Implementation of a Standardized Algorithm for CoronarY CaLcificatiOn with PlaquE Modification using UltraSound Guidance to Improve Procedural and Clinical Outcomes (CYCLOPES)

CYCLOPES

Clinical Investigation Plan

Version 1.1

Date: 11 Aug 2024

Cardiovascular Research Institute Dublin,

Mater Private Network & RCSI University

Dublin, D07KWR1, IRELAND

SPONSOR PROTOCOL AGREEMENT PAGE

The signatories have read and understood the clinical protocol and agree to conduct the clinical investigation in compliance with this Clinical Investigation Plan (CIP).

SPONSOR – Royal College of Surgeons Ireland (RCSI)

Name: Prof. Fergal O'Brien

_____

Title: Prof. Fergal O'Brien is Professor of Bioengineering & Regenerative Medicine, Deputy Vice Chancellor for Research & Innovation

Date: _____

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other clinical conduct procedures provided by the Sponsor.
- To ensure that the requirements for obtaining informed consent from each subject are met.
- Not to implement any changes to the protocol without written agreement from the Sponsor and prior review and written approval from the independent ethics committee (IEC), if applicable, except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study and control devices, as described in this protocol and any other information provided by the Sponsor.
- That I am aware of and will comply with the principles of good clinical practice and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study algorithm and procedures and have been trained in their study-related duties and functions as described in the protocol.

Site name: _____

Principal Investigator Name (print): _____

Principal Investigator's Signature: _____ Date: _____

CLINICAL RESEARCH ORGANIZATION (CRO) PROTOCOL AGREEMENT PAGE

The signatories have read and understood the clinical protocol and agree to conduct the clinical investigation in compliance with this Clinical Investigation Plan (CIP).

CVRI (Cardiovascular Research Institute) Dublin, Mater Private Network Dublin

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Name: Prof. Prof. Robert A. Byrne

_____

Title: Director

Date: _____

CERC (Cardiovascular European Research Center SAS)

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Name: Dr. Marie-Claude Morice

_____

Title: CEO

Date: _____

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REVISION HISTORY

Version	Date	Reason for Change
1.0	01 MAR 2024	First version
1.1	11 AUG 2024	Modifications: - Added contact details of Clinical research organizations (CROs), imaging Corelab, EDC provider - Added page of signature for CROs, investigation sites - Updated study staff - Removed incorrect reference to DSMB - Clarified timeline requirement for 12 lead ECG prior to discharge - Clarification on when a pregnancy test should be undertaken - Amendment of 30 day and 12 month follow-up intervals - Include reference to Data Safety Plan - Include reference to EU General Data Protection Regulation (GDPR 2016/679). - Include reference to EU MDR 2017/745

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Electronic Data Capture (EDC) Provider	Clean web Telemedecines Technologies SAS 121 rue d'Aguesseau 92100, Boulogne-Billancourt France	Email: hotline@tentelemed.io

PROTOCOL SUMMARY

Title:	Implementation of a Standardized Algorithm for **C**oronar**Y** **C**a**L**cificati**O**n with **P**laqu**E** Modification using Ultra**S**ound Guidance to Improve Procedural and Clinical Outcomes **(CYCLOPES)**
Investigational strategy:	Calcium modification algorithm (Figure 1) to guide coronary intervention with an HD IVUS imaging guided pathway that provides a systematic approach to coronary modification.
Study Population:	Patients with coronary artery disease with evidence of moderate to severely calcified coronary arterial lesions that are planned for percutaneous intervention requiring calcium modification.
Design:	CYCLOPES is a prospective, multicenter, open-label, single arm trial assessing the feasibility and efficacy of an intracoronary ultrasound guided algorithm (Figure 1) for calcium modification in patients undergoing percutaneous coronary intervention (PCI) for chronic calcific coronary artery disease. The study will enroll 500 patients who will undergo PCI with calcium modification. Participants will be enrolled prospectively in 25 sites in Ireland, Switzerland, the United Kingdom, Spain, France, Italy and Germany (7 countries). All patients will have coronary angiography (QCA) and intravascular ultrasound (IVUS) imaging with 60MHz HD IVUS of the calcified lesion at baseline. The lesion will be characterized based on calcium distribution and morphology as assessed by HD IVUS. Depending on the specific lesion characteristics, the appropriate method for calcium modification will be chosen and performed in line with the CYCLOPES calcium modification algorithm included in the study protocol. The calcific lesion will be imaged for a second time by 60MHz HD IVUS following calcium modification. The operator will then proceed, if no further lesion preparation is required, to deploy a bioabsorbable polymer Everolimus eluting stent using standard stenting techniques, post dilatation will be performed at the operator's discretion. The treated lesion will be assessed again using intravascular ultrasound following stent deployment and optimization.

	The primary end points will be the post stenting minimal stent area (MSA) at the site of maximum calcification relative to reference lumen area assessed with 60MHz HD IVUS and target lesion failure (TLF) at 1-year post-procedure. All HD IVUS determined endpoints will be assessed at an independent imaging core laboratory. Participants will be assessed with clinic or phone visits at hospital discharge, 1 month and 12-month time points post procedure.
Objectives:	The aim of this study is to validate a comprehensive and intravascular imaging-based calcium modification algorithm for the treatment of moderate to severely calcified coronary lesions.
Primary Endpoints:	The study will have co-primary endpoints: 1. Minimum stent area (MSA) at the site of maximum calcification measured at the end of the index procedure 2. Target lesion failure (TLF) (cardiovascular death, non-fatal myocardial infarction (MI) related to the target vessel, unplanned ischemia-driven target lesion revascularization) at 1 year
Secondary Endpoints:	1. Individual components of TLF at 1 month and 1 year 2. Minimum stent area (MSA) at the end of the index procedure 3. Strategy success defined as: a) Successful stent delivery b) ≥ 80% stent expansion c) Complete stent apposition d) No edge dissection e) Full lesion coverage with <50% plaque burden at proximal and distal references f) TIMI 3 flow 4. Target vessel revascularization (TVR) 5. Target lesion revascularization (TLR) 6. Stent thrombosis 7. Stroke 8. Cardiovascular death

	9. Acute kidney injury 10. Major bleeding, categorized as class 3-5 according to the Bleeding Academic Research Consortium [BARC] 11. Procedure time 12. Fluoroscopy time 13. Radiation exposure (dose-area-product) 14. Cost effectiveness analysis
Sample size:	500 patients
Inclusion Criteria:	1. Documented myocardial ischaemia. 2. At least one moderate to severely calcified native coronary artery lesion confirmed by QCA and/or 60MHz HD IVUS, with the presence of significant calcium, ≥70% diameter stenosis by visual estimation (in a reference vessel diameter of ≥2.5mm and ≤4.0mm) and TIMI 3 flow at baseline that is suitable for PCI. a. Significant calcium at the target lesion site is defined as either: i. The presence of radiopacities involving both sides of the arterial wall >10mm and involving the target lesion on angiography. or ii. The presence of >270° arc of superficial calcium on HD intravascular imaging with a length >5mm or the presence of 360° arc of calcium on HD intravascular imaging. [1] 3. It is possible to cross the calcified lesion with a coronary guidewire. 4. Age ≥ 18 years. 5. Patient is willing and able to comply with the study procedures and follow-up.
Exclusion Criteria:	1. Patients with cardiogenic shock. 2. ST-segment elevation myocardial infarction. 3. Instent re-stenosis. 4. Stent thrombosis. 5. Coronary artery dissection. 6. Chronic total occlusion in a major artery. 7. Left ventricular ejection fraction ≤30%.

	8. Need for coronary artery bypass graft surgery. 9. Documented allergy to everolimus or to any stent material 10. Any contraindication for dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for at least 3 months (except for patients on oral anticoagulation). 11. For female, pregnancy, breastfeeding or intend to become pregnant within 1 year 12. Life expectancy <1 year. 13. Participation in another study with an investigational product. 14. Inability to provide informed consent.
Study oversight:	An independent clinical events committee (CEC) will adjudicate clinical events that are primary or secondary endpoints or components of same. The study will be monitored per a monitoring plan, data will be collected in an electronic case report form (eCRF). QCA and HD IVUS data will be assessed by independent core laboratories.
Study organization:	**- Sponsor:** Royal College of Surgeons in Ireland **- CRO for study management in Ireland**: Cardiovascular Research Institute (CVRI) Dublin, Mater Private Network Dublin **- CRO for study management in other countries**: CERC (Cardiovascular European Research Center)n
Antiplatelet Therapy:	Dual anti-platelet therapy (DAPT) (P2Y12 inhibitor plus aspirin) should be prescribed for 6 months, but the duration may be adjusted in keeping with the prescribing physician's usual clinical discretion and depending on clinical bleeding risk.
Follow-up:	1. On the day of discharge from the index procedure 2. 30 days +/- 7-day window (clinic or phone visit) 3. 12 months +/- 30-day window (clinic or phone visit)
Study Duration:	The expected duration of the study is approximately 36 months (18 months to complete enrollment, plus 12 months to complete follow-up and 6 months for data freeze, core lab analysis and statistical analysis): subjects will be followed for 1 year with clinic or phone visit at 1 month and 12 months.

GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ISO EN 14155 2020 (as well as all national legal and regulatory requirements). [2]

FIGURE 1a: PROPOSED CALCIUM MODIFICATION ALGORITHM

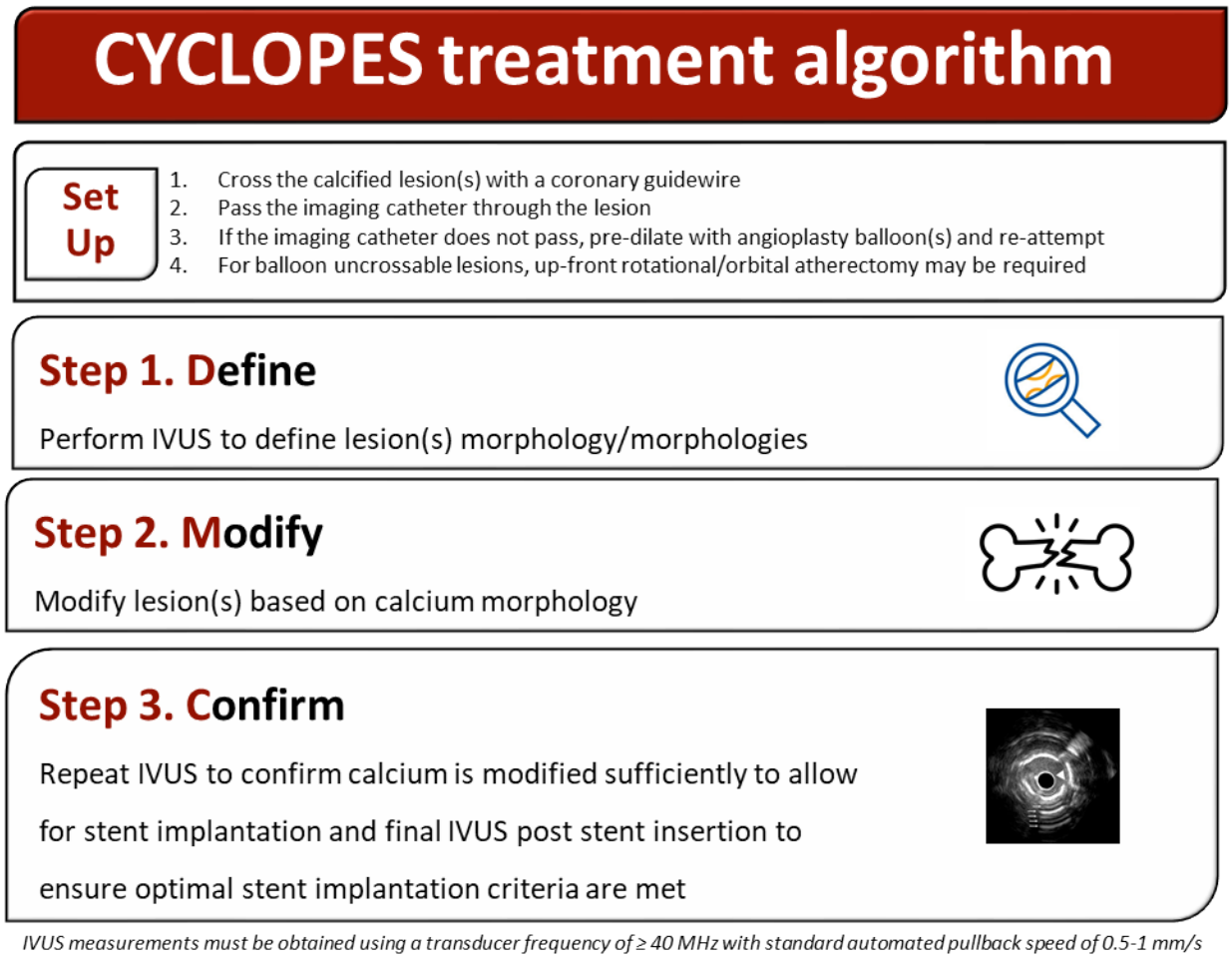


Figure 1a CYCLOPES calcium modification algorithm, summary version including set-up. The proposed algorithm uses the acronym DMC (Define, Modify, Confirm) to outline the steps to successful calcium modification. Step 1: Define, involves intravascular ultrasound to define the characteristics of the calcified lesion. Step 2: Modify involves the use of calcium modification devices to modify the calcified lesion. Step 3: Confirm requires a repeat intravascular ultrasound acquisition to confirm whether the modification process was successful or not. Dependent on the outcome of the confirm step, a recommendation to insert a stent or repeat calcium modification is made.

FIGURE 1b: PROPOSED CALCIUM MODIFICATION ALGORITHM

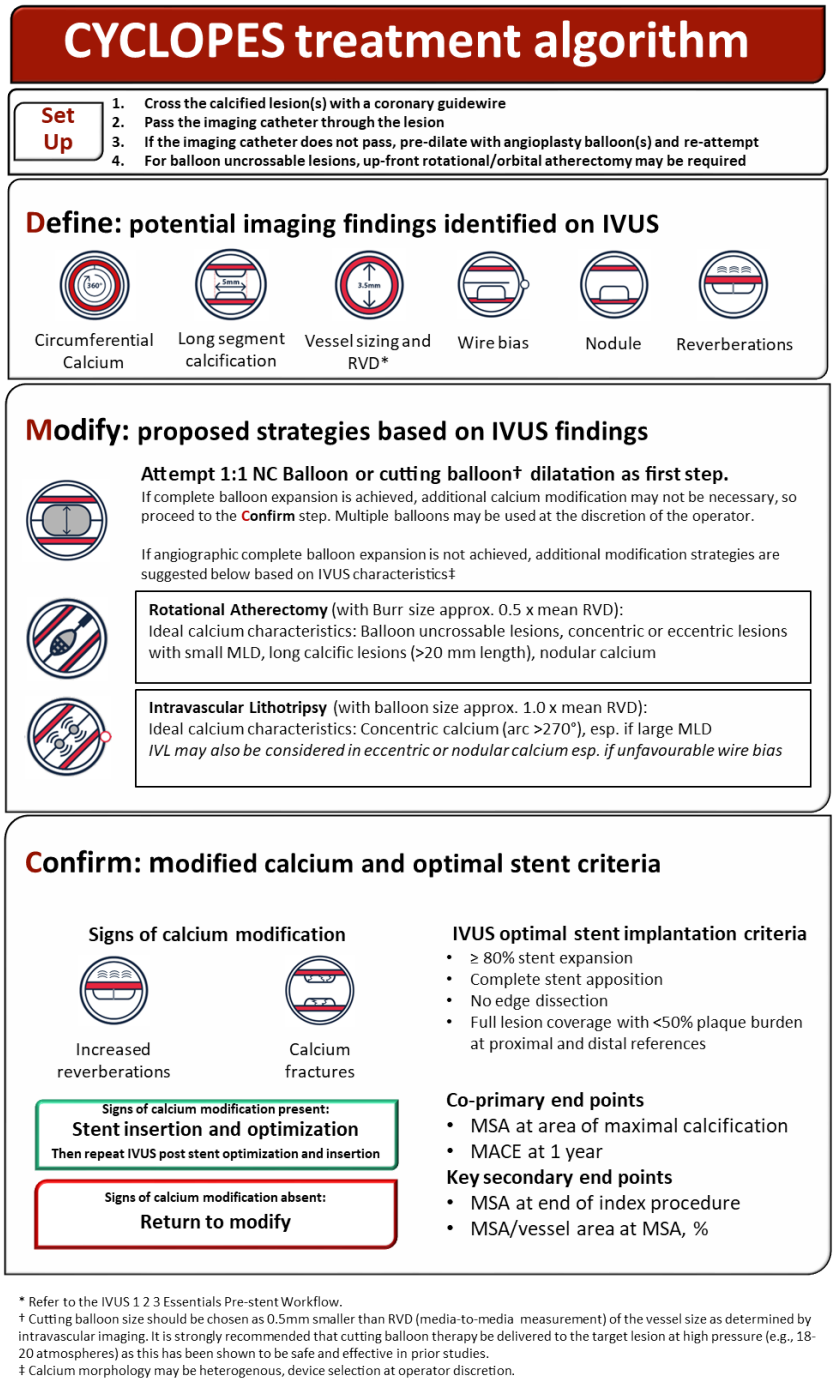


Figure 1b CYCLOPES calcium modification algorithm. Detailed version.

FIGURE 1c: PROPOSED CALCIUM MODIFICATION ALGORITHM

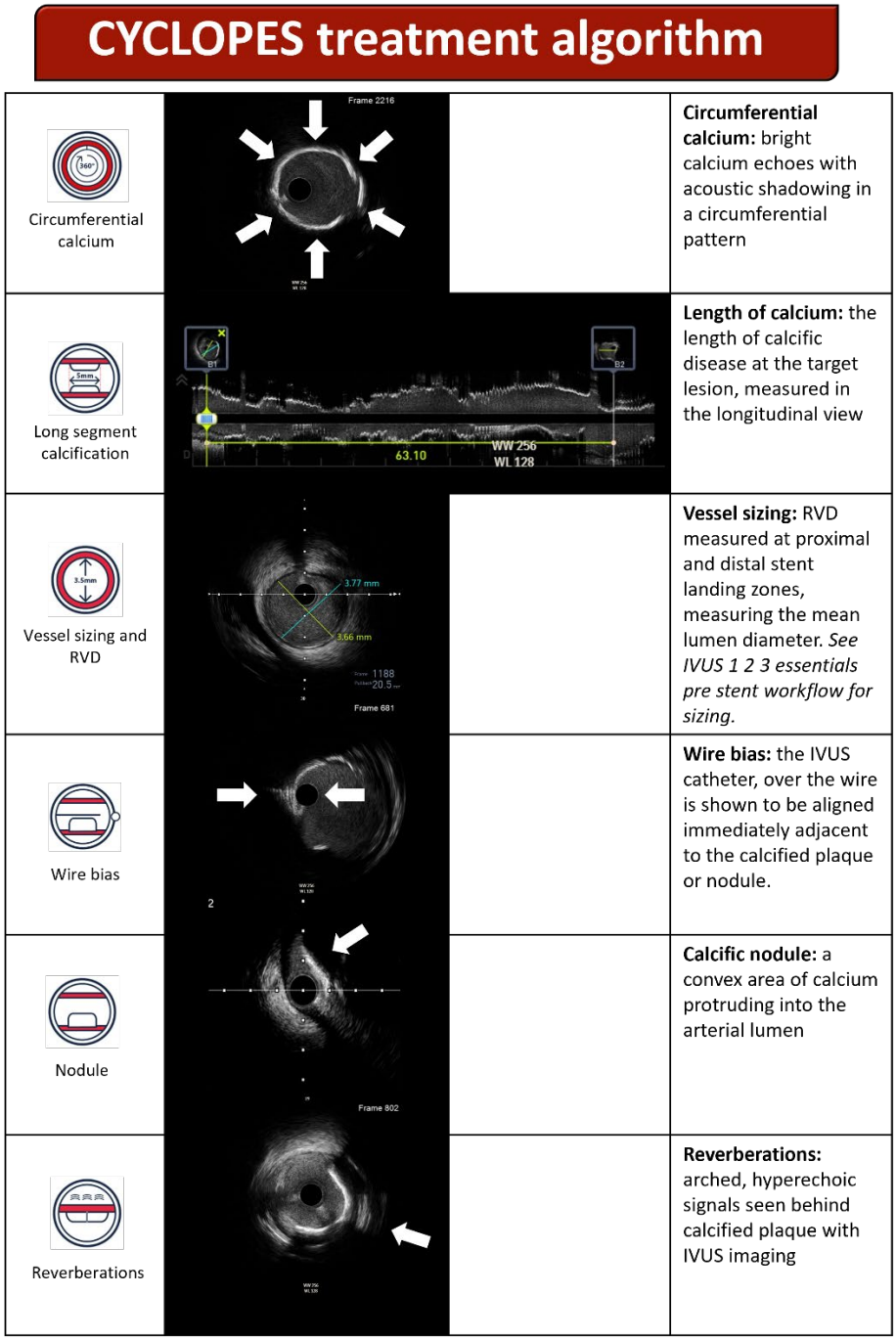


Figure 1c Guideline for 60 MHz HD IVUS image interpretation

FIGURE 1d: IVUS Pre-stent Workflow. Adapted from IVUS 1 2 3 Essentials.

CYCLOPES treatment algorithm

Pre Stent Workflow

Adapted from IVUS 1 2 3 Essentials

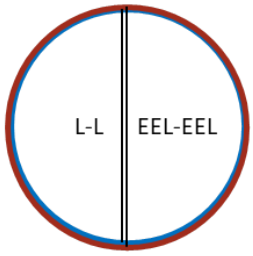
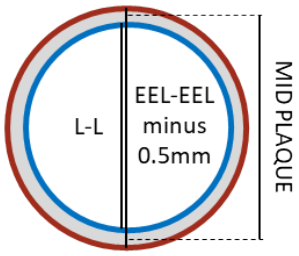
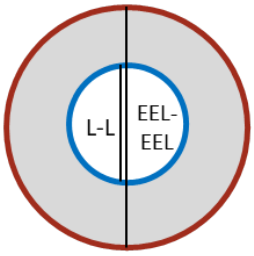
Landing zone	No disease or minimal plaque burden	Mild or moderate plaque burden ≤50%	Heavy plaque burden ≥50% plaque burden
Measurements	 Lumen-Lumen and EEL-EEL show minimal difference	OR  Lumen-Lumen and EEL-EEL differ by ≥1mm	 Lumen-Lumen and EEL-EEL differ substantially
Distal edge stent diameter	Size stent to L-L measurement to minimize risk of edge dissection	Size stent to L-L measurement to minimize risk of edge dissection	This is not an appropriate landing zone for a stent – seek less diseased segment
Proximal or distal postdilation balloon diameter	Size postdilation balloon to EEL but do not exceed EEL-EEL measurement	Size postdilation balloon to EEL. Downsize by 0.5mm or aim to size half way between lumen and EEL	Postdilation balloon should not be sized to EEL-EEL measurements in areas of heavy plaque burden. Balloons are likely to be oversized due to positive remodelling.

Figure 1d IVUS Pre-stent Workflow. Adapted from IVUS 1 2 3 Essentials.

TABLE 1: TIME SCHEDULE/DATA COLLECTION

Study Period	**Screening/ Enrollment**			
Visit	**1: (day 1/week 0)**	**2: (hospital discharge)**	**3: (day 30 ± 3 days)**	**4: (1 year ± 2 weeks)**
Mode of visit	Clinical	Clinical	Phone	Phone/Clinical[1]
Screening	x			
Patient information and informed consent	x			
Review of in-/exclusion criteria	x			
Demographics	x			
Medical history	x			
Physical examination	x			(x)
Cardiac enzymes[2]	x	x		
Review of laboratory data[3], ECG	x	x		(x)
Review of concomitant medications	x	x	x	x
Coronary angiography and PCI (with 60 MHz HD IVUS guidance and use of calcium modification devices according to a specific algorithm)[4]	x			
Adverse event assessment/reporting		x	x	x
Assessment of endpoints		x	x	x
Final status				x

[1] Follow-up assessments may consist of a structured telephone interview, or if standard of care, an office visit. [2] High sensitivity troponin is mandatory for pre-index procedure, 18-24 hours post-index procedure (or at immediately prior to discharge, if discharged before 18 hours post-procedure) and **in case of a clinical event**; [3] Full blood count, serum creatinine, HbA1c, lipid profile (non-fasting acceptable). [4] For all subjects, coronary angiography and raw 60 MHz HD IVUS image recordings from 3 specified time points (baseline, post lesion preparation and post stent insertion) will be sent to the independent Imaging Core Laboratory for evaluation of primary endpoint (MSA). [5] One post-procedural 12 lead ECG should be performed prior to hospital discharge. A repeat 12 lead ECG may be performed if clinically indicated.

1. INTRODUCTION

1.1. Background Information

Up to a third of patients undergoing coronary angiography present with coronary artery lesions with significant calcium. [3, 4] Given the ageing of the population, the prevalence of calcified lesions and the number of patients undergoing complex percutaneous coronary intervention (PCI) are expected to rise further. The presence of coronary calcifications is associated with an increased procedural complexity, including challenging device delivery and prolonged procedures, as well as worse procedural and clinical outcomes.

Coronary lesion modification is important to ensure optimal stent delivery, expansion, and apposition. Dedicated devices have been developed and approved to allow for coronary calcium modification before stent implantation. These devices include non-compliant balloons, super high-pressure balloons, scoring and cutting balloons, rotational atherectomy devices [5] and intravascular lithotripsy (IVL) devices. [3, 6]

Cutting balloons are dedicated non-compliant balloons characterized by fixed, microsurgical atherotomes that anchor to tissue and precisely dilate calcified lesions at low pressures. Rotational atherectomy can effectively ablate calcified plaques, facilitating in many cases stent delivery and expansion. Intravascular lithotripsy balloons emit pulsatile sonic pressure waves, thereby creating microfractures in intimal and medial calcium in the vessel wall. Intravascular lithotripsy balloons have received CE Mark and are available in Europe since 2017, following the DISRUPT CAD I and II studies. [6, 7] 60 MHz HD Intravascular ultrasound (IVUS) imaging performed after delivering a coronary guidewire allows for a detailed assessment of the severity and distribution (concentric or eccentric, deep or superficial, calcium arc) of calcifications, thereby facilitating optimal procedural planning and lesion preparation. [8]

Given this armamentarium available in contemporary catheterization laboratories, calcium modification algorithms are needed as guidance for optimal device selection. The calcium modification algorithm proposed by Oksnes and McEntegart integrates lesion assessment by intravascular ultrasound and provides a systematic approach to coronary plaque modification. [9] This study aims to evaluate the impact of the systematic utilization of this calcium modification algorithm on procedural and clinical outcomes in patients undergoing complex PCI.

1.2. Study Rationale

This study will validate a calcium modification algorithm for coronary lesion preparation in a large cohort of patients with complex coronary artery disease and thereby provide evidence for a

structured approach to the treatment of calcified coronary lesions. Further, the database will allow us to identify clinical and imaging risk predictors for procedural success and clinical outcomes in patients with calcified coronary lesions undergoing percutaneous coronary intervention (PCI).

1.3. Study Objective

The aim of this study is to validate a comprehensive and intravascular imaging-based calcium modification algorithm for the treatment of moderate to severely calcified coronary lesions.

2. DEVICE INFORMATION

All devices are approved for use during percutaneous coronary intervention, including the listed specialist calcium modification devices, are used in line with standard clinical practice, and are not under investigation. Only CE marked devices are used.

Standard procedural devices used for percutaneous coronary interventions include:

1. Standard coronary guide catheters
2. Standard coronary angioplasty wires
3. Second generation bioabsorbable polymer everolimus-eluting stents
4. Intravascular ultrasound catheters
5. Standard compliant and non-compliant angioplasty balloons

Specialist calcium modification devices:

1. Wolverine™ cutting balloon, Boston Scientific, Marlborough, Massachusetts
2. Rotablator atherectomy system™, Boston Scientific, Marlborough, Massachusetts
3. Shockwave Coronary Rx Lithoplasty System™, Shockwave Medical Inc, Santa Clara, California

3. Study Design

3.1. General

This study is an international, multi-centre, observational, single-arm study. A total of 500 patients will be enrolled at 25 centers in Europe.

Patients will be screened before coronary angiography, and patients with planned PCI for moderate to severely calcified native coronary artery lesion will be eligible.

All procedures will be performed by fully trained operators with at least 50 prior rotablation procedures and several years of interventional experience. [5] All procedures will be performed according to current guidelines and international standards using a biodegradable-polymer,

Everolimus-eluting stent. [8, 10] In all patients, HD 60 MHz HD IVUS imaging will be performed according to a study-specific algorithm (outlined in section 5.6.3) after 1. crossing the lesion with a coronary guidewire, 2. after lesion preparation, and 3. after stent implantation to ascertain an optimal procedural result.

Baseline characteristics, vital signs, concomitant diseases, cardiovascular risk factors, medication, routine laboratory analyses, ECG data, coronary angiography, and procedural data (coronary angiogram, HD IVUS images, procedural characteristics, and periprocedural complications), and follow-up data will be collected.

The co-primary end points are minimum stent are (MSA) at the site of maximum calcification at the end of the index procedure (as assessed by 60MHz HD IVUS imaging) and rates of target lesion failure (TLF), a composite of cardiovascular death, non-fatal myocardial infarction related to the target vessel, and unplanned ischemia-driven target lesion revascularization, at 1 year.

Coronary angiograms and HD IVUS images will be analyzed by an independent angiography and HD IVUS Core Lab. Follow-up will be performed at discharge, at 30 days, and at 1 year.

The study will be conducted in accordance with the investigation plan, the current version of the Declaration of Helsinki, and national legal and regulatory requirements. [2]

3.2. Study duration

The total expected duration of the study is approximately 36 months.

Enrollment will take place over a period of 18 months. Follow up is planned for 12. There will be an additional 6 months for data freeze, core lab analysis and statistical analysis.

3.3. Endpoints

3.3.1. Co-Primary Endpoint

1. Minimum stent area (MSA) at the site of maximum calcification at the end of the index procedure
2. Target lesion failure (TLF) (cardiovascular death, non-fatal myocardial infarction related to the target vessel, unplanned ischemia-driven target lesion revascularization) at 1 year

3.3.2. Secondary Endpoints

1. Individual components of TLF at 1 month and 1 year.
2. Minimum stent area (MSA) measured at the end of the index procedure.
3. Strategy success defined as:
    - Successful stent delivery
    - ≥ 80% stent expansion

- Complete stent apposition
- No edge dissection
- Full lesion coverage with <50% plaque burden at proximal and distal references
- TIMI 3 flow

4. Target vessel revascularization (TVR)
5. Target lesion revascularization (TLR)
6. Stent thrombosis
7. Stroke
8. Cardiovascular death
9. Acute kidney injury
10. Major bleeding, categorized as class 3-5 according to the Bleeding Academic Research Consortium [BARC]
11. Procedure time
12. Fluoroscopy time
13. Radiation exposure (dose-area-product)
14. Cost effectiveness analysis

4. Study Population

4.1 Patient Population

Patients with coronary artery disease with evidence of calcified coronary arterial lesions who are planned for percutaneous intervention requiring calcium modification.

4.2 Eligibility criteria

4.2.1 Inclusion Criteria

Subjects will be assessed to ensure they meet all the inclusion criteria to be eligible for study enrollment:

1. Clinical indication for PCI in the setting of chronic coronary syndrome or non-ST-segment elevation myocardial infarction due to symptoms or documented myocardial ischaemia.

3. At least one moderate to severely calcified native coronary artery lesion confirmed by QCA and/or 60MHz HD IVUS, with the presence of significant calcium, ≥70% diameter stenosis by visual estimation (in a reference vessel diameter of ≥2.5mm and ≤4.0mm) and TIMI 3 flow at baseline that is suitable for PCI.

b. Significant calcium at the target lesion site is defined as either:

ii. The presence of radiopacities involving both sides of the arterial wall >10mm and involving the target lesion on angiography.

or

iii. The presence of >270° arc of superficial calcium on intravascular imaging with a length >5mm or the presence of 360° arc of on intravascular imaging. [1]

2. It is possible to cross the calcified lesion with a coronary guidewire.
3. Age ≥ 18 years.
4. Patient is willing and able to comply with the study procedures and follow-up.

Patient is willing and able to comply with the study procedures and follow-up. [6, 11]

4.2.2 Exclusion Criteria

Subjects will be assessed to ensure they do not meet any of the exclusion criteria to be eligible for study enrollment:

1. Patients with cardiogenic shock.
2. ST-segment elevation myocardial infarction.
3. Instent re-stenosis.
4. Stent thrombosis.
5. Coronary artery dissection.
6. Chronic total occlusion in a major artery.
7. Left ventricular ejection fraction ≤30%.
8. Need for coronary artery bypass graft surgery.
9. Documented allergy to everolimus or to any stent material
10. Any contraindication for dual antiplatelet therapy with aspirin and a P2Y12 inhibitor for at least 3 months (except for patients on oral anticoagulation).
11. Female pregnancy, breastfeeding or intend to become pregnant within 1 year
12. Life expectancy <1 year.
13. Participation in another study with an investigational product.
14. Inability to provide informed consent.

5. Study Procedures

This chapter describes the procedures the Investigator must follow for each study phase in detail. Table 1 summarizes clinical study assessments, procedures, and information collected on case report forms (CRFs).

5.1. Screening

Patients meeting the general inclusion and exclusion criteria (defined in section 4.2) will be informed about the study and asked to read the patient information leaflet. In case they agree to participate in the study, they will be asked to sign the consent form.

All patients who are screened and offered study participation and/or are consented for the study and/or are participating in the inclusion/exclusion process must be entered into the subject screening log regardless of their study eligibility. Patients must be entered into the log sequentially.

5.2. Informed Consent

Prior to participation in this study, before collection of any study specific data, the patient must complete an informed consent process involving reading the study information leaflet and then signing and dating the consent form. Designated center staff will explain the purpose of the study, data to be collected, how data will be used, time and travel commitments and other expectations of a study subject. The patient will be given the opportunity to discuss the study with the investigator, including any medical aspect of their disease or the study treatment. If the patient decides to participate, he/she will sign and date the informed consent form along with the Investigator and other staff participating in the consent process and the treatment visit will be scheduled. A copy of the informed consent form will be given to the subject.

No patient will be enrolled without signing the informed consent. Any new significant information on the study algorithm or procedure that may be relevant to the subject's willingness to participate or to continue participation in the study will be provided to new and existing subjects throughout the clinical investigation. If new information that can significantly affect a subject's future health and medical care becomes available, this information shall be provided to the subjects affected. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

5.3. Enrollment

After completing the informed consent, the final screening check takes place during the angiography: this will be confirmed and documented. Only once the below criteria are fulfilled can the patient be considered enrolled in the study:

All angiographic inclusion and exclusion criteria outlined in section 4.2 are fulfilled.

For the purposes of this clinical study, patients will be considered subjects after enrollment has been confirmed.

If a patient has provided informed consent but has not met one of the above criteria for enrollment inclusion into the study, he/she will be considered a screen failure.

5.4. Baseline Assessment

Prior to treatment, each patient's medical history and demographics will be collected. Preoperative procedures include a physical examination, documentation of disease, relevant medical history and medication or coronary intervention.

Furthermore, the subject must complete a series of assessments at the time preceding index treatment. These assessments include:

- Laboratory Tests – full blood count, serum creatinine, cardiac troponin (cTn), HbA1c, and lipid profile (non-fasting acceptable).
- Pregnancy test (βHCG subunit) - to be performed for women of childbearing potential if the last Menstrual Period does not fall within the last 10 days.
- If it is not possible to perform the pregnancy test for women of childbearing potential in urgent cases, such patients will not be included in the study.

5.5. Pre-Procedure

Beyond the anti-platelet regimen, patients are to be medicated as per institutional procedures. All anti-platelet and oral medication administered will be captured in the medical notes for subsequent capture in the electronic case report form (eCRF).

5.6. Procedure Visit

5.6.1. Index Procedure

Angiography, calcium modification techniques and HD IVUS imaging will be performed according to current international guidelines.

Once the decision to proceed to PCI is made, prior to guidewire insertion, all patients will be administered heparin or bivalirudin according to the standard practice. All patients undergoing PCI will receive a loading dose of an ADP receptor antagonist. Patients not already receiving aspirin will be treated with an oral or intravenous loading dose of aspirin.

After intracoronary injection of nitroglycerin, baseline angiography of the target vessel (TV) will be performed where single worst projection will be recorded for QCA analysis showing the target lesion (TL) for all subjects.

5.6.2. Intravascular ultrasound (IVUS)

Intravascular imaging of the lesion will then be performed using HD 60 MHz IVUS. Standard HD IVUS procedures should be followed as per the product manufacturer guideline during each HD IVUS recording. Automated pullback must be performed to image the full extent of the lesion from at least 10mm distal to the distal edge of the lesion to at least 10mm proximal to the

proximal edge of the lesion for each recording. A pullback speed of 0.5-1mm/s should be used. Longitudinal and cross-sectional planes must be recorded for each recording.

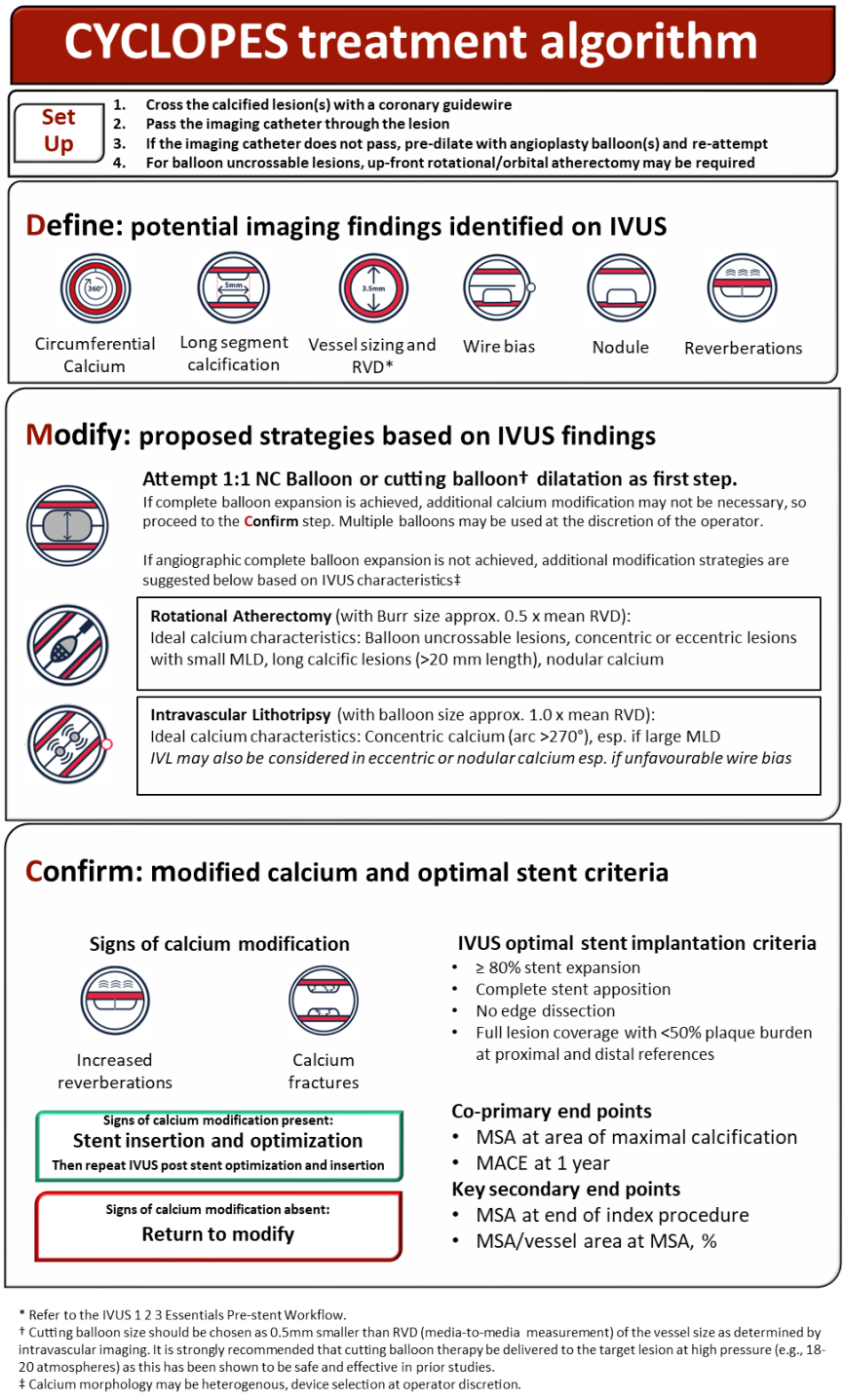
The first, baseline HD IVUS recording will take place after the guidewire has crossed the lesion. This will allow for determination of baseline lesion characteristics, which can be input into the calcium modification algorithm. The characteristics that are to be assessed for the calcium modification algorithm include the degree of calcium arc, the lesion length, the reference vessel diameter, and the presence/absence of nodular calcium. The individual operator will make their assessment of the target lesion calcium characteristics and proceed to use the calcium modification algorithm (Section 5.6.3). The operator will then implement the lesion preparation method recommended by the calcium modification algorithm.

Once the recommended calcium modification and lesion preparation has been completed, a second HD IVUS imaging recording will be performed using the same protocol as the baseline HD IVUS recording. This post lesion preparation HD IVUS recording will assess for calcium fractures and for luminal gain as compared to the baseline HD IVUS recording. The lesion characteristics assessed by the operator will be input to the next stage of the calcium modification algorithm, which will provide the next recommended action.

If the individual operator is satisfied that optimal lesion preparation has been achieved by the presence of calcium fractures or acceptable luminal gain (or at the clinical discretion of the operator), they can proceed to treat the lesion with bioabsorbable polymer everolimus eluting stent(s). The operator may use their own clinical judgement to choose the appropriate stent type for the individual patient and lesion characteristics. If optimal lesion preparation has not been achieved by the above criteria, then further lesion preparation is recommended by the calcium modification algorithm. Each time that further calcium modification is performed, an additional HD IVUS recording is required to assess for optimal lesion preparation. Once optimal lesion preparation is achieved, the operator will then proceed to stent insertion. Pre-dilatation and post-dilatation may be performed by the operator as per their usual practice. Should the operator opt to avoid stent insertion during the index procedure based on their clinical decision, no further HD IVUS recordings will be required at this time point. Should a staged procedure be planned, and a stent inserted later, the final result should be assessed with HD IVUS, and recordings uploaded to the eCRF.

Following stent insertion, a third and final HD IVUS recording of the target lesion will be performed. If additional stent optimization, such as with further post-dilatation with non-compliant angioplasty balloon is required, this is permitted and must be followed by another HD IVUS recording such that the final HD IVUS recording shows the final optimized result. The baseline HD IVUS, the post lesion preparation HD IVUS (single or multiple runs) and the final HD IVUS recorded images must be uploaded to the eCRF for core lab analysis.

5.6.3. Calcium modification protocol



* Refer to the IVUS 1 2 3 Essentials Pre-stent Workflow.
† Cutting balloon size should be chosen as 0.5mm smaller than RVD (media-to-media measurement) of the vessel size as determined by intravascular imaging. It is strongly recommended that cutting balloon therapy be delivered to the target lesion at high pressure (e.g., 18-20 atmospheres) as this has been shown to be safe and effective in prior studies.
‡ Calcium morphology may be heterogenous, device selection at operator discretion.

Figure 2 The CYCLOPES calcium modification algorithm provides a systematic approach to selection of the appropriate calcium modification device.

The CYCLOPES calcium modification algorithm illustrated in Figure 2 offers a 3-step process for the management of coronary calcification "Define, Modify, Confirm" (DMC). The algorithm is guided by intravascular ultrasound to be performed with mechanical pullback, using HD IVUS. The IVUS 1, 2, 3 Essentials Workflow should be performed at each HD IVUS acquisition throughout the algorithm[12].

CYCLOPES treatment algorithm

Pre Stent Workflow
Adapted from IVUS 1 2 3 Essentials

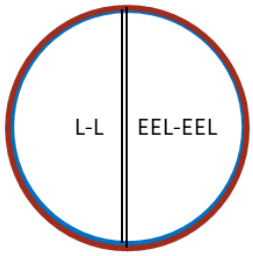
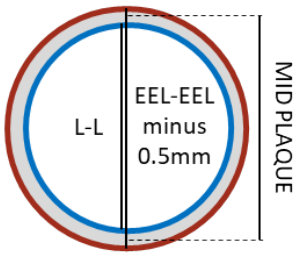
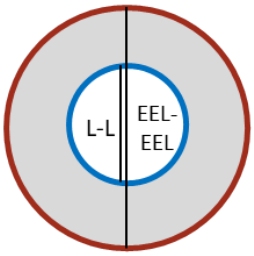
Landing zone	No disease or minimal plaque burden	Mild or moderate plaque burden ≤50%	Heavy plaque burden ≥50% plaque burden
Measurements	 Lumen-Lumen and EEL-EEL show minimal difference	OR  Lumen-Lumen and EEL-EEL differ by ≥1mm	 Lumen-Lumen and EEL-EEL differ substantially
Distal edge stent diameter	Size stent to L-L measurement to minimize risk of edge dissection	Size stent to L-L measurement to minimize risk of edge dissection	This is not an appropriate landing zone for a stent – seek less diseased segment
Proximal or distal postdilation balloon diameter	Size postdilation balloon to EEL but do not exceed EEL-EEL measurement	Size postdilation balloon to EEL. Downsize by 0.5mm or aim to size half way between lumen and EEL	Postdilation balloon should not be sized to EEL-EEL measurements in areas of heavy plaque burden. Balloons are likely to be oversized due to positive remodelling.

Figure 3 Pre-stent workflow based on IVUS 123 Essentials workflow

Having met the eligibility criteria outlined in section 4.2, including QCA assessment, the set-up step is initiated. This involves crossing the calcified lesion with a coronary guidewire and attempting to cross the lesion with the imaging (IVUS) catheter. If the imaging catheter does not pass through the lesion, the lesion should be predilated with an angioplasty balloon to facilitate crossing the lesion with the imaging catheter at a second attempt. For any lesions that are not crossable with an angioplasty balloon, an upfront rotational/orbital atherectomy strategy may be required to proceed.

Once the IVUS catheter is passed distal to the lesion, the first step of the DMC process, "Define" is initiated. The first HD IVUS acquisition takes place to define the potential characteristics of coronary calcification seen with intravascular imaging. The six features to assess are circumferential calcium, long segment of calcification, vessel sizing and reference vessel diameter (RVD), wire bias, calcific nodule, and reverberations. Circumferential calcium refers to the presence or absence of circumferential calcium. A long segment of calcification is assessed by the operator as a segment of calcified disease >20mm. Vessel sizing and reference vessel diameter (RVD) is assessed and recorded by the operator using the IVUS 123 Essentials workflow method [13]. Wire bias is defined as wire bias towards calcium or away from calcium. Calcific nodule refers to the presence or absence of a calcified nodule on HD IVUS. Reverberations refer to the presence of reverberations seen on HD IVUS.

Once the lesion has been defined, move to the "Modify" step. The first part of this step involves attempting to pre-dilate the lesion with a non-compliant balloon or cutting balloon. For non-compliant balloon dilatation, ideally a balloon sized in a 1:1 ratio to the reference vessel diameter as assessed by HD IVUS. For cutting balloon dilatation, the cutting balloon size should be chosen as 0.5mm smaller than media-to-media measurement of the vessel size as determined by intravascular imaging. It is strongly recommended that cutting balloon therapy be delivered to the target lesion at high pressure (e.g., ~18-20 atmospheres) as this has been shown to be safe and effective in prior studies[1].

If 1:1 balloon expansion is achieved with angiographic evidence of complete balloon expansion, then the lesion may be sufficiently prepared and additional calcium modification may not be required, so proceed to step 3, "Confirm". If there is incomplete balloon expansion, then additional calcium modification methods may be required. Using the characteristics assessed with HD IVUS in the "Define" step, choose an additional modality for calcium modification. It is important to note that calcium characteristics may be heterogenous, as such, the final choice of calcium modification modality is at the discretion of the operator.

Ideal calcium characteristics for rotational atherectomy include balloon uncrossable lesions and long calcific lesions and calcified nodules, particularly if the wire is biased towards the nodule. Burr size should be approximately 0.5 x mean RVD.

Ideal calcium characteristics for intravascular lithotripsy include the presence of a calcium arc >270° in large vessels. IVL may also be considered for eccentric or nodular calcium where wire is biased away from the nodule.

Once the chosen modality for calcium modification has been used, move to the "Confirm" step, which involves post calcium modification HD IVUS imaging to assess the outcome of the "Modify" step. If signs of calcium modification are present, defined as the presence of calcium fractures or increased reverberations visualized on HD IVUS, then the algorithm directs the operator to DES insertion and optimization. Following DES insertion and optimization, a final HD IVUS acquisition takes place to assess the optimal stent implantation criteria. These criteria include at least 80% stent expansion, complete stent apposition, no edge dissection and full lesion coverage with less than 50% plaque burden at proximal and distal references.

Further post-dilatation for DES optimization may be required at this point if the optimal stent implantation criteria is not met. This should be performed at the operator's discretion. If additional DES optimization is performed, a final HD IVUS acquisition should be obtained showing the result.

If at the "Confirm" step signs of calcium modification are absent, then the algorithm re-directs back to the modify step. At this point the choice of calcium modification modality is at the discretion of the operator. Multiple modalities may be used. The "Confirm" step must be completed after repeating the "Modify" step.

5.6.4. Quantitative Coronary Angiography (QCA)

Quantitative coronary angiography (QCA) images will need to be obtained at baseline (pre-procedure and post-procedure) displaying the coronary lesion in the projection demonstrating the severity of the lesion, after intracoronary administration of nitrate (recommended 100-200 µg, unless clinically contraindicated). At least two orthogonal, or near orthogonal views should be obtained.

Quantitative analysis of the coronary angiographic images will be performed by an independent core laboratory for all subjects.

5.6.5. Antithrombotic Drug Treatment

Appropriate anticoagulant therapy must be provided to the patient prior to the angioplasty procedure and must be maintained during the procedure.

5.6.6. Post-Operative Procedures

Following interventional treatment, patients will receive DAPT including a P2Y12 inhibitor in combination with aspirin for 6 months. The duration of DAPT may be changed by the prescriber at their usual clinical discretion or to account for increased bleeding risk, or co-prescription of anticoagulation.

A post-procedural 12 lead electrocardiogram (ECG), will be performed prior to hospital discharge. In addition, in the event of development of symptoms after PCI a 12-lead ECG is required to document any suspicious cardiac ischemic episode.

Cardiac troponin (cTn) (per institutional standard) will be measured in all cases at least once post procedure with one of the measurements at 18-24 hours post-procedure. If the patient is discharged prior to 18 hours post procedure, it will be measured immediately prior to discharge.

Every effort must be made to obtain cardiac enzyme values within the specified time range to help determine presence or absence of MI post-procedure. In the case of multiple measurements prior to discharge, the first enzyme measurement and the peak value should be documented on the case report forms.

If any cTn values above the reference range are noted post-procedure, per the Fourth Universal Definition, cTn measurements should continue to be performed every 6 hours for 24 hours, as per clinical practice starting from when the first elevation is noted. MI will be adjudicated according to the Fourth universal definition.

Clinical status will be assessed at discharge. All cardiac medications will be recorded.

A letter will be sent to the patient's referring physician/general practitioner, explaining his/her participation in the study and a detailed schedule of required study activities and follow up time points.

5.7. Follow-up

Follow-up assessment visits will be at the following intervals following the index procedure:

- Hospital discharge
- 30 days (± 1 week)
- 12 Month (± 1 month)
- Unscheduled visit

The following assessments and information will be collected at all follow-up visits:

- Review of concomitant medications including antithrombotic medications
- Endpoint collection
- Adverse event assessment/reporting

In addition to above assessments, for the **12-month follow-up** the following assessments will need to be performed as well:

- Physical examination
- Review of laboratory data
- 12-lead ECG

All follow-up time-points, except for 12-month time-point for which the subject needs to attend the clinic, may be completed by phone call (or if standard hospital practice during an office visit).

A summary of required follow-up procedures is listed in Table 1.

5.8. Unscheduled Visit

Investigators may see the subjects, at their professional discretion, outside of the visits described in the study protocol. If an SAE is reported during an unscheduled visit, the SAE and its treatment (CABG, re-PCI if any) should be documented in the same manner as for a study visit, per section 6.2. No additional data collection or CRFs are required at the unscheduled visit.

5.9. Subject Discontinuation

Subjects will participate in the study until they complete the 12-month post treatment assessments (per protocol). Subjects who do not complete the study per protocol may be withdrawn from the study in the following manner:

5.1.1. Withdrawal prior and/or during index procedure

Patients who have signed an informed consent form, but that are screen failures, will be documented as such on the subject screening log.

For patients who were declared eligible for the study but who are discontinued for any reason,

- either, prior to the commencement of PCI procedure or,
- during the procedure, as it was not possible to cross the lesion with either the guidewire or the HD IVUS catheter.

These patients will also be considered screen failures. Data until that period will be collected and the patient will be immediately exited from study. The reason for the early withdrawal must be documented in the subject screening log.

Patients that have not passed screening will not be enrolled in the study and further follow-up of these patients shall proceed according to the hospital standard procedures.

5.1.2. Patient withdrawal

Subjects may withdraw their consent and discontinue participation in the study at any time for any reason or no reason, without jeopardizing their medical care. If a subject withdraws consent it will be documented on the study exit form, and the reason for withdrawal will be requested.

All data obtained until the date of withdrawal will be kept and entered into the efficacy and safety analysis. If the patient explicitly requests complete deletion of the records, they will be made aware that data pertaining to serious adverse events (SAEs) will be retained. This should be documented by the site. Subjects will not be replaced.

Once the subject is withdrawn, further follow-up of the patients shall proceed according to the hospital standard procedures.

5.1.3. Investigator Withdrawal

Subjects may be withdrawn by the investigator prior to receiving a study treatment for the following reason:

> If, on the day of procedure, it is determined by the investigator that the subject is no longer an appropriate candidate for the index procedure then the patient will be withdrawn from the study and will not receive the treatment.

The investigator may decide to withdraw the subject from the study at any time based on medical judgment. In all instances of withdrawal, data collected up to the time of subject withdrawal may be used in the study. Subjects withdrawn from the study after being treated based on the study algorithm or procedures will not be replaced. The site should complete a study exit form.

5.1.4. Lost to Follow-up

If the subject cannot be reached for a follow-up visit, at least three telephone contacts (or attempts) should be made prior to recording a missed follow-up visit. The subject however remains in the study until the 1-year follow-up. The subject will only be considered as 'Lost to follow-up' if he/she cannot be reached for the final 1-year follow-up.

NOTE:

- More than three attempts can be made, but three is the minimum required.

- In the event contact with the subject cannot be established, the investigator will immediately contact the referring physician. If the referring physician has not had contact with the subject, information from the subjects identified point of alternative contact will be utilized.

5.10. Premature Termination or Suspension of the Study

The Sponsor may decide to suspend or prematurely terminate the clinical study in one or more investigation sites if e.g. information that the risk to the study subjects is higher than initially indicated becomes available.

In the case of an early termination of the study, the regulatory authority(ies) and ethic committee(s) (ECs) should be informed according to local and national regulations. The reasons for termination should be provided and documented. An appropriate schedule for termination will be instituted.

For patient safety reasons, patients already enrolled in the study will continue to be followed for the planned course of study described in this protocol.

Patients will be informed that the study has been prematurely terminated and about the reason for this termination.

5.11. Description of Assessments and CRFs

All data to be collected is described below.

Demographic Information
Demographics collected will include but are not limited to gender, height, weight, age and race (if permitted).

Medical History
Relevant medical history will be collected but are not limited to conditions as diabetes mellitus, atrial fibrillation, peripheral vascular disease, previous MI(s), previous PCI/CABG, congestive heart failure, renal insufficiency, hypertension, previous cerebrovascular event and history of malignancy.

Physical examination
The physical examination is to include evaluations of blood pressure and heart rate as appropriate for the subject's condition.

Medication review
Information regarding concomitant medication, clopidogrel, ticlopidine, prasugrel, ticagrelor, aspirin and oral anticoagulation medication use will be obtained.

12-Lead ECG
Information regarding Q-waves, bundle-branch block and atrial fibrillation will be obtained pre-procedure at 6-month and **in case of a clinical event**.

Laboratory Tests
Blood tests will be performed to collect information regarding full blood count, serum creatinine, HbA1c and lipid profile. Troponin will be collected at time points specified and **in case of a clinical event.**

Angiography and Intravascular ultrasound (IVUS)
At baseline (pre-and post-intervention), quantitative coronary angiography and HD IVUS imaging is mandatory as outlined in section 5.6 for all subjects and analyzed by Imaging Core Laboratory. **In case of a clinical event** an angiogram may also be acquired.

NOTE: It is left at the discretion of the physician and standard of care of hospital to perform coronary angiography at any time point or any other imaging.

Endpoint Collection
The following events will be adjudicated via the CEC:

- Death
- MI
- Any repeat revascularization
- Target lesion thrombosis (TLT)

5.12. Additional Case Report Forms

Adverse Events (AEs)
AE forms will document a description of the AE, onset date and duration, severity, seriousness, treatment, and relatedness. The form will also document whether the event was anticipated or unanticipated.

Study Exit Form
This form will document termination of each subject's study participation and capture the reason for study exit.

NOTE: screen failures will not be captured into the eCRF.

Protocol Deviation Form
This form will document deviations from the study protocol.

6. Safety Reporting

6.1. Definition of Adverse Events (AEs)

The following definitions are from ISO 14155:2011.

Adverse Events (AEs)

Table 2. Classification of AEs

Non-serious	Adverse Event (AE) (includes all categories)
Serious	Serious Adverse Event (SAE) (includes all categories that are serious)

Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons.

Exceptions include events that are pre-existing (prior to index-procedure) and have not changed in severity or intensity. Once a pre-existing complication or event has changed in severity or intensity, it should be reported as an AE.

Serious Adverse Event (SAE)

A SAE is defined as an AE that:

a. Led to a death, injury or permanent impairment to a body structure or a body function.
b. Led to serious deterioration in the health of the subject, that either resulted in
    i. a life-threatening illness or injury, or
    ii. a permanent impairment of a body structure or a body function, or
    iii. in-patient or prolonged hospitalization, or
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect.

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

Adverse Event (AE) Assessment and Reporting

As all devices used in this study are CE-mark approved and will only be used within the remit of their license, only adverse events, which in the opinion of the investigator, may represent a severe adverse advent, need to be reported.

Each AE record must include a description of the event, date of onset, date investigator (or designee) became aware of AE, resolution, severity, action taken, relationship to procedure and seriousness criteria.

Each AE must be recorded separately (each medical condition or symptom if no diagnosis is made).

Severity will be assessed by the investigator using the following definitions:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: minimal, local, or noninvasive intervention indicated; limiting
- Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling

Relationship to the study procedure or algorithm will be assessed by the investigator for each AE using the following definitions (according to EU MDR 2017/745 and MEDDEV 2.7/3 revision 3):

1. Not related: the relationship to the algorithm or procedures can be excluded when:
    - The event is not a known side effect of the study algorithm or procedure.
    - The event has no temporal relationship with the study algorithm or procedure.
    - The event is biologically implausible.
    - The event involves a body-site, or an organ not expected to be affected by the study algorithm or procedure.
    - The event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors).
    - The event does not depend on a false result given by the study algorithm or procedure used for diagnosis, when applicable.
    - Harms to the subject are not clearly due to use error.
    - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of procedures and the event.

2. Unlikely: the relationship with the use of the study algorithm or procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may need to be obtained.
3. Possible: the relationship with the use of the study algorithm or procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as 'possible'.
4. Probable: the relationship with the use of the study algorithm or procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may need to be obtained.
5. Causal relationship: the event is associated with the study algorithm or procedure is beyond reasonable doubt when:
    - The event has a temporal relationship with the study algorithm or procedure.
    - The event follows a known response pattern to the study treatment algorithm or procedure (if the response pattern is previously known).
    - Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out.
    - Harm to the subject is due to error in the use of the study algorithm or procedure.
    - The event depends on a false result given by the study algorithm or procedure used for diagnosis, when applicable.
    - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the event.

Seriousness: If the AE meets any of the SAE criteria mentioned in section 0 it is regarded as serious.

6.2. Reporting and Documentation

All SAEs that occur either during the index procedure (after calcium modification) or during the 1-year follow-up phase of the study will be documented as described above and entered into the eCRF as soon as possible upon knowledge of the event.

6.2.1. Report by the investigator to the Sponsor

The Principal Investigator (or designee) shall report all AEs to the Sponsor, or in case of discrepancy according to national regulations.

SAEs must be reported to the Sponsor immediately but in any event no later than 3 calendar days of occurrence or of the time the investigator becomes aware of the event. All information on the AE form must be made available to the Sponsor as early as possible.

The Investigator is responsible for reporting all SAEs and new findings/updates in relation to already reported events to the EC if required by national regulations or by the EC according to local regulations.

In case of early termination of the study, further follow-up of the study subject shall proceed according to this study protocol.

Further details regarding safety definitions and reporting are described in study safety plan.

7. RISKS EVALUATION

7.1. Potential adverse events (AEs)

The potential AEs that may be associated with the use of a calcium modification devices including non-compliant balloons, rotational atherectomy devices, intravascular lithotripsy devices and cutting angioplasty balloons in native coronary arteries include, but not limited to, are listed below.

- Haematoma at the vascular access site
- Pseudoaneurysm
- Acute myocardial infarction
- Pulse arrhythmia
- Angina pectoris
- Arterial perforation
- Spasm of coronary arteries
- Death
- Cerebral circulatory disorders
- General bleeding
- Side effects due to the accompanying medication
- Thrombus formation
- Arterial rupture
- Dissection of the coronary vessel
- Hypotension
- Ventricular fibrillation
- Ischaemia
- Arterio-venous fistulas
- Palpitations
- Vascular complications which necessitate a surgical intervention
- Infections
- Vessel trauma requiring surgical repair or re-intervention
- Emergent Coronary Artery Bypass Graft Surgery (CABG)
- Arrhythmia, including ventricular fibrillation
- Total occlusion of a coronary artery
- Restenosis of prior treated target vessel segment

7.2. Methods to Minimize Risks

Several procedures have been incorporated into this protocol to protect study subjects.

- Specific inclusion/exclusion criteria ensure that patients at increased risk are not enrolled in the study (e.g. patients presenting with cardiogenic shock, ACS or left main stenosis).
- Study subjects will be closely monitored post-procedure to detect and capture events.
- Qualified physicians will participate as investigators and have experienced staff to perform.

8. Statistical Consideration/Evaluation

8.1. Statistical Considerations and Analysis

The statistical analysis plan will be finalized prior to data freeze and will include an in-depth technical description of the statistical analyses described in this section. This section provides a summary of the planned statistical analyses of primary endpoints and key secondary endpoints as listed in section 3.3.

8.2. Analysis sets

Screened set

All potentially eligible subjects meeting the general inclusion and exclusion criteria, who have signed an informed consent form, have had the index procedure and have been entered into the eCRF will be included in this set. These subjects will be followed up until discharge. This set also includes subjects who complete 12 months of follow up.

Full analysis set (FAS)

This set includes all subjects who have signed an informed consent form, have been entered into the eCRF, have had the index procedure completed and have met all inclusion and exclusion criteria. These subjects will have been assessed using the CYCLOPES calcium modification algorithm and will have been followed up to the end of study (12 months).

Per protocol set (PP)

This set will include all subjects from the FAS who have had no major protocol deviations. As outlined in section 11.3.

8.3. Statistical analyses

8.3.1. General considerations

The study design aim is to validate a comprehensive, IVUS guided calcium modification algorithm for moderate to severely calcified coronary lesions and its effects on the primary and secondary outcomes outlined in section 3.3 herein. As such, no statistical hypothesis has been formulated

in accordance with the single arm, observational design. Descriptive statistics and graphical displays will be used to summarize the study findings and outcomes.

Continuous variables will be summarized by the number of observations, arithmetic mean, standard deviation (SD), median, minimum, maximum and interquartile range unless otherwise stated. For categorial variables, frequency tables with be produced including counts and percentages. Time to event variables will be assessed using Kaplan-Meier curves. There will be no imputation of missing values, unless otherwise described in the statistical analysis plan.

Estimates will be provided with corresponding two-sided 95% Confidence Intervals. No adjustments will be made for multiple testing.

Continuous variables will be reported as mean and standard deviation or median and interquartile range, as appropriate. The distribution of continuous variables will be assessed by the Shapiro-Wilk test. Categorical variables will be reported as counts and percentages and compared by Pearson χ^2 or Fisher exact test, as appropriate. In general, the denominator for the percentage calculation will be based upon the number of non-missing values available, unless otherwise specified.

For time-to-event analysis other than the primary endpoint for the de-novo patients, Kaplan-Meier survival curves as well as confidence intervals based on the log-log transformation will be reported.

8.3.2. Description of baseline variables

Baseline variables will include:

- Demographic characteristics
- Medical history
- Past and concomitant anti-thrombotic medications
- Clinical status at study entry
- Baseline lesion characteristics

8.3.3. Primary analysis

The study will have co-primary endpoints. The co-primary endpoints are minimum stent area (MSA) at the site of maximum calcification measured at the end of the index procedure and target lesion failure (TLF) defined as the composite of cardiac death, non-fatal myocardial infarction related to the target vessel, and unplanned ischemia-driven target lesion revascularization at one-year post-procedure. MSA is a numerical measurement in millimeters, measured at the independent imaging core laboratory. TLF is a binary endpoint (TLF or no TLF).

The primary analysis will be conducted on the FAS and will estimate the proportion of TLF at 1-year with corresponding exact two-sided 95% CI. Descriptive analyses for MSA will be performed.

8.3.4. Secondary analysis

All secondary endpoints will be summarized by timepoint (see section 7.3 for details) using appropriate descriptive statistics as detailed above. 95% two-sided confidence intervals will also be calculated for the frequency and mean estimates at each timepoint, as appropriate. Time to event endpoints will be assessed using Kaplan-Meier curves.

Specific details of the analysis of each secondary endpoint, including the rules for handling missing values, will be provided in the SAP.

8.3.5. CIP deviations

Major CIP deviations are deviations from the CIP which potentially could have a meaningful impact on study conduct, or on the primary or secondary outcomes for an individual subject. The criteria for identifying major CIP deviations will be defined within the appropriate CIP-specific document at study start. Major CIP deviations will be reviewed as part of the ongoing data cleaning process and all-important deviations will be identified and documented prior to database lock to confirm inclusion or exclusion from analysis sets. The analysis will be conducted on the FAS.

CIP deviations will be summarized for all deviations and by type, with event counts and number of subjects with at least one deviation.

8.3.6. Subgroup analysis

Analyses will be performed to investigate potential differences in primary and secondary outcomes between, but not limited to, the following baseline groups:

1. Individual subjects, vessel or lesion characteristics defining procedures of increased complexity.
2. Gender (female/male).
3. Age (<75 years/≥75 years).
4. Vascular access site (radial/femoral/other).

8.4. Sample size

Target recruitment of 500 patients.

8.5. Missing Data

There will be imputation for missing data. Partial dates may be handled as follows: if the day is missing then it will be imputed as 1, if the month is missing it will be imputed as January. Missing years will not be imputed.

9. DATA COLLECTION, HANDLING AND RETENTION

9.1. General

Data will be managed as per EU General Data Protection Regulation (GDPR 2016/679).

9.2. Source Document Verification (SDV)

Source document Verification (SDV) for this study will be maintained to capture the course of treatment and to substantiate the integrity of the trial data. SDV will include, but is not limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, imaging results, device accountability records, medical consultations and laboratory results and reports.

9.3. Electronic Data Entry

When using electronic data handling or remote electronic trial data systems, the Sponsor or the Sponsor's representative will:

- Ensure and document that the electronic data processing system(s) conforms to the Sponsor established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).
- Maintain SOPs for using these systems.
- Ensure that systems are designed to permit changes to the data in such a way that the data changes are documented and there is no deletion of any edited or entered data (i.e., maintains an audit trail).
- Maintain a security system to prevent unauthorized access to the data and to uniquely identify individuals who access the data entry system.
- Maintain a list of individuals authorized to make data changes.
- Maintain adequate data backup.

Primary data collection based on source-documented hospital and /or clinic chart reviews will be performed clearly, timely, adequately, and accurately by site personnel trained on the protocol and eCRF completion. Sponsor or designee will perform clinical monitoring as specified in Monitoring Plan.

.1.1. Data Confidentiality and Data Protection

A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail). Images collected are encrypted.

9.4. Study Records Retention

All eCRF information, study records, reports and Source Documents (SD) that support the eCRF must be retained in the files of the responsible investigator for a minimum 7 years following notification by the Sponsor or designee that all investigations have been completed and will further be retained in accordance with local and international guidelines as identified in the Investigator Site Agreement.

The core laboratory will also maintain study records. They will maintain study records until the Sponsor notifies them that research is completed/terminated under the clinical investigation in compliance with national law. All study data will be archived for a minimum of 7 years after study termination or premature termination of the study.

10. REPORTING

10.1. Annual Progress Report

Annually, as requested by independent ethics committee (IEC) or national regulations.

10.2. End of Study Report

The investigator should notify the IEC in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to regulatory authorities where required.

10.3. Other Reporting

The reporting requirements of the investigator also include, but are not limited to:

- Inform the Sponsor of IEC approval withdrawal.
- Major deviations from the clinical study protocol to the Sponsor
- Report or ensure the reporting, to the IEC by the Principal Investigator(s) as required by national regulations or the clinical study protocol or by the IEC.

11. MONITORING, QUALITY CONTROL AND ASSURANCE

11.1. Site Monitoring Plan

The investigators will allow onsite inspection of subjects' SD as requested by the Sponsor or required by an IEC or regulatory authorities. Monitoring activities may take place at the trial center or any ancillary facility where study conduct takes place. The investigators will provide access to all SD and adequate workspace. The investigators will be available to the Sponsor, IEC, or other regulatory authorities to discuss study issues as requested.

Sites will be initiated and trained on the clinical study requirements. Assurance of the accuracy and reliability of data will consist of checking the consent forms and consent process, on site and remote monitoring. All required data for this study will be collected into an eCRF. Appropriate computer editing programs will be run to verify the accuracy of the data.

There will be 100% informed consent verification, and all primary and secondary endpoint events up to 1 year will be adjudicated by an independent Clinical Events Committee (CEC). Verification of other SD will be performed as specified in the monitoring plan.

Data monitoring will occur at the Sponsor's discretion and in all cases where data irregularities are identified. As needed, intermittent monitoring visits may be conducted to compare data entered into the database to the subjects' SD.

Further details are outlined in the Monitoring Plan.

11.2. On-site Audits

The investigators will allow on-site inspection of subjects' SD as requested by the Sponsor or required by an IEC or regulatory authorities. Monitoring activities may take place at the trial center or any ancillary facility where study conduct takes place. The investigators will provide access to all SD and adequate workspace. The investigators will be available to the Sponsor, IEC, or other regulatory authorities to discuss study issues as requested.

If an Investigator is contacted by a Regulatory Agency in relation to this clinical trial/investigation, the Investigator will notify the Sponsor immediately and EC as appropriate.

11.3. Protocol Deviations

Investigators are not allowed to deviate from this CIP without prior authorization by the Sponsor except under emergency situations when necessary to preserve the rights, safety or well-being of study subjects.

Deviations and non-compliances will be recorded together with an explanation. Deviations or non-compliances that impact the rights, welfare, or safety of subjects shall be reported as soon as possible to the Sponsor and IEC, as required.

If appropriate, corrective, and preventive actions will be discussed by the Sponsor, investigator, and/or the IEC to determine a suitable course of action.

Deviations include, but are not limited to the following list:

- Failure to receive assigned treatment.
- Failure to obtain informed consent prior to conducting study specific activities.
- Inclusion/exclusion criteria not met.
- Incorrect version of the CIP/PIL used.
- Subject could not be reached for a follow-up visit or follow-up visit was outside window.
- AEs not reported by investigators in the required timeframe as specified in the protocol.
- Source data permanently lost.

Site compliance regarding deviations will be reviewed by the clinical study manager on a regular basis. In addition, all deviations from the protocol will be documented in the final report.

11.4. Protocol Amendments

Investigators will not modify, change, or otherwise amend the protocol without prior written consent of the Sponsor. As applicable, if a protocol amendment substantially alters the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continued participation in the study, the subject should generally be re-consented on an updated and approved (as required by local law and regulation) ICF. New procedures or processes which substantially alter the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continued participation the study will not be implemented until an approval or favorable opinion has been granted by the reviewing IEC, as applicable.

11.5. Core Laboratory

Two independent core laboratories will be used to perform quantitative coronary analysis (QCA) and intravascular ultrasound (IVUS) imaging analysis at:

- Baseline for the index procedure
- Post-calcium modification
- Post-PCI for all subjects
- Endpoints requiring a re-PCI in the treated lesion.

12. More details can be found in the study specific Core laboratory Plan.ETHICS AND REGULATORY

12.1. Regulation statement

This protocol has been developed and the study will be run in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013). [1] Further the study will be run in compliance with ISO 14155 (2nd edition) 2011. Both investigators and Sponsor will conduct this study in accordance with any applicable local or regional laws and regulations. Investigators will neither conduct procedures specific to the study nor collect subject data without prior approval or favorable opinion of any IEC under whose jurisdiction the conduct of this study falls. It is acknowledged that in some geographic areas IEC review and approval of study data collection activities may not be required.

During the conduct of study activity, the investigators and the Sponsor shall act in accordance with any further requirements as imposed by an IEC or regulatory agency.

12.2. Informed Consent Procedure

Any new information or protocol amendment that substantially alters the scientific validity of the study or affects the subjects' rights, safety, welfare, or their willingness to continue participation in the study, will result in the re-consenting of currently active subjects on an updated and approved (as required by local law and regulation) ICF.

12.3. Subject Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects to be identified.

12.4. Selection of Investigators/Sites

Qualified investigators and their sites will be selected based on experience running clinical studies, having adequate numbers of the target subject population and appropriate facilities, time and staff and commitment to conduct the clinical study, for participation.

12.5. Training requirements

Investigators and relevant staff will be trained on the following elements prior to enrollment of the first subject at a site:

- Clinical Investigational Plan (CIP)
- Electronic data capturing system
- Informed consent procedure
- Core lab interaction
- Study documentation and administration
- Investigator and Sponsor responsibilities
- Role of the EC and regulatory authority
- AE reporting procedures
- Protocol deviation reporting procedures
- Monitoring requirements and expectations
- Applicable regulatory requirements

Training will be done on an individual basis during a site visit before the first enrollment at each participating center. Additional training may be provided as needed. A training log will be used to document that training has been done. This will be filed in the site binder. When a new member joins the study site staff, the investigator/delegate or CRO will provide the appropriate training prior to their performing any study related activity.

13. PUBLICATION POLICY

CVRI Dublin and RCSI acknowledge that the Institution and/or Investigator may have a legitimate interest in publishing relevant parts of the Study Information. If the Institution and/or Investigator wants to publish such study information in appropriate scientific journals or other professional publications or present such information at scientific conferences/symposia, they may do so with respect to the following conditions:

(a) only if the publication is consistent with the rules and conventions governing clinical studies and regulatory submissions in all relevant jurisdictions, and only if drafts of the material have been reviewed by CVRI Dublin and the Steering Committee (SC).

(b) Institutional data, sub-analysis or any other experience in the study may not be published until the multi-center collective results of primary endpoints at 1 year follow-up, as a whole, are published. The results of the study will have no bearing on the submission of the manuscript for publication. This publication of the primary endpoints will be submitted to a peer-reviewed journal within six (6) months of the outcome of all of the primary measures being met (i.e. within six months of all patients having completed one-year follow-up.) In the event that the study is terminated early, manuscript submission will occur within 90 days of study termination.

(c) the Investigator and/or the Institution shall deliver the material intended for publication to CVRI Dublin at least sixty (60) days prior to the first intended submission for publication. CVRI Dublin will review and respond with its comments, if any, within (30) days of receipt of such a copy.

14. STUDY COMMITTEES

14.1. Steering Committee (SC)

The SC membership will include, but not limited to, the Coordinating Investigator, Director Core Lab- CVRI Dublin, CVRI Dublin biostatistician and the CVRI Dublin Project Manager. The role of SC is to provide overall supervision of the study. The Coordinating Investigator will review and input into the study protocol and any protocol amendments and provide advice to the investigators on all aspects of the study. The Project Manager will be responsible for the management of the study. This committee will meet periodically by teleconference (TC) or in person to monitor the progress of the study, including patient enrollment, clinical site progress and protocol compliance. This committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and the selection of secondary projects and publications.

14.2. Data Safety Monitoring Board (DSMB)

Due to the nature of the study, specifically that all devices used in this study have received CE-Mark approval and will only be used within the remit of this approval, DSMB is not applicable for this study.

14.3. Clinical Event Committee (CEC)

The CEC is made up of three (3) interventional cardiologists who are not participants in the study. Study Investigators are not permitted to be CEC members to avoid conflict of interest.

The CEC is responsible for adjudicating all primary and secondary endpoint related events reported during the study following established explicit rules in the CEC charter which outlines the data required and the algorithm followed in order to classify a clinical event.

The CEC will adjudicate events using either the independent review method or the consensus meeting method described in the study CEC charter. CEC findings will be summarized and documented in the CEC reports.

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APPENDIX A - Definitions

DEATH

(Academic Research Consortium-2 [ARC 2] definition) [2]

Type of Death Definition

- Cardiovascular death

Cardiovascular death is defined as death resulting from cardiovascular causes. The following categories may be collected:

1. Death caused by acute MI
2. Death caused by sudden cardiac, including unwitnessed, death
3. Death resulting from heart failure
4. Death caused by stroke
5. Death caused by cardiovascular procedures
6. Death resulting from cardiovascular hemorrhage
7. Death resulting from other cardiovascular cause

- Non cardiovascular Death

Non cardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be collected:

1. Death resulting from malignancy
2. Death resulting from pulmonary causes
3. Death caused by infection (includes sepsis)
4. Death resulting from gastrointestinal causes
5. Death resulting from accident/trauma
6. Death caused by other non-cardiovascular organ failure
7. Death resulting from other non-cardiovascular cause

- Undetermined

Undetermined cause of death is defined as a death not attributable to any other category, because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination.

DISSECTION

(NHLBI [National Heart, Lung, and Blood Institute] classification)

Type A Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Type B Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Type C Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Type D Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.

Type E Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Type F Filling defect accompanied by total coronary occlusion.

MYOCARDIAL INJURY AND MYOCARDIAL INFARCTION

(Fourth Universal Definition of Myocardial Infarction 2018)

Criteria for acute myocardial infarction (MI)

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following:

- Symptoms of myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.

Criteria for coronary procedure–related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*.
Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*.

Coronary procedure–related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a >5 or >10-fold increase and manifest a change from the baseline value of >20%.

In addition, at least 1 of the following characteristics must be present:

- New ischemic ECG changes (this criterion is related to type 4a MI only.
- Development of new pathological Q waves.
- Imaging evidence of loss of viable myocardium that is presumed to be new and, in a pattern, consistent with an ischemic etiology.
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.
-

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the prespecified thresholds for PCI and CABG.
Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.
Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior myocardial infarction

Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of nonischemic causes.

- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology.
- Patho-anatomical findings of a prior MI.

NO REFLOW
Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERCUTANEOUS CORONARY INTERVENTION (PCI) PROCEDURE
A PCI procedure will be considered to have commenced at the time the guidewire crosses the first lesion to be treated.

PERFORATION
Perforations will be classified as follows:

Angiographic perforation: perforation detected by the clinical site or the core laboratory at any point during the procedure.

Clinical perforation: perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, abrupt closure, myocardial infarction, or death.

Pericardial haemorrhage/tamponade: perforation resulting in cardiac tamponade.

REFERENCE VESSEL DIAMETER (RVD)
Defined as the average diameter of normal segments within 10 mm proximal and distal to the TL from two (2) orthogonal views by visual estimate.

TARGET LESION THROMBOSIS (TLT)
(ARC II definition)
Target lesion thrombosis should be reported as a cumulative value over time and at various individual time points as specified below. ***Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the Cath lab.***

We recognize three categories of evidence in defining stent thrombosis inside the target lesion.

1. **Definite stent/scaffold thrombosis**

Angiographic confirmation of stent/scaffold thrombosis*
The presence of a thrombus† that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least 1 of the following criteria:

- Acute onset of ischemic symptoms at rest
- New electrocardiographic changes suggestive of acute ischemia

- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)
- Or

Pathological confirmation of stent/scaffold thrombosis

- Evidence of recent thrombus within the stent/scaffold determined at autopsy
- Examination of tissue retrieved following thrombectomy (visual/histology)

2. Probable stent/scaffold thrombosis

Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/scaffold thrombosis and in the absence of any other obvious cause.

3. Silent stent/scaffold occlusion

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.

Timing of ST (duration after stent implantation)

Acute 0–24 h
Subacute >24 h–30 d
Late >30 d–1 y
Very late >1 y

Early stent thrombosis is 0 to 30 days (acute plus subacute stent thrombosis). MI indicates myocardial infarction.

*Definite stent/scaffold thrombosis is considered to have occurred by either angiographic or pathological confirmation.

†Occlusive thrombus: Thrombolysis in Myocardial Infarction grade 0 or 1 flow within or proximal to a stent/scaffold segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

‡When the stented/scaffolded segment is in the left circumflex coronary artery or in the presence of preexisting electrocardiographic abnormalities (e.g. left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee adjudication is based on review of all available evidence.

§Defined as the moment the patient is undraped and taken off the catheterization table

TARGET LESION (TL)

The TL is the portion of the coronary artery that was in immediate contact with the DCB plus a margin of 5 mm on both ends.

TARGET VESSEL (TV)
The TV is defined as the index coronary artery which was in physical contact with any component (guiding catheter, guide wire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

TARGET LESION FAILURE (TLF)
(ARC 2 definition)
Cardiovascular death, target-vessel myocardial infarction, or clinically driven target-lesion revascularization.

TARGET VESSEL FAILURE (TVF)
(ARC 2 definition)
Cardiovascular death, target-vessel myocardial infarction, driven target-vessel revascularization

TARGET LESION REVASCULARIZATION (TLR)
Defined as any repeat percutaneous intervention of the TL or bypass surgery of the target vessel.

Clinically driven revascularizations are those in which the patient has a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms. Revascularization of a TL with an in-lesion diameter stenosis ≥70% (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms.

Non-clinically driven repeat target lesion revascularizations are those in which the patient undergoes a non-emergent revascularization for a diameter stenosis <50% (by QCA). Non-emergent repeat target lesion revascularization for a diameter stenosis <70% (by QCA) in patients without either a positive functional study or angina are also considered non-clinically driven defined as any repeat revascularization of the target site whether by PCI or bypass surgery.

TARGET VESSEL REVASCULARIZATION (TVR)
Any target vessel revascularization, death, or MI attributed to the target vessel.

TIMI CLASSIFICATION

TIMI 0	No perfusion.
TIMI 1	Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.
TIMI 2	Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the

	coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.
TIMI 3	Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

APPENDIX B - Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AE	Adverse Event
AHA	American Heart Association
ARC	Academic Research Consortium
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCS	Chronic Coronary Syndrome
CEC	Clinical Events Committee
CRO	Clinical Research Organization
CIP	Clinical Investigation Plan
cTn	Cardiac Troponin
CVRI Dublin	Cardiovascular Research Institute Dublin
DAPT	Dual Anti-Platelet Therapy
DCB	Drug Coated Balloon
DCS	Drug Coated Stent
DES	Drug Eluting Stent
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
FFR	Fractional Flow Reserve
GCP	Good Clinical Practices
HbA1c	Glycated Haemoglobin
IEC	Independent Ethics Committee
iFR	Instantaneous Free-wave Ratio
IFU	Instructions for Use
ISR	In-Stent Restenosis
ITT	Intent to Treat
IVUS	Intravascular Ultrasound
LLL	Late Lumen Loss
MACE	Major Adverse Cardiac Events

MB	Main Branch
MI	Myocardial Infarction
NHLBI	National Heart, Lung, and Blood Institute
NOAEL	No Observed Adverse Effect Level
Non-TV	Non-Target Vessel
OCT	Optical Coherence Tomography
%DS	Percent Diameter Stenosis
PCI	Percutaneous coronary intervention
PK	Pharmacokinetic
PTCA	Percutaneous Transluminal Coronary Angioplasty
QCA	Quantitative Coronary Analysis
RCSI	RCSI University of Medicine and Health Sciences
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SB	Side Branch
SC	Steering Committee
SCAI	Society for Cardiac Angiography and Interventions
STD	Standard Deviation
SD	Source Documentation
SDV	Source Document Verification
STEMI	ST-elevation Myocardial Infarction
ST	Stent thrombosis
SVD	Small Vessel Disease
TC	Teleconference
TL	Target Lesion
TLF	Target Lesion Failure
TIMI	Thrombolysis In Myocardial Infarction
TLR	Target lesion Revascularization
TV	Target Vessel
TV-MI	Target Vessel Myocardial Infarction
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
URL	Upper Reference Limit