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Statistical Analysis 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)

Statistical Analysis Plan (SAP)

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Statistical Analysis Plan

Signature Page

Author:
Aaron Crowley, MA
Senior Biostatistician
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

DocuSigned by:
Aaron Crowley
Signer Name: Aaron Crowley
Signing Reason: I approve this document
Signing Time: 11-May-2020 | 09:59 EDT
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Signature

11-May-2020 | 09:59 EDT

Date (DD-MMM-YYYY)

Approvers:
Ovidiu Dressler, MD
Director, Medical Analytics & Programming
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

Signature

Date (DD-MMM-YYYY)

Melek Ozgu Issever, MS
Director, Biostatistics & Data Management
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

Signature

Date (DD-MMM-YYYY)

Karin Jensevik, MSc
Biostatistician
Uppsala Clinical Research Center (UCR)
Uppsala Science Park, Hubben
Dag Hammarskjölds väg 38
751 85 UPPSALA

Signature

Date (DD-MMM-YYYY)

Statistical Analysis Plan

Signature Page

Author:

Aaron Crowley, MA
Senior Biostatistician
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

_____ Signature

_____ Date (DD-MMM-YYYY)

Approvers:

Ovidiu Dressler, MD
Director, Medical Analytics & Programming
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

DocuSigned by:
Signer Name: Ovidiu Dressler
Signing Reason: I approve this document
Signing Time: 12-May-2020 | 12:08 EDT
61BDFC950C334703A6830EF692872965
Signature

12-May-2020 | 12:08 EDT
Date (DD-MMM-YYYY)

Melek Ozgu Issever, MS
Director, Biostatistics & Data Management
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

DocuSigned by:
Signer Name: Melek Ozgu Issever
Signing Reason: I approve this document
Signing Time: 12-May-2020 | 12:54 EDT
BB9F5C7BEFEC430B93BD14738DA29B99
Signature

12-May-2020 | 12:54 EDT
Date (DD-MMM-YYYY)

Karin Jensevik, MSc
Biostatistician
Uppsala Clinical Research Center (UCR)
Uppsala Science Park, Hubben
Dag Hammarskjölds väg 38
751 85 UPPSALA

_____ Signature

_____ Date (DD-MMM-YYYY)

Statistical Analysis Plan

Signature Page

Author:
Aaron Crowley, MA
Senior Biostatistician
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

Signature _____ Date (DD-MMM-YYYY) _____

Approvers:
Ovidiu Dressler, MD
Director, Medical Analytics & Programming
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

Signature _____ Date (DD-MMM-YYYY) _____

Melek Ozgu Issever, MS
Director, Biostatistics & Data Management
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

Signature _____ Date (DD-MMM-YYYY) _____

Karin Jensevik, MSc
Biostatistician
Uppsala Clinical Research Center (UCR)
Uppsala Science Park, Hubben
Dag Hammarskjölds väg 38
751 85 UPPSALA

Signature Kan Jensevik Date (DD-MMM-YYYY) 04 MAY 2020

Study Chairs:
David Erlinge, MD, PhD
Professor of Cardiology
Department of Cardiology, Lund University
Skane University Hospital
SE-22185 Lund, Sweden

Signature — Date (DD-MMM-YYYY): 29 April 2020

Gregg W. Stone, MD
Professor of Medicine
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

Signature — Date (DD-MMM-YYYY)

Sponsor:
Lars Wallentin, MD, PhD
Professor of Cardiology
Uppsala Clinical Research Center (UCR)
Uppsala Science Park, Hubben
Dag Hammarskjölds väg 38
751 85 UPPSALA

Signature — Date (DD-MMM-YYYY): 27. April 2020

Study Chairs:

David Erlinge, MD, PhD
Professor of Cardiology
Department of Cardiology, Lund University
Skane University Hospital
SE-22185 Lund, Sweden

_____ _____
Signature Date (DD-MMM-YYYY)

DocuSigned by:
Gregg Stone
Signer Name: Gregg Stone
Signing Reason: I approve this document
Signing Time: 12-May-2020 | 14:46 EDT
7439058DD61A414ABAFE44BE11E86152

12-May-2020 | 14:46 EDT

Gregg W. Stone, MD
Professor of Medicine
Cardiovascular Research Foundation
Clinical Trial Center
1700 Broadway, 9th Floor, New York, NY 10019

_____ _____
Signature Date (DD-MMM-YYYY)

Sponsor:

Lars Wallentin, MD, PhD
Professor of Cardiology
Uppsala Clinical Research Center (UCR)
Uppsala Science Park, Hubben
Dag Hammarskjölds väg 38
751 85 UPPSALA

_____ _____
Signature Date (DD-MMM-YYYY)

Statistical Analysis Plan

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1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in PROSPECT II (Natural History Study) and PROSPECT ABSORB (Randomized Trial). This document may modify and supersede the plans outlined in the protocol; all major modifications of the primary endpoint definition or its analysis will be described and justified (refer to Section 9.0).

1.1 Study Design

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 the intracoronary imaging modalities intravascular ultrasound (IVUS) and near infrared spectroscopy (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 Bioresorbable Vascular Scaffold (BVS) plus guideline directed medical therapy (GDMT) safely increases the minimum luminal area (MLA) at 24 months compared with GDMT alone.

PROSPECT II is a multicenter, prospective, natural history study of acute coronary syndromes (ACS) patients undergoing standard of care angiography and percutaneous coronary intervention (PCI) for treatment of the initial culprit lesion(s). Participants will be examined with IVUS and NIRS in all three coronary arteries. There is no randomization. Clinical follow-up for up to 15 years with a minimum of 24 months for all patients will identify new coronary events. Routine follow-up angiography is not performed in the PROSPECT II cohort, but 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 longest follow-up available, with a minimum of 24-months follow-up for all patients.

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 via block randomization with random block sizes, stratified by site, in a 1:1 fashion (Absorb 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 PROSPECT ABSORB lesion will be selected by the site and declared prior to randomization allocation. 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 imaging 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 study. The patients will be enrolled from approximately 16 sites in Sweden, Denmark, and Norway.

The study flowchart is presented in Appendix 1.

1.2 Study Objectives

1.2.1 Primary Objectives

PROSPECT II

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

PROSPECT ABSORB

To determine whether the Absorb 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 plaque burden 70%).

1.2.2 Secondary Objectives

PROSPECT II

1. To determine in patients with successfully treated ACS the proportion of major adverse cardiac events (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 maximum lipid core burden index over a 4-mm length ($maxLCBI_{4mm}$) in untreated NCLs as a signature for high-risk plaques causing future ACS.

3. To examine the association of $maxLCBI_{4mm}$ and lipid core burden index (LCBI) with 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 examine the association of an algorithm for cap stability (under development) with future NCL-related, vessel-related, and patient-related MACE.

7. To assess the safety and procedural success of 3-vessel IVUS/NIRS imaging during PCI.

8. To identify serologic biomarkers that correlate with findings on angiographic, IVUS, and NIRS imaging and subsequent coronary events.

9. To identify genetic markers that correlate with findings on angiographic, IVUS, and NIRS imaging and subsequent coronary events.

Objectives 8 and 9 will be analyzed within two separate substudies, and their respective analyses will be detailed in separate SAPs, as appropriate.

PROSPECT ABSORB

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 25-month follow-up.

    c. Results in significant plaque regression at approximately 25-month follow-up.

    d. Results in the conversion of a high-risk plaque phenotype (a1. large lipid core plaque; b1. thin fibrous cap) to a low-risk phenotype (a2. small or absent lipid core plaque; b2. thick fibrous cap) at approximately 25-month follow-up.

    e. Results in a low 2-year absolute rates of NCL-MACE arising from the randomized lesion and vessel, with fewer NCL-MACE than in those patients treated with GDMT alone. Although this trial is under-powered for clinical events, the results will serve to inform a large pivotal randomized trial.

    f. Results in low 2-year absolute rates of NCL-TLR and NCL-TVR arising from the randomized lesion and vessel, with fewer NCL-TLR and NCL-TVR than in those patients treated with GDMT alone. Although this trial is under-powered for clinical events, the results will serve to inform a large pivotal randomized trial.

2.0 ENDPOINTS

All potential clinical endpoint events will be assessed and adjudicated by members of an independent Clinical Events Committee (CEC). The results generated by the CEC will be the results used for all event rate reporting. The details of the adjudication process are described in the CEC Charter.

Angiographic images will be assessed by an independent angiographic core lab (ACL) and IVUS/NIRS images will be assessed by an independent intravascular imaging core lab (IVI). The results generated by the core labs will be the results used for all angiographic, IVUS, and NIRS endpoint reporting. In addition, the ACL will 1) provide data to the CEC identifying segments with rapid lesion progression, and 2) will be responsible for determining whether adjudicated events arose from an original a) culprit lesion; b) randomized NCL; c) non-randomized NCL; or d) an indeterminate location.

2.1 Primary Endpoints

PROSPECT II

Patient level rate of NCL-related MACE (NCL-MACE) evaluated at the longest follow-up available, assessed at the time when the last patient enrolled reaches at least 24-month follow-up. NCL-MACE is defined as an event arising from an originally untreated NCL consisting of the composite of 1) cardiac death; 2) myocardial infarction (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. Refer to Appendix 2.4 for definition of rapid lesion progression. The definition of nonprocedural MI will be based on the Third Universal MI definition (1) and the SCAI criteria (2) will be used for procedural MI.

PROSPECT ABSORB

The MLA at the randomized NCL site in patients treated with Absorb BVS + GDMT compared to GDMT alone on a qualifying follow-up IVUS examination (refer to Appendix 2.3 for definition).

2.2 Secondary Endpoints

PROSPECT II

Major Secondary Endpoint: Lesion level rate of NCL-MACE evaluated at the longest follow-up available, assessed at the time when the last patient enrolled reaches at least 24-month follow-up.

Secondary Clinical Endpoints: Total MACE, culprit lesion-related MACE, NCL-MACE, indeterminate MACE, and the components of MACE at the patient level, vessel level, and lesion level, measured at 1 month, 12 months, 24 months, and yearly through 15 years.

PROSPECT ABSORB

Secondary Imaging Endpoints: Angiographic diameter stenosis, plaque burden/regression and remodeling, external elastic membrane (EEM) area, thrombus, plaque ulceration/rupture, max$LCBI_{4mm}$, LCBI, NIRS plaque composition, and other angiographic, IVUS, and NIRS measures at 25 months in randomized lesions (and their change from baseline to 25-month follow-up) as well as in other non-randomized NCLs. In randomized lesions, the number of BVS strut discontinuities, new malapposition, and intra-luminal scaffold dismantling will also be assessed. Refer to Appendix 2.2 and Appendix 2.3 for definitions of qualifying angiograms and IVUS images, respectively.

Secondary Clinical Endpoints: Total MACE, culprit lesion-related MACE, NCL-MACE, randomized lesion-related MACE, indeterminate MACE and their components at the patient level, vessel level, and lesion level measured at 1 month, 6 months, 12 months, 24 months, and yearly through 15 years.

2.3 Safety Endpoints

PROSPECT II

Primary Safety Endpoint: Major complications of IVUS/NIRS imaging during the hospitalization in which the imaging was performed. Major complications of IVUS/NIRS imaging are defined as imaging-related death or vessel dissection/perforation/spasm or other complications requiring percutaneous or surgical treatment (including pericardiocentesis).

Other Safety Endpoint:

- 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.

PROSPECT ABSORB

Primary Safety Endpoint: Randomized target lesion failure (TLF) defined as a composite of cardiac death, target-vessel MI (TV-MI), or ischemia-driven target lesion revascularization (ID-TLR) 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 yearly through 15 years
- Scaffold thrombosis (definite or probable per ARC definition (3)) as per CEC and core lab adjudication measured at 1 month, 6 months, 12 months, 24 months, and 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

3.0 MEASUREMENTS OF INTEREST

Multiple measurements will be made and used in the analyses and assessed for their prognostic value. These include but are not limited to:

1. maxLCBI$_{4mm}$ (with two pre-specified cutoffs: greater than or equal to the upper quartile of observed data and ≥400) in untreated NCLs.

2. maxLCBI$_{4mm}$ (with two pre-specified cutoffs: greater than or equal to the upper quartile of observed data and ≥400) in culprit segments treated with PCI at inclusion.

3. Total LCBI in all coronary arteries, and total LCBI and LCBI over 10 mm and 30 mm segments in coronary arteries not 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 area 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 degrees.

10. Angiographic diameter stenosis, minimum luminal diameter, reference vessel diameter, and lesion length.

11. Angiographic measures of plaque rupture, including ulceration and thrombosis.

4.0 ANALYSIS SETS

PROSPECT II

Full Analysis Set (FAS): All patients enrolled into the PROSPECT II study in whom NIRS imaging of at least one coronary artery was successful (refer to Appendix 2.1).

Safety Analysis Population (SA): All patients enrolled into the PROSCPECT II study in whom an IVUS/NIRS catheter exited the guiding catheter and entered a coronary artery after successful and uncomplicated target lesion PCI (refer to Appendix 2.1.1 and Appendix 2.1.2).

PROSPECT ABSORB

Intention To Treat Population – PROSPECT ABSORB (ITT): All patients who were randomized into the PROSPECT ABSORB substudy. Patients will be analyzed according to randomized treatment, regardless of the treatment actually received.

Per Protocol Population – PROSPECT ABSORB (PP): 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. Patients who are randomized to Absorb BVS + GDMT and did not have at least one BVS implanted or randomized to GDMT alone and underwent PCI of the randomized lesion, will be excluded.

Safety Analysis Population – PROSPECT ABSORB (SAA): All patients randomized into PROSPECT ABSORB, excluding thos randomized to Absorb BVS + GDMT in whom the Absorb BVS did not exit the guide catheter, whether implanted or not.

5.0 GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis for PROSPECT II will be performed after the last patient enrolled has at least 24-month follow-up (i.e. 24 ± 1 month) (25-month follow-up for PROSPECT ABSORB – i.e. 25 months ± 1 month), all relevant data issues have been resolved, and the database is locked. After the primary analysis, patients will continue to be followed yearly for up to 15 years through the Scandinavian medical registers.

5.1 Determination of Sample Size

PASS 2008 Software (NCSS LLC, Kaysville, UT) was used to calculate sample sizes.

PROSPECT II

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 plaque burden ≥70% by IVUS Core Lab assessment and lesions with/without $\text{maxLCBI}_{4\text{mm}}$ greater than or equal to the upper quartile of all measured values.

All analyses examine the relationship between high-risk plaque and clinical outcomes on a patient level and on a lesion level. For all analyses the patient level relationships will be tested first. For all analyses, the relationship between NIRS high-risk plaque and outcomes will be tested first, followed by the relationship between IVUS high-risk plaque and outcomes.

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

$$\lambda(t|x) = \lambda_0(t)e^{\beta X}$$

where $\lambda_0(t)$ is the baseline hazard at time t, and X is an indicator variable for patients or lesions with and without the high-risk imaging characteristic.

Null and alternative hypotheses in the Cox regression model are:

$$H_0: \beta = 0$$

$$H_A: \beta \neq 0$$

where β (the log hazard ratio of the two groups) is the regression slope coefficient for X.

Power Analysis and Sample Size Calculation

Assumptions used in the power calculations are as follows:

- Proportional hazards (Cox regression model)
- 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)

Patient Level Analysis

The primary (first) analysis is tested on the patient level. The sample size estimation is based on the results for plaque burden reported in the original PROSPECT study (4) and considers all patients with untreated lesions (including all randomized untreated lesions from PROSPECT ABSORB). 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 is calculated based on testing the ability of the two coronary artery imaging modalities (IVUS and NIRS) to identify patients with angiographically non-obstructive vulnerable plaques that are subsequently responsible for future unanticipated coronary events. In particular, lesions with core laboratory-assessed plaque burden ≥70% or MLA ≤4.0 mm^2 by IVUS and lesions with $maxLCBI_{4mm}$ greater than or equal to the upper quartile or >400 of all measured values are pre-specified as high-risk plaques.

In the original PROSPECT study, by grayscale IVUS, 220 patients were identified among 660 patients with at least 1 lesion with plaque burden ≥70%. Among these 220 patients, 288 observed lesions had plaque burden ≥70%, which equates to 1.3 high-risk lesions per patient.

For the purpose of the sample size calculation, approximately 900 patients in PROSPECT II will be entered directly into the natural history study with no lesions with plaque burden ≥70%. In the randomized substudy approximately 300 patients will have a mean of 1.3 lesions per patient with plaque burden ≥70%. 150 of these patients are randomized to GDMT alone. 150 of these patients will have 1 plaque burden ≥70% lesion treated by BVS and thus will have mean 0.3 untreated lesions per patient with plaque burden ≥70%, equivalent to 45 patients with 1 untreated plaque burden ≥70% lesion.

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 NCL-MACE rate attributed to patients with ≥1 lesion with plaque burden ≥70% was 17.7% vs 6.0% in patients with no lesions with plaque burden ≥70%. Thus, the assumed overall per patient 2-year NCL-MACE rate given the calculations above is 8.5%.

The principal analysis of the primary endpoint will be adjusted for covariates, chosen a priori and partly based on the results of the original PROSPECT study. An unadjusted analysis will also be conducted. The power calculations will be presented under both conditions.

In an adjusted analysis for plaque burden ≥70%, assuming an overall event rate of 8.5% (~77 events), 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 NCL-MACE. The adjusted hazard ratio of 2.5 is based on the results for adjusted model for plaque burden ≥70% at 24 months in the original PROSPECT study. Regarding NIRS, it is expected that a similar or higher rate of high-risk patients will be detected based on $maxLCBI_{4mm}$ greater than or equal to the upper quartile of observed values. Based on the VH-TCFA data from PROSPECT (in which 22.3% of lesions were classified as TCFAs according to VH-IVUS, and 53.9% 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 $maxLCBI_{4mm}$ greater than or equal to the upper quartile of observed values. Therefore, assuming a prevalence of 50% high-risk patients, assuming 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 assuming 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 hazard ratio for VH-TCFA was 1.7. For the patient level analysis in PROSPECT II, it is assumed that the HR for $maxLCBI_{4mm}$ will be similar to the hazard ratio for ≥70% plaque burden, thus the adjusted hazard ratio of 2.5 is based on the results for ≥70% plaque burden in the original PROSPECT study.

In an unadjusted analysis for plaque burden, assuming an overall event rate of 8.5%, an unadjusted hazard ratio 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 plaque burden ≥70%) and NCL-MACE. The unadjusted hazard ratio of 3.0 is based on the results for plaque burden ≥70% 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 study will have >99% power to detect an unadjusted hazard ratio of 3.0 on a patient level analysis. In the patient level analysis, it is again assumed that the hazard ratio for $maxLCBI_{4mm}$ will be similar to the hazard ratio for ≥70% plaque burden, and thus the unadjusted hazard ratio of 3.0 is based on the results for ≥70% plaque burden in the original PROSPECT study.

Note that the above power analyses were based on 2-year patient level NCL-related event rates from PROSPECT. For all principal analyses in PROSPECT II, all patient level NCL-related events will be counted, including those beyond 2 years. Thus, assuming that the hazard related to baseline high-risk lesions remain as strongly associated with future patient level NCL events beyond 2 years as before 2 years, the estimates above may be conservative.

Lesion Level Analysis

The major secondary analysis is tested on the lesion level. 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 plaque burden <70% there will be 2820 NCL detected. Based on grayscale IVUS in the original PROSPECT study, 288 lesions with plaque burden ≥70% were identified in 220 patients, or approximately 1.3 lesions per patient. Thus, in the 300 patients randomized into PROSPECT ABSORB, it is estimated that 1020 untreated NCL with plaque burden <70% and 240 untreated NCL with plaque burden ≥70% will be detected. This includes 195 untreated NCL with plaque burden ≥70% and 510 untreated NCL with plaque burden <70% in the 150 patients from the

control arm of the PROSPECT ABSORB, and 45 untreated NCL with plaque burden ≥70% and 510 untreated NCL with plaque burden <70% in the 150 patients from the Absorb BVS arm of PROSPECT ABSORB. Assuming 2% of the images will be unable to be read leaves a total of 3763 untreated NCL with plaque burden <70% and 235 untreated NCL with plaque burden ≥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 plaque burden ≥70% as assessed by the site are randomized 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 plaque burden ≥70% was 8.7% vs 0.8% in lesions with plaque burden <70%. Thus, the assumed overall per-lesion 2-year event rate given the number of lesions calculated above is 1.3%.

The principal analysis of the major secondary endpoint will be adjusted for covariates, chosen a priori and partly based on the results of the original PROSPECT study. 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 NCL-MACE on the binary independent variable (positive versus negative observation), the power for various scenarios are shown below.

In an adjusted analysis for plaque burden ≥70%, assuming an overall event rate of 1.3%, an adjusted hazard ratio of 5.0 and 3998 lesions (of which 5.9% are high-risk lesions), there would be 73.7% power to detect the relationship between high-risk NCL and NCL-MACE. The adjusted hazard ratio of 5.0 is based on the results for plaque burden ≥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 $maxLCBI_{4mm}$ greater than or equal to the upper quartile of observed values compared with plaque burden. Based on the VH-TCFA data from PROSPECT, it is assumed that the prevalence of high-risk lesions based on $maxLCBI_{4mm}$ 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 hazard ratio of 3.5. The adjusted hazard ratio of 3.5 is conservatively based on the results for VH-TCFA in the original PROSPECT study, although it is expected that analysis for $maxLCBI_{4mm}$ will result in a stronger association.

In an unadjusted analysis for plaque burden, assuming an overall event rate of 1.3%, an unadjusted hazard ratio 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 NCL-MACE. The unadjusted hazard ratio of 8.0 is based on the results for plaque burden in the original PROSPECT study.

Assuming again that the prevalence of high-risk lesions based on $maxLCBI_{4mm}$ 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 hazard ratio of 4.0. The unadjusted

hazard ratio of 4.0 is conservatively based on the results for VH-TCFA in the original PROSPECT study, although it is expected that analysis for maxLCBI$_{4mm}$ will result in a stronger association.

Note that the above power analyses were based on 2-year NCL-level event rates from PROSPECT. For all principal analyses in PROSPECT II, all NCL-related events will be counted, including those beyond 2 years. Thus, assuming that the hazard related to baseline high-risk lesions remain as strongly associated with future NCL-level events beyond 2 years as before 2 years, the estimates above may be conservative.

PROSPECT ABSORB

Power Analysis and Sample Size Calculation

Patients are entered into the randomized trial with lesions with site-determined plaque burden ≥65%, which should be equivalent to core laboratory assessed plaque burden ≥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 plaque burden ≥70%), and assuming the MLA at 25 months will decrease in the control group to 4.01 ± 1.60 mm^2 versus 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 paired baseline and follow-up IVUS in 140 patients with 1 lesion with plaque burden ≥70% randomized 1:1 to Absorb BVS plus GDMT vs. GDMT alone yields 99% power to demonstrate this difference with a 2-sided α = 0.05. Alternatively, 196 subjects randomized and 75% angiographic follow-up would provide 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 plaque burden ≥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.

5.2 Controlling for Multiplicity

If PROSPECT II meets the principal analysis of its primary endpoint, e.g. if the association between covariate adjusted maxLCBI$_{4mm}$ (using a cutoff defined as the upper quartile of observed NCL values) and NCL-MACE on a patient level is established, then additional hypothesis tests will be performed for other measures of interest in a fixed sequence. This preserves the familywise type I error rate at 0.05.

The order of the hypothesis tests is specified below. No further hypothesis testing will be performed once a hypothesis test has failed. However, statistical comparisons may be reported for hypothesis generating research and publication purposes.

1. Patient level maxLCBI$_{4mm}$ (using a cutoff defined as the upper quartile of observed NCL values), covariate-adjusted

2. Patient level plaque burden ≥70%, covariate-adjusted

3. Lesion level maxLCBI$_{4mm}$ (using a cutoff defined as the upper quartile of observed NCL values), covariate-adjusted

4. Lesion level plaque burden ≥70%, covariate-adjusted

5. Patient level MLA ≤4.0 mm^2, covariate-adjusted

6. Lesion level MLA ≤4.0 mm^2, covariate-adjusted

Caution must be exercised when interpreting p-values displayed for analyses other than those performed for the primary endpoints, as the study was not powered to detect differences on any of those other variables. The resulting p-values, whether or not less-than 0.05, may be a result simply due to chance, and are displayed for hypothesis generating purposes only.

5.3 Interim Analyses and Summaries

No formal interim analyses are planned for this study.

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.

5.4 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 two-sided $\alpha = 0.05$ significance level.

Descriptive statistics of continuous variables will include mean, standard deviation, median, quartiles, range, and number of available observations. For categorical variables, descriptive statistics will include count, percentage, and number of available observations.

Survival analysis techniques will be used to analyze time to event variables that occur at or after 30 days of follow-up. Time to event analysis will be performed for each time point separately (up to 30 days, 6-months (180 days), 1 year (365 days), 2 years (730 days) and at time to last follow-up), and will be summarized by the number of events, Kaplan-Meier estimated event rate, and 95% confidence interval computed using Greenwood's formula. Survival curves will also be constructed using Kaplan-Meier estimation.

All time to event analyses will be performed up at the time of first occurrence of event. Subjects without events will be censored at their early withdrawal date or the last known event-free time point. When analyzing composite endpoints, time is measured from enrollment date to the first occurrence of any event within the composite.

5.4.1 Methods for Patient Level Data

Continuous variables will be compared using analysis of variance (ANOVA) for normally distributed variables. Normality of the distribution will be tested using the Shapiro-Wilk test. If there is evidence of departure from normality ($P < 0.05$ per Shapiro-Wilk test), comparisons will be performed using the non-parametric Wilcoxon rank-sum test.

Categorical variables will be compared using the Chi-square test. If 20% or more of the expected cell frequencies are less than 5 then Fisher's exact test will be used.

Time to event variables will be compared using the log-rank test. Hazard ratios and 95% confidence intervals will be estimated using Cox proportional hazards regression, when applicable.

5.4.2 Methods for Vessel and Lesion Level Data

Continuous variables will be compared using linear mixed effects model, adjusting for patient as a random effect. Normality of the distribution will be tested using the Shapiro-Wilk test. If there is evidence ($P < 0.05$) of departure from normality, comparisons will be performed using the non-parametric Friedman's test.

Categorical variables will be compared using a generalized linear mixed effects model, adjusting for patient as a random effect. Binary data will be modeled assuming a binomial distribution with logit link, count data assuming a Poisson distribution with log link, and categorical data assuming a multinomial distribution with cumulative logit link.

For time to event variables, hazard ratios, 95% confidence intervals, and p-values will be estimated using the Wei-Lin-Weissfeld method (5) to handle clustered data. A robust sandwich covariance matrix estimate will be used to account for within-patient dependencies (correlations of lesions within each patient).

5.5 Methods to Manage Missing Data

For descriptive analyses, no statistical techniques to impute missing data will be used. A complete case analysis will be performed, that is, only available data will be analyzed. All missing data will be excluded from the denominator of the relevant analyses.

Patients who are lost to follow-up will be censored at their last known status time and patients who withdraw will be censored at the date of withdrawal.

The last date on study will be defined, for subjects not lost to follow up, as the study completion/discontinuation date or the death date, whichever is the earlier. For the subjects lost to follow-up, the last date on study will be the date of the last visit or telephone contact with the subject.

Completely or partially missing AE start dates will be imputed with the earliest possible date since enrollment, i.e., the enrollment if completely missing, the first of the month if day is missing (provided that the first of the month is after enrollment), etc.

For covariate adjusted analyses, multiple imputation will be used to account for missing covariate data (refer to Section 6.3).

5.6 Definition and Use of Visit Windows in Reporting

Summaries will be presented at the following periods of time: in-hospital, 1 month (30 days), 6 months (180 days), 12 months (365 days), 24 months (730 days), and then yearly (1 year = 365 days) up to 15 years. The window for the 1 month visit is ±7 days, the window for the 6, 12, and 24 month visits is ±14

days, and the window for yearly visits between 3 and 15 years is ±1 month (30 days). For PROSPECT ABSORB, the window for the 25 month visit ranges between 24.5 and 28 months.

6.0 ANALYSES AND SUMMARIES

PROSPECT II

Analyses of the primary and secondary endpoints will be conducted in the FAS population. Safety analyses will be conducted in the SA population.

These analyses will include all untreated lesions with valid angiographic and/or IVUS/NIRS images from the a) PROSPECT II natural history study (approximately 600 patients); b) the GDMT alone arm from the PROSPECT ABSORB randomized trial (approximately 150 patients); and c) Absorb BVS arm of the PROSPECT ABSORB randomized trial excluding the BVS-treated randomized NCL (approximately 150 patients) will be included in the analysis.

Pre-specified criteria for high-risk (vulnerable) plaque:

1) For NIRS the principal pre-specified cutoff is defined as the highest quartile (25%) of the maxLCBI$_{4mm}$. As a secondary sensitivity analysis a cutoff of ≥400 will be used (6,7).

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.

Patient level analyses will be presented for patients with versus without lesions containing high-risk features (including core lab assessed maxLCBI$_{4mm}$ greater than or equal to the upper quartile cutoff (and ≥400 for sensitivity analysis), plaque burden ≥70%, and/or MLA ≤4.0 mm^2). In patients with multiple lesions, the worst lesion characteristics will be used, including the largest maxLCBI$_{4mm}$, largest plaque burden, largest LCBI, and smallest MLA. Additional exploratory analyses at the lesion and subject level (refer to Section 6.1 below) may be conducted to identify other high-risk features of vulnerable plaque and patients.

PROSPECT ABSORB

Analyses of the primary and secondary endpoint will be conducted in the ITT and PP populations. The primary analysis will be performed in the ITT population and a secondary analysis will be performed in the PP population. Safety analyses will be conducted in the SAA population.

6.1 Baseline and Other Summaries and Analyses

PROSPECT II

Baseline demographic, clinical, angiographic, grayscale IVUS, NIRS, and outcome variables will be summarized for patients and lesions with and without vulnerable plaque defined by both NIRS and IVUS, as well as the overall FAS 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, plaque burden ≥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). Descriptive statistics and comparisons will be reported according to Section 5.4.

PROSPECT ABSORB

Baseline demographic, clinical, angiographic, grayscale IVUS, NIRS, and outcome variables (including follow-up imaging data) will be summarized for Absorb BVS + GDMT versus GDMT alone, as well as the overall ITT population. Descriptive statistics and comparisons will be reported according to Section 5.4.

6.2 Study Conduct and Subject Disposition

PROSPECT II

The frequency and percentage of subjects enrolled overall and broken down by country and site will be provided as a table. The number of subjects screened, enrolled, and discontinued, with reasons for discontinuations (e.g., subject died, withdrew consent, was lost to follow-up, etc.) as documented on the case report form will be presented. Adherence to study inclusion/exclusion criteria and protocol deviations as documented on the case report form will be also be tabulated. Compliance to the follow-up visit schedules will be summarized for all enrolled patients and by site. A by-subject listing of discontinuations and protocol deviations will be reported.

PROSPECT ABSORB

The frequency and percentage of subjects enrolled overall and broken down by country and site will be provided as a table. The number of subjects screened, randomized, and discontinued, with reasons for discontinuations (e.g., subject died, withdrew consent, was lost to follow-up, etc.) as documented on the case report form will be presented overall and by treatment arm. Adherence to study inclusion/exclusion criteria and protocol deviations as documented on the case report form will also be tabulated. A by-subject listing of discontinuations and protocol deviations will be reported.

6.3 Primary Endpoints

PROSPECT II

The primary endpoint is patient level NCL-MACE throughout the whole study period at the time when the last patient enrolled has been followed for at least 24 months. Data will be summarized in patients with versus without vulnerable plaques, and the overall FAS population. Summaries will include the number of events and Kaplan-Meier event rates with 95% confidence intervals. Cox proportional hazards regression will be used to test the relationship between patients with vulnerable plaques and NCL-MACE. Hazard ratios with 95% confidence intervals and p-values will be reported. Principal analyses will be based on results from covariate adjusted models.

The assumption of proportional hazards will be assessed by plotting the log-negative-log survival curves vs the log of survival time for each group. If it is determined that the proportional hazard assumption is

violated, then a logistic regression will be performed adjusting for follow-up time. In this case, odds ratios with 95% confidence intervals and p-values will be reported.

Both unadjusted and covariate adjusted analyses will be performed. The following covariates, chosen a priori and partly based on the results of the original PROSPECT study, will be included in the primary models:

- 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)
- Total imaged NIRS-IVUS length (mm)

The primary analysis will test for an association between $maxLCBI_{4mm}$ (using a cutoff defined as the upper quartile of observed NCL values) and NCL-MACE using covariate adjusted models. Secondary analyses will test for an association between plaque burden ≥70% and MLA ≤4 mm^2. A cutoff of plaque burden $\geqslant$65% and $maxLCBI_{4mm}$ cutoffs of (1) $\geqslant$400, (2) $\geqslant$lower quartile vs <lower quartile, and (3) $\geqslant$ 400 vs $\geqslant$100 and <400 vs <100 (definition of LRP category) will be examined as sensitivity analyses.

Exploratory analyses will also assess the relationship between NCL-MACE and $maxLCBI_{4mm}$, LCBI, and plaque burden. These individual parameters will be modeled as linear continuous variables and non-linear continuous variables using spline transformations. An analysis of the classification of NIRS/IVUS plaque phenotype as described in Appendix 2.5 will also be performed.

Robustness analyses will be performed on the following sub-populations:

- Excluding patients who experienced events arising from NCLs without images at baseline
- Excluding events in patients who experienced events arising from NCLs without images at baseline

- Excluding patients who had a single randomized vulnerable plaque (PROSPECT ABSORB randomized cohort) and who had no other vulnerable plaque lesions (defined as plaque burden ≥70% as assessed by the core lab)

A sensitivity analysis of the primary endpoint will be performed by imputing missing covariate data by using multiple imputation by the MCMC algorithm using 10 imputed datasets, including the covariates specified above.

PROSPECT ABSORB

The primary efficacy endpoint is MLA at the randomized NCL site in patients treated with Absorb BVS + GDMT compared to GDMT alone on a qualifying IVUS study (refer to Appendix 2.3 for definition of qualifying IVUS). The adjusted mean and 95% confidence interval for each group, and difference with 95% confidence interval, and p-value will be calculated using an analysis of covariance model (ANCOVA), adjusted for baseline MLA. The primary analysis will be conducted in the ITT population and a secondary analysis will be performed in the PP population.

For the primary endpoint, the follow-up MLA will be determined at the vessel cross-section corresponding to the original baseline MLA cross-section, compared between the two groups adjusted for baseline MLA (analysis of covariance [ANCOVA]). As a sensitivity analysis, the follow-up MLA will be determined within the entire randomized NCL and compared between the two groups adjusted for the baseline lumen area cross section corresponding to the follow-up MLA.

When the follow-up angiogram shows a total occlusion (ie, TIMI 0 or 1 flow), the MLA value will be imputed as 0.0 mm^2. When the angiogram shows a non-total occlusion (ie, TIMI ≥2 flow) and the operators require pre-balloon dilatation to cross the IVUS catheter, the MLA value will be imputed as 1.3 mm^2 (the cross-section area of the IVUS imaging sheath). If the IVUS was performed after pre-balloon dilatation, all morphology except MLA will be used as measured.

For the primary analysis, MLA data missing at follow-up will not be imputed. As a sensitivity analysis, missing follow-up MLA data will be imputed by multiple imputation with MCMC algorithm using 10 imputed datasets, including the following covariates: age, sex, diabetes, prior PCI, discharge use of high-dose statin or any PCSK9 inhibitor, and the following baseline IVUS parameters, EEM area, plaque burden, MLA, lesion length, vessel (LM/LAD, LCX, RCA), distance from ostium to MLA, max calcium angle at the lesion. The resulting estimates and 95% confidence intervals will be presented.

6.4 Secondary Endpoints

PROSPECT II

Major Secondary Endpoint

The major secondary endpoint is the covariate-adjusted lesion level NCL-MACE throughout the whole study period until last patient has been followed for at least 24 months. Data will be summarized in patients with versus without vulnerable plaques, and overall FAS population. Summaries will include the

number of events and Kaplan-Meier event rates with 95% confidence intervals. The Wei-Lin-Weissfeld method will be used to test the direct relationship between lesions with vulnerable plaques and NCL-MACE. Hazard ratios with 95% confidence intervals and p-values will be reported. A robust sandwich covariance matrix estimate will be used to account for the within-patient dependencies (correlations of lesions within each patient).

Details of the analyses are as described above for the primary endpoint. When possible, variables will be defined on the lesion level.

Sensitivity analyses on the lesion level will consider the following additional covariates:

- LM/LAD, LCX, versus RCA
- Remodeling index, categorized into the following groups
    - Positive remodeling is a remodeling index >1.0
    - Negative remodeling is remodeling index <0.88
    - Intermediate remodeling is a remodeling index ≥0.88 and ≤1.0
- Lesion length (cutoff defined as the median of observed NCL values)
- Disease angle ≥330 degrees
- Distance from the coronary ostium to the MLA, per main epicardial vessel (cutoff defined as the median of observed NCL values)

Analyses of the major secondary endpoint will be repeated using a shared frailty model, adjusting for within-patient correlations using a random effect term, as a robustness analysis.

Secondary Clinical Endpoints

Secondary clinical endpoints will be analyzed in a similar way as the primary and major secondary endpoints above, or as applicable, as described in the Section 6.3. Univariate analyses will be performed for all study timepoints at patient, vessel, and lesion level, as applicable.

<u>PROSPECT ABSORB</u>

Secondary imaging endpoints will be analyzed in a similar way as the primary endpoint (Section 6.3), or as applicable, as described in the Section 5.4. Univariate analyses will be performed for all study timepoints at patient, vessel, and lesion level, as applicable.

Secondary Clinical Endpoints

Secondary clinical endpoints will be analyzed in a similar way as the primary and major secondary endpoints above, or as applicable, as described in the Section 6.3. Univariate analyses will be performed for all study timepoints at patient, vessel, and lesion level, as applicable.

6.5 Additional Endpoints

PROSPECT II

The correlation between maxLCBI$_{4mm}$, plaque burden, MLA, and other continuous variables will be summarized using Spearman correlation coefficients with 95% confidence intervals.

The diagnostic utility of plaque burden, maxLCBI$_{4mm}$, and MLA will be quantified using the Area Under the Receive Operating Characteristic Curve (AUROC) for the primary and major secondary endpoint. The AUC and 95% confidence interval will be reported based on logistic regression models. Optimal cutoffs, defined as the cutoff that maximizes Youden's J statistic (Youden's index), and associated diagnostic statistics (sensitivity, specificity, etc.) will also be reported. Two additional versions of concordance statistics, Harrel's (8) and Uno's (9) C-statistics will also be reported. These newer statistics are specifically designed to analyze right-censored survival data. Time-dependent ROC curves will also be explored.

PROSPECT ABSORB

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

A multivariable analysis of NCL-MACE will be performed by treatment for all covariates in the primary and major secondary endpoint analysis of PROSPECT II, at all study time points, and at patient, vessel, and lesion levels.

6.6 Subgroup Analyses

PROSPECT II

Forest plots will be constructed for the primary endpoint, major secondary endpoint, and all safety endpoints to test for interactions between high-risk and low-risk features. The following subgroups will be analyzed:

- Age (cutoff defined as the median of observed values)
- Sex
- Diabetes mellitus (none, medically-treated without insulin, insulin-treated)
- Prior history of MI

- Prior PCI
- Clinical presentation (STEMI versus NSTEMI)
- maxLCBI$_{4mm}$ (cutoff defined as the upper quartile of observed NCL values)
- maxLCBI$_{4mm}$ (cutoff defined as the median of observed NCL values)
- maxLCBI$_{4mm}$ $\geqslant$400 vs. < 400
- maxLCBI$_{4mm}$ categorized into 3 groups: $\geqslant$upper quartile vs <upper quartile and $\geqslant$lower quartile vs <lower quartile
- maxLCBI$_{4mm}$ categorized into 3 groups: $\geqslant$400 vs $\geqslant$100 and <400 vs <100
- Plaque burden (≥70% versus <70%)
- Plaque burden (<40% vs. ≥40% to <50% vs. ≥50% to <60% vs. ≥60% vs. <70% vs. ≥70% to <80% vs. >80%)
- Plaque burden (cutoff defined as the median of observed NCL values)
- MLA (≤4 versus >4 mm^2)
- MLA (cutoff defined as the median of observed NCL values)
- Remodeling index by IVUS, categorized into the following groups
    - Positive remodeling is a remodeling index >1.0
    - Negative remodeling is remodeling index <0.88
    - Intermediate remodeling is a remodeling index ≥0.88 and ≤1.0
- Lesion length by IVUS (cutoff defined as the median of observed NCL values)
- Distance from the coronary 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
- LDL (cutoff defined as the median of observed values)

- HDL (cutoff defined as the median of observed values)
- hs-CRP (cutoff defined as the median of observed values)

Interaction p-values <0.10 for subgroups will be considered positive but nonetheless hypothesis generating.

PROSPECT ABSORB

Forest plots will be constructed for the primary efficacy and primary safety endpoints to test for interactions between treatment arms. The subgroups specified for PROSPECT II will be re-analyzed in PROSPECT ABSORB, in addition to the following:

- Reference lumen area by IVUS (median)
- Presence of calcification by IVUS (<180 versus ≥180 degrees)

6.7 Multicenter Studies

Primary analyses will be performed pooling data across study sites.

The site effect will be tested at a 15% level of significance. Sites enrolling <10 subjects will be combined for these analyses.

PROSPECT II

Primary analyses will be repeated including an interaction between high- and low-risk features and study site.

PROSPECT ABSORB

Primary analysis will be repeated including an interaction between treatment and study site.

6.8 Safety Summaries and Analyses

PROSPECT II

Safety analyses will be conducted in the SA population.

The primary safety endpoint in PROSPECT II is major complications of IVUS/NIRS imaging, defined as imaging-related death, vessel dissection/perforation/spasm or other complication requiring percutaneous or surgical treatment (including pericardiocentesis), during the hospitalization in which the imaging was performed. Data will be summarized by the number of events, proportion, and exact 95% confidence interval (Clopper-Pearson (10)) on a patient level for the entire study, not broken down by imaging risk group. For patients undergoing planned staged procedures, all IVUS/NIRS imaging-

related complications from both procedures will be included. Other safety endpoints will be analyzed similarly.

PROSPECT ABSORB

Safety analyses will be conducted in the SAA population.

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. Data will be summarized for each trial arm and the overall by the number of events and Kaplan-Meier estimated event rate. Hazard ratio with 95% confidence interval will be estimated using a Cox proportional hazards regression model. Other safety endpoints will be analyzed similarly.

6.8.1 Adverse Events

Site reported death, myocardial infarction, hospitalization for unstable or progressive angina, symptom-driven revascularization, and scaffold thrombosis events will be summarized in the SA population for PROSPECT II and in the SAA population for PROSPECT ABSORB as described in the Section 5.4.

6.8.2 Laboratory Data

The following clinical laboratory measurements will be collected at baseline and summarized in the FAS population for PROSPECT II and the ITT population for PROSPECT ABSORB using descriptive statistics:

- Hemoglobin
- WBC
- Platelet count
- Creatinine
- HbA1C
- Total Cholesterol, HDL, LDL, Triglycerides (fasting)
- P-glucose
- hs-CRP

Units of all laboratory measurements will be converted into U.S. Conventional units before any descriptive analyses are performed. The collected units for each laboratory parameter and their conversion to Conventional units are presented in Table 1:

Table 1. Conversion of Laboratory Parameters

Laboratory Parameter (unit)	Collected unit	Conversion to Conventional
White Blood Cell (10^3/µL)	10^9/L	= 10^3/µL
	10^3/mm^3	= 10^3/µL
	Cells/mm^3	x 0.001 = 10^3/µL

Platelet Count (10^3/µL)	10^9/L	= 10^3/µL
	10^3/mm^3	= 10^3/µL
	Cells/mm^3	x 0.001 = 10^3/µL
Hemoglobin (g/dL)	g/L	x 0.1 = g/dL
	mmol/L	x 1.611 = g/dL
Creatinine (mg/dL)	µmol/L	x 0.01131 = mg/dL
Total Cholesterol (mg/dL)	mmol/l	x 38.66 = mg/dL
LDL (mg/dL)	mmol/l	x 38.66 = mg/dL
HDL (mg/dL)	mmol/l	x 38.66 = mg/dL
Triglycerides (mg/dL)	mmol/l	x 88.5 = mg/dL

The following cardiac biomarkers will be collected at baseline and post-procedure, and summarized in the SA population for PROSPECT II and in the SAA population for PROSPECT ABSORB using descriptive statistics:

- Standard or high sensitivity troponin (hs-Troponin)

For troponin measures, the frequency and percentage of subjects falling into each of the following categories will be presented separately for pre- and post-procedure:

- ≤1x the 99th percentile of URL , >1x the 99th percentile of URL, ≥1-3x the 99th percentile of URL, ≥3x the 99th percentile of URL, ≥3-5x the 99th percentile of URL, ≥5x the 99th percentile of URL, ≥5-10x the 99th percentile of URL, ≥10x the 99th percentile of URL, ≥10-35x the 99th percentile of URL, ≥35x the 99th percentile of URL, ≥35-70x the 99th percentile of URL, ≥70x the 99th percentile of URL. For patients with 99th percentile URL reference data, the ULN will be substituted.

6.8.3 Concomitant Medications

Concomitant medication use will be summarized by in the FAS population for PROSPECT II and the ITT population for PROSPECT ABSORB by the frequency (number and percentage of subjects) at each visit for all subjects based on the FAS analysis population for PROSPECT II, and ITT for PROSPECT ABSORB. In addition to concomitant medication use, antithrombotic medication use will be summarized for pre- (within 24 hours), during, and post-procedure.

7.0 REFERENCES

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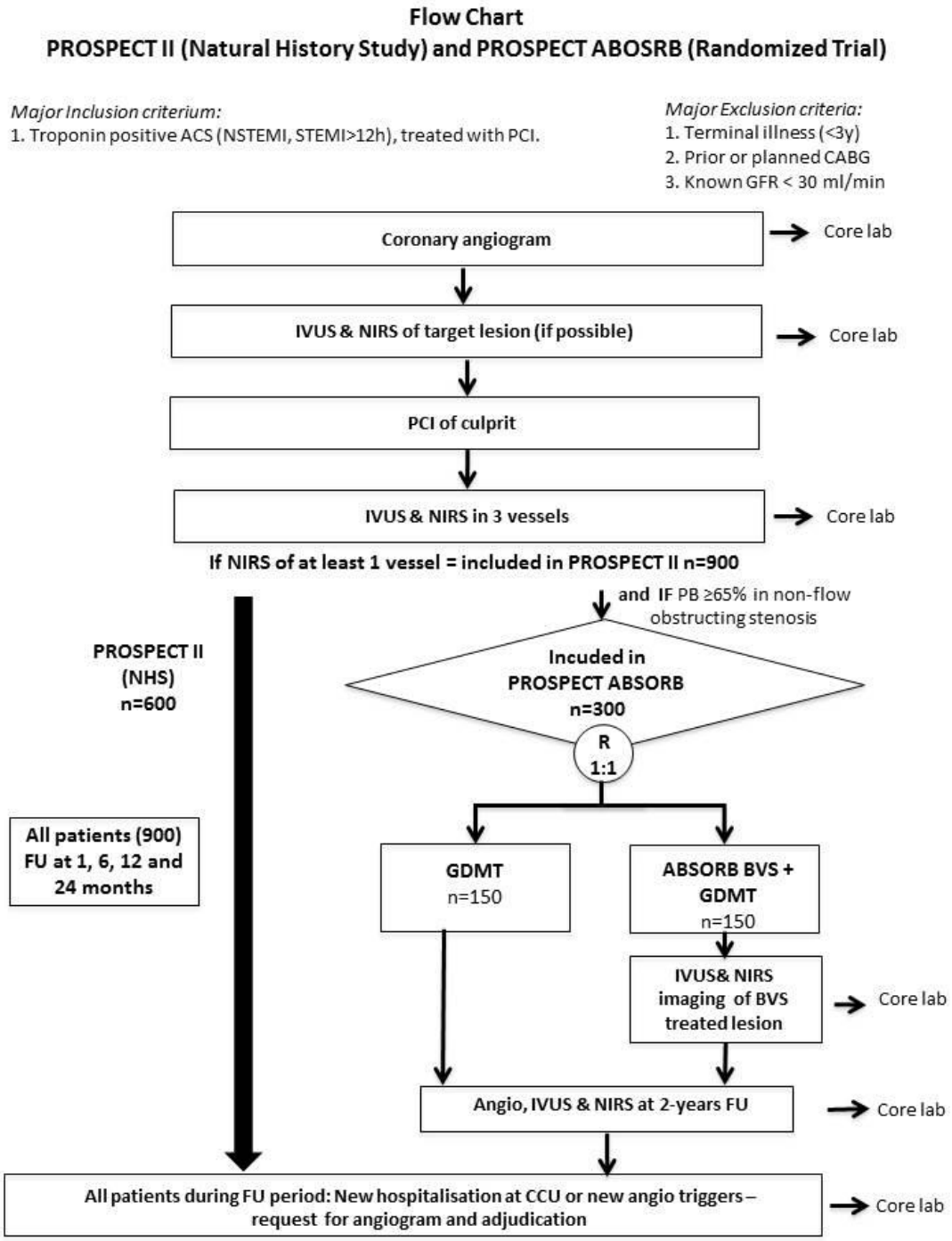
8.0 APPENDICES

Appendix 1. Study Flowchart



Appendix 2. Definitions

Appendix 2.1. Definition of Study Enrollment

Patients will be considered formally enrolled in PROSPECT II only after PCI of all intended target culprit lesions have been successfully completed and after the study imaging catheter is passed out of the guide catheter into a coronary artery. If staged procedures are 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) and the final stage is completed within 4 weeks of patient presentation with ACS.

Appendix 2.1.1. Definition of Successful PCI

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

Appendix 2.1.2. Definition of Uncomplicated PCI

PCI will be considered uncomplicated if all of the following occur:

a) The patients has had no intra-procedural chest pain lasting >10 minutes

b) The patients 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, residual dissection (>Type B)

d) The patient has not required cardiopulmonary resuscitation

e) The patient has not had ventricular arrythmias requiring cardioversion or intravenous medication or conduction system disease requiring temporary pacemaker insertion

f) The patients 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 judgement of the investigator may result in MACE within 30 days, including the likely diagnosis of periprocedural MI (SCAI criteria, see CEC Charter).

Appendix 2.2. Definition of Qualifying Follow-up Angiogram Study

A qualifying angiogram includes all angiographic images obtained within the valid window, as defined herein:

- For BVS-treated patients with definite scaffold thrombosis or angiographic restenosis (core lab DS >50% or TLR performed), that angiogram meets the criteria as a qualifying angiogram. For GDMT alone-treated patients, any new thrombotic or plaque ulceration event or progressive disease with core lab DS >50% or undergoing TLR, that angiogram meets the criteria as a qualifying angiogram.

- For BVS-treated patients without definite scaffold thrombosis or angiographic restenosis and without TLR, angiographic follow-up ≥12 months will qualify. For GDMT alone-treated patients, without any new thrombotic or plaque ulceration event or progressive disease with core lab DS >50% and without TLR, angiographic follow-up ≥12 months will qualify.

- For patients with multiple angiographic follow-up procedures without TLR, the latest qualifying valid angiogram that is closest to the protocol 25-month angiographic follow-up window will be used.

Appendix 2.3. Definition of Qualifying Follow-up IVUS Study

A qualifying IVUS includes all IVUS images obtained within the valid window, as defined herein:

- For BVS-treated patients with definite scaffold thrombosis or angiographic restenosis (core lab DS >50% or TLR performed), that IVUS meets the criteria as a qualifying IVUS. For GDMT alone-treated patients, any new thrombotic or plaque ulceration event or progressive disease with core lab DS >50% or undergoing TLR, that IVUS meets the criteria as a qualifying IVUS.

- For BVS-treated patients without definite scaffold thrombosis or angiographic restenosis and without TLR, IVUS follow-up ≥12 months will qualify. For GDMT alone-treated patients, without any new thrombotic or plaque ulceration event or progressive disease with core lab DS >50% and without TLR, IVUS follow-up ≥12 months will qualify.

- For patients with multiple IVUS follow-up procedures without TLR, the latest qualifying valid IVUS that is closest to the protocol 25-month angiographic follow-up window will be used.

Appendix 2.4. Definition of Rapid Lesion Progression and Lesion Regression

- Angiographic rapid lesion progression of a NCL is defined as QCA ≥10% increase + absolute diameter stenosis (DS) ≥50% on the follow-up angiogram compared with the baseline angiogram

OR new thrombosis or ulceration or aneurysm or intimal flap on the follow-up angiogram (regardless of DS progression or absolute value). This is the primary definition of "rapid lesion progression" which is a component of the primary endpoint (i.e. IVUS rapid lesion progression is not considered for the primary endpoint determination).

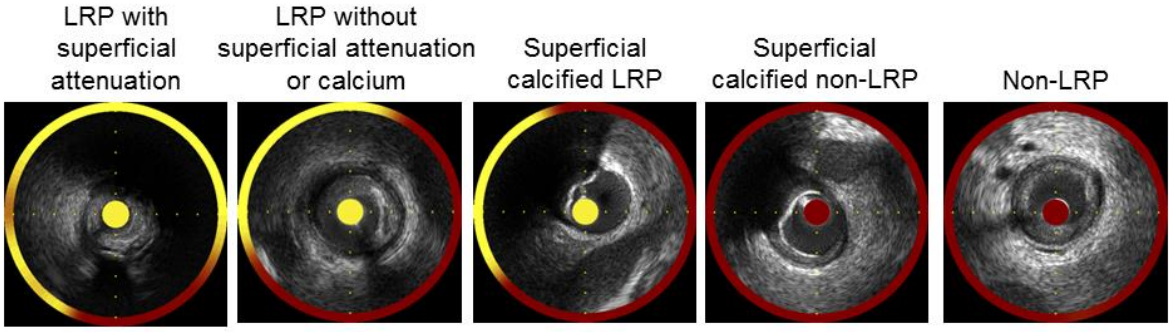
- Angiographic lesion regression of a NCL is defined as a ⩾10% decrease of diameter stenosis by QCA from index to follow-up.

- IVUS rapid lesion progression is defined as 1) ≥0.5mm^2 decrease of MLA from index to follow-up; or 2) ≥10% relative increase of plaque burden from index to follow-up, or 3) presence of new thrombus or plaque rupture at follow-up as assessed by the IVUS core laboratory.

- IVUS lesion regression is defined as 1) ≥0.5mm^2 increase of MLA from index to follow-up; or 2) ≥10% relative decrease of plaque burden from index to follow-up.

Appendix 2.5. Classification of NIRS/IVUS Plaque Type (11,12)

Plaques are categorized as: (1) Lipid-rich plaque (LRP) with superficial attenuation (>30^o in more than 3 consecutive frames, presumably indicating the presence of necrotic core or lipid pool); (2) LRP without superficial attenuation or calcium; (3) Superficial calcified LRP (superficial calcium >90^o) presumably indicating the presence of necrotic core or lipid pool; (4) Superficial calcified non-LRP (superficial calcium >90^o); and (5) Non-LRP (Figure). LRP will be defined as maxLCBI4mm >upper-quartile of maxLCBI$_{4mm}$ or 400. In lesions having multiple plaque types within the lesion, the lesion phenotype with the greatest maxLCBI$_{4mm}$ will be used. In lesions having multiple plaque types within the maxLCBI$_{4mm}$ segment, the following hierarchy will be used; LRP with superficial attenuation, LRP without superficial attenuation or calcium, superficial calcified LRP, superficial calcified non-LRP, and non-LRP. In lesions without LRP (i.e. maxLCBI$_{4mm}$ < the cut-off value), the plaque type at the MLA will be evaluated.



9.0 DEVIATIONS FROM PROTOCOL ANALYSIS PLAN

The following modifications have been made to the plans outlines in the protocol.

Table 2. Summary of Changes from Original Protocol Analysis Plan

Deviation	Rationale
Analysis of PROSPECT II has been extended to include the maximum follow-up available for all patients, requiring a minimum of at least 24-month follow-up in all patients.	To maximize statistical power, the analysis will utilize the entirety of each patient's follow-up and additionally include clinically important revascularizations.
Definition of NCL-MACE has been clarified and expanded to include progressive symptoms with rapid lesion progression	Not all cases of progressive symptoms will undergo revascularization. Rapid lesion progression is consistent with vulnerable plaque progression.
Analysis of lesion level time-to-event variables will be performed using the Wei-Lin-Weissfield method to adjust for clustered data.	Standard errors in traditional Cox proportional hazards regression models are too small, resulting in inflated type I error rates.

10.0 VERSION HISTORY

This SAP for PROSPECT II and PROSPECT ABSORB is based on protocol version 4 dated APR 2020.

Table 3. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Initial version