
FASA	Full analysis set – PROSPECT ABSORB
FFR	Fractional flow reserve
GDMT	Guideline-directed medical therapy
GCMP	Good clinical manufacturing practice
GCP	Good clinical practice
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HR	Hazard ratio
hs-CRP	high-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
iFR	Instantaneous wave-free ratio
IFU	Instructions for use
IRB	Investigational review board
IVUS	Intravascular ultrasound
LAD	Left anterior descending coronary artery
LCBI	Lipid core burden index
LCP	Lipid core plaque
LCX	Left circumflex coronary artery
LDL	Low-density lipoprotein
LRP	Lipid-rich plaque
MACE	Major adverse Cardiac event

$maxLCBI_{4mm}$	Maximum lipid core burden index over a 4-mm length
MI	Myocardial infarction
MLA	Minimum lumen area
MLD	Minimum lumen diameter
NCL	Non-culprit lesion
NC-MACE	Non-culprit major adverse cardiac event
NIRS	Near-infrared spectroscopy
NSTEMI	Non–ST-segment elevation myocardial infarction
OC	Operations Committee
PB	Plaque burden
PCI	Percutaneous coronary intervention
PDLLA	Polymer poly (D,L-lactide)
PLA	Polyactic acid
PLLA	Polymer poly (L-lactide)
PPA	Per protocol – PROSPECT ABSORB
QCA	Quantitative coronary angiography
OCT	Optical coherence tomography
RCA	Right coronary artery
RVD	Reference Vascular Diameter
SA	Safety analysis set
SAA	Safety analysis set – PROSPECT ABSORB
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SCAI	Society for Cardiac Angiography and Interventions
STEMI	ST-segment elevation myocardial infarction
TCFA	Thin-cap fibroatheroma
TIMI	Thrombolysis In Myocardial Infarction
TLF	Target lesion failure
TLR	Target lesion revascularization
UCR	Uppsala Clinical Research Center
USADE	Unanticipated serious adverse device effect
VH-IVUS	Virtual histology-intravascular ultrasound
VH-TCFA	Virtual histology intravascular ultrasound- derived thin-cap fibroatheroma

APPENDIX II STUDY FLOW CHART/SCHEDULE OF PROCEDURE



Schedule of Procedure

PROSPECT II/ PROSPECT ABSORB	All Patients	Telephone Follow-up (All patients)				PROSPECT Absorb (Randomized trial)	Unexpected Visits up to 24 months follow-up	Optional Telephone FU Yearly FU Years 3-15[8]
Schedule of Procedures	**Baseline/enrollment**	**1 month (30 days) ± 7 days**	**6 months (180 days) ± 14 days**	**12 months ± 30 days**	**24 months[7] ± 14 days**	**25 months (range 24.5 – 28 months)**		
Eligibility criteria[1]	x							
Informed consent	x							
Coronary angiogram[2]	x					X[10]	X	
IVUS&NIRS imaging of target lesions (if possible)	x					X[10]		
PCI of culprit	x						X	
IVUS& NIRS imaging for all 3 coronary vessels[1,2]	x					X[10]	X	
Check for possible randomization to PROSPECT ABSORB (Randomized trial)[3]	x							
PROSPECT ABSORB: IVUS& NIRS imaging of BVS treated lesion[2]	x							
Concomitant medication[4]	x	x	x	x	x	X	X	X[8]
Safety laboratory[5]	x							
Biobank samples[6]	x							
Adverse Event/Adverse Device Event	x	X[9]	X[9]	X[9]	X[9]	X	X[9]	
Events for Adjudication (CEC)	x	x	x	x	x	X	X	X[8]

1. Patient is enrolled in PROSPECT II if the catheter is advanced out of the guide catheter. If the imaging catheter passed into a coronary artery for imaging a non-culprit segment of the coronary tree and no non-culprit segment imaging data is obtained (e.g. the catheter fails and a second catheter is not used), the patient will be disenrolled (discontinued) from the study, and only be followed up for safety purposes for 30 days.
2. All films will be transferred to the Core Lab according to Study Manual of Operations
3. If PB (plaque burden) ≥ 65% in non-flow obstructing stenosis patient is eligible for randomization to PROSPECT ABSORB (Randomized Trial)
4. All prescribed cardiac medications will be recorded at the admission, during the catheterization and hospitalization, at discharge and at the schedule follow-ups. See protocol section 9.6
5. Hemoglobin, WBC, platelet count, creatinine, HgbA1C, cholesterol, LDL, HDL, triglycerides, p-glucose, hs-Troponin (before and after PCI) and hs-CRP at local laboratory
6. Samples for cardiac biomarker/genetic analysis should be taken from the arterial sheath after diagnostic angiogram and before the PCI is performed. See protocol section 9.7.2
7. For patients in PROSPECT ABSORB clinical (telephone) follow-up at 24 months must occur PRIOR to 25 months angiogram/IVUS/NIRS.
8. Contingent on approval by the Executive Committee
9. Only SADEs will be reported. See protocol section 10.5.
10. 25-month angiographic follow-up will not be required in PROSPECT-ABSORB randomized patients who either a) have had scaffold thrombosis or in-scaffold restenosis (DS>50% as determined by the angiographic core laboratory) at any time point prior to 25 months, OR b) have had a repeat angiogram ≥12 months after enrollment and in whom IVUS/NIRS of the randomized target lesion was performed.

APPENDIX III ANGIOGRAPHY GUIDELINES

Angiographic Core Laboratory
Angiographic Protocol

PROSPECT II
Instruction to the sites

1) Use ≥ 5 Fr diagnostic or guiding catheters, and provide documentation stating the size of the catheter
2) Administer 100-200 mcg IC nitroglycerin and record in the Case Report Form before the baseline, final (post intervention) and follow-up angiograms, unless judged inappropriate by the investigator.
3) Provide 2 matched orthogonal views of the lesion at baseline, after final intervention and at follow-up.
4) Ensure the catheter is visible in all frames.
5) Avoid overlapping of vessel, superposition with diaphragm, and the presence of foreign body in the angiogram (e.g. EKG leads).
6) Film as much detail of the intervention as possible (pre and post stent placement, intraprocedural images, complications etc…). Film all intraprocedural adverse events – e.g. side branch closure, new thrombus, dissection, distal embolization, decreased flow, etc.
7) Film all stent deployments so that we can accurately assess areas of stent overlap / gap.
8) Make sure that you image at least 3 cardiac cycles of the culprit vessel at baseline, final intervention, and at follow-up for assessment of TIMI flow. Make sure that the entire vessel, including the distal vasculature, is fully imaged.
9) Make sure that you remove the wire for the final view (post intervention)/
10) At follow-up (angiographic sub-study or for clinical events requiring angiography) please provide the same 2 orthogonal views as at baseline intervention.
11) Use a DICOM CD-R or DVD for pre, final, follow-up and event angiograms if not otherwise specified in the study manual of operations.
12) For DICOM CD-R or DVD labels must include your site ID, the patient ID, the procedure date, and the procedure type (baseline, follow-up or event).

Shipping Instruction

Shipping of Baseline Procedural Angiogram and Follow-up or Event Angiogram to the core lab is specified in the study manual of operations.

APPENDIX IV IVUS/NIRS GUIDELINES

(See also the Study Manual of Operations.)

Imaging: Pre-intervention in the culprit vessel and post-intervention in all three vessels

1. Anticoagulation with either heparin or bivalirudin should be administered prior to IVUS/NIRS imaging. ACT should be monitored and should be above 250 seconds (and 200 seconds with heparin and concomitant glycoprotein 2b/3a use).
2. Make sure that the IVUS catheter is properly flushed at least 3 times.
3. Administer 100-200 µg (200 µg is recommended) of intracoronary nitroglycerine before all NIRS/IVUS examinations.
4. Place the tip of NIRS/IVUS catheter as distally as possible in the coronary artery (minimum 6 cm if possible).
5. Disengaging the guiding catheter before imaging is recommended.
6. Start automatic pullback until the ostium of each vessel is reached and imaged.

IVUS analysis at site to determine eligibility and lesion selection for PROSPECT-ABSORB:

1. Non-culprit lesion can be located in the culprit vessel as well as non-culprit vessel, but must be at least 10mm apart from the edge of a previous PCI (Figure1).
2. Non-culprit lesion is defined as a segment ≥2mm in length which has ≥40% plaque burden in at least 3 slices.
3. Non-culprit lesions are considered separate if there is a ≥5mm-long normal segment with <40% plaque burden between them (Figure2).
4. Once you recognize a non-culprit lesion, look around the minimum lumen area (MLA) site which usually co-locates to the maximum plaque burden site.
5. Contour both lumen and vessel area for 2-3 potential slices (Figure2).
6. If the largest plaque burden ≥65%, this non-culprit lesion qualifies for randomization.
7. In cases that have multiple non-culprit lesions with plaque burden ≥65%, the more proximal lesion should be randomized to PROSPECT ABSORB (example: NC lesion 1 should be randomized, Figure1).

Figure 1

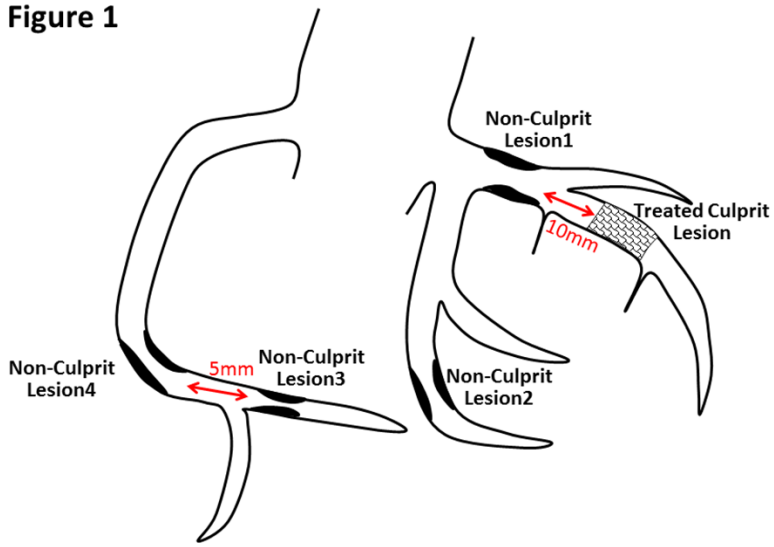
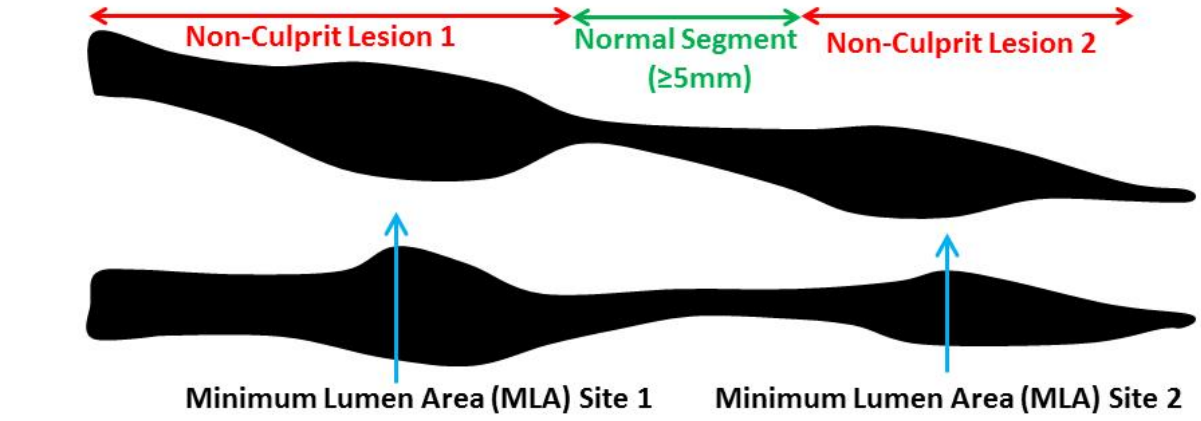


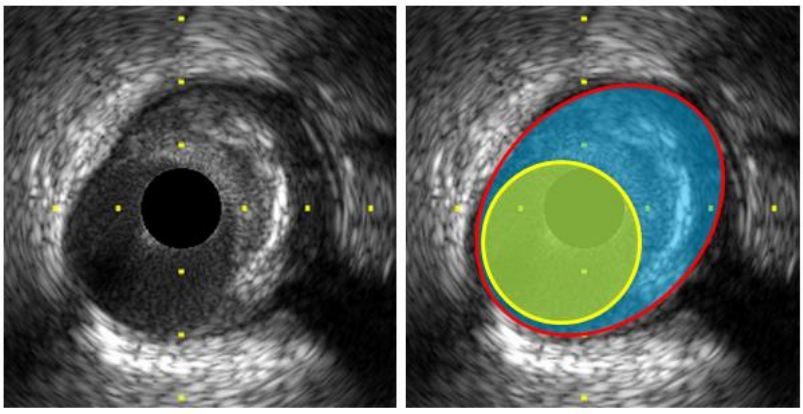
Figure 2



Plaque Burden (%)= ◯ / ◯

◯ = Plaque Area (mm^2)

◯ = Vessel Area (mm^2)



APPENDIX V: ENDPOINT DEFINITIONS (COPIED FROM CEC CHARTER)

Death

All deaths reported post-randomization will be recorded and adjudicated.
Deaths will be sub-classified by CV and non-CV primary cause. CV death includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to a cerebrovascular event, death due to other CV causes (e.g., pulmonary embolism, aortic disease, CV intervention), and deaths for which there was no clearly documented non-CV cause (presumed CV death).

Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to a cerebrovascular event, and death due to other cardiovascular causes, as follows:

1. *Sudden Cardiac Death:* refers to death that occurs unexpectedly and includes any of the following deaths:

a. Death witnessed and instantaneous without new or worsening symptoms
b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)
d. Death after unsuccessful resuscitation from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology
e. Death > 24hrs after a patient has been successfully resuscitated from cardiac arrest and without identification of a non-cardiovascular etiology
f. Unwitnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided if available)

2. *Death due to Acute Myocardial Infarction (MI):* refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause. The acute MI should be verified by the diagnostic criteria outlined for acute MI (including autopsy findings showing recent MI or recent coronary thrombus) and there should be no conclusive evidence of another cause of death.
Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood should be considered death due to acute myocardial infarction. Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI. If death occurs before biochemical

confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence. Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

3. *Death due to Heart Failure or Cardiogenic Shock:* refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure not in the context of an acute MI and without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include <u>any of the following</u>:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure.

b. Heart failure symptoms or signs requiring continuous intravenous drug therapy or oxygen administration

c. Confinement to bed predominantly due to heart failure symptoms

d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin or
- Oliguria (urine output < 30 mL/hour) or
- Altered sensorium or
- Cardiac index < 2.2 L/min/m2

Cardiogenic shock can also be defined as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour. This category will include sudden death occurring during an admission for worsening heart failure.

4. *Death due to Cerebrovascular Event* (intracranial hemorrhage or non-hemorrhagic stroke). Refers to cerebrovascular event and/or the sequelae of which lead to death, generally within 30 days. The cerebrovascular event should be verified by the diagnostic criteria outlined for cerebrovascular events (including autopsy findings) and there should be no conclusive evidence of another cause of death.

5. *Death due to Other Cardiovascular Causes:* death must be due to a fully documented cardiovascular cause not included in the above categories (e.g. pulmonary embolism, aortic disease (dissection or rupture), pericardial tamponade, or cardiovascular intervention).

6. *Presumed cardiovascular death:* All deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint. Of note, Coronary Heart Disease death will include the following categories; Sudden Cardiac Death, Death due to Acute MI, and the subset of Death due to other Cardiovascular Causes that are secondary to a coronary revascularization procedure.

Cardiac death
The composite of sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to arrhythmia, or death not due to known vascular or non-CV causes.

Non-Cardiovascular Death
Non-cardiovascular death is defined as any death not covered by cardiovascular death and falling into one of the following categories:

- Pulmonary failure
- Renal failure
- Gastrointestinal causes
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g. SIRS)
- Hemorrhage that is neither CV bleeding or stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose
- Neurological (non-cardiovascular)
- Malignancy
- Other, please specify.

Definition of Myocardial Infarction

The Third Universal MI definition (Thygesen et al. Eur Heart J 2012;33:2551-67) will be used as the study specific MI criteria during adjudication of spontaneous and demand ischemia MI and MI resulting in death when biomarkers are not available (Type I, II, III). For PCI related MI (Type 4a) and CABG related MI (type 5) the SCAI criteria will be used for primary endpoint adjudication with the Third Universal MI definition used as a secondary analysis.

Criteria for acute myocardial infarction
The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with <u>at least one</u> of the following:
  - Symptoms of ischaemia
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)

- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased

- PCI-related MI is defined based on biomarker elevation measured within 48 hrs of the PCI as well as additional criteria as delineated below as per the SCAI definitions. In addition, the CEC will adjudicate to the alternative 3rd Universal Definition of MI.

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL

- CABG-related MI is defined by elevation of cardiac biomarker values as measured within 48 hrs after the procedure as well as ECG changes and clinical presentation as defined by the SCAI criteria (see below). In addition the CEC will adjudicate to the alternative 3rd Universal Definition of MI (see below).

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes

- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause

- Pathological findings of a prior MI

Third Universal Classification of MI

The following classification will be used by the CEC for classification of MI and will not be captured in the eCRFs.

- Type 1: Spontaneous MI

  Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing

myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD

- Type 2: Myocardial infarction secondary to an ischaemic imbalance

  In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy

- Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

  Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected

- Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

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

- Type 4b: Myocardial infarction related to stent thrombosis

  Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL. Definitions according to ARC will be used. see below.

- Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

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

occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Post-PCI (Type 4a) and post-CABG (Periprocedural) MIs (Type 5):

Periprocedural "clinically relevant" MIs for post-PCI and post-CABG events will be primarily defined based on the SCAI definitions [2] as follows:

1) In patients with normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI, the peak Troponin rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. In the absence of troponins, the peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB,

2) In patients with elevated baseline cTn (or CK-MB) in whom the biomarker levels are stable or falling: The cTn (or CK-MB) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3) In patients with elevated cTn (or CK-MB) in whom the biomarker levels have not been shown to be stable or falling: The cTn (or CK-MB) rises by an absolute increment equal to those levels recommended above *plus* new ST-segment elevation or depression *plus* signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

[1] Thygesen, K, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol, 2012. **60**(16): p. 1581-98.

[2] Moussa, ID, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization an expert consensus document from the society for cardiovascular angiography and interventions (SCAI). JACC 2013;62: 1563-1570.

Unstable Angina

The diagnosis of unstable angina will require ischemic chest pain (or equivalent) at rest considered to be myocardial ischemia upon final diagnosis and without elevation in cardiac biomarkers of necrosis, and the presence of objective evidence of ischemia as defined by at least 1 of the following criteria:

1. New or worsening ST or T wave changes in ≥2 anatomically contiguous leads on a resting ECG (in the absence of LVH and LBBB):
   a) transient (<20 minutes) ST elevation at the J point ≥ 0.2 mV in men (> 0.25 mV in men < 40 years old) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads, or
   b) horizontal or down-sloping ST depression ≥ 0.10 mV, or
   c) T-wave inversion ≥ 0.2 mV

2. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall

motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress), or during physiologic lesion testing during cardiac catheterization (e.g. positive FFR or iFR) that is believed to be responsible for the myocardial ischemic symptoms/signs.

3. Angiographic evidence of ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

Progressive angina

The diagnosis of progressive angina will require increase in angina class or CEC-adjudicated angina equivalent symptoms (e.g. dyspnea on exertion) compared with the most recent stable period considered to be due to myocardial ischemia based on ECG changes, non-invasive testing, FFR/iFR, prompting unplanned angiography, not meeting criteria for myocardial infarction or unstable angina, with one of both of the following.

a. Requiring PCI or CABG, or
b. With angiographic rapid lesion progression

Rapid lesion progression is defined as = angiographic core laboratory-determined QCA ≥10% increase + absolute diameter stenosis (DS) ≥50% OR new thrombosis or ulceration or aneurysm or intimal flap (regardless of DS progression or absolute value)

Definition of Stent Thrombosis

Stent thrombosis will be classified as per the definite or probable Academic Research Consortium Definitions (Cutlip DE et al. Circulation 2007;115:2344-2351). The CEC adjudication result will be compared with the outcome of the ACL angiographic evaluation. Any disagreements will be reconciled between the two parties by regular meetings, see 7.5.

Definite Stent Thrombosis – is considered to have occurred by either angiographic or pathological confirmation.

- The presence of thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour window (The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis {silent occlusion}):

    - Acute onset of ischemic symptoms at rest
    - New ischemic ECG changes that suggest acute ischemia
    - Typical rise and fall in cardiac biomarkers that represent a spontaneous MI
    - Non-occlusive Thrombus: Intracoronary thrombus defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency

surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

- Occlusive Thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

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

Probable Stent Thrombosis – Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days

- Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause