CLINICAL INVESTIGATION PLAN
BIONICS 38 mm Trial

EluNIR Ridaforolimus Eluting Coronary Stent System (EluNIR)
In Coronary Stenosis Trial

Clinical Investigation Plan (CIP) Number: EluNIR-004

Investigational Sites	Up to 10 sites in Israel
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Core Laboratories (Angiographic,) **Data Management / Data Analysis** **Clinical Events Committee** **Data Safety Monitoring Board**	Cardiovascular Research Foundation 1700 Broadway New York NY 10019 USA
Clinical Investigation Plan Version and Date	Version 1.1, 23-July-2018

This Clinical Investigation Plan has been written in accordance with Annex A of EN ISO 14155 (2011): Clinical investigations of medical devices for human subjects – Good Clinical Practice and ICH E6 Guidelines. In accordance with EN ISO 14155, where information is held within other trial documentation e.g. in the Investigator Brochure, this is referenced where appropriate.

Compliance Statement

The trial will be conducted in accordance with the design and specific provisions of this clinical investigation plan, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), EN ISO 14155, ICH E6, and the applicable regulatory requirements.

Clinical Investigation Plan Review

I, the undersigned, have reviewed and approved the clinical investigation plan specified above and agree on its content.

Sponsor Representative's Signature

Dina Kofler D.K — Sponsor Representative Name

31 / July / 2018 — Date

CLINICAL INVESTIGATION PLAN REVISION SUMMARY

Version	Release Date	Summary of Changes
1.0	6-June-2018	Initial release
1.1	23-July-2018	Revised per FDA's comments

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

EluNIR Ridaforolimus Eluting Stent System In Coronary Stenosis

BIONICS 38 mm Trial

CIP Number: EluNIR-004

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice), as well as local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the Sponsor and by regulatory authorities.

Primary Investigator (print)	
Primary Investigator (signature)	Date
Sub-Investigator (print)	
Sub-Investigator (signature)	Date
Institution Name/Location (print)	

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1 SYNOPSIS OF THE CLINICAL INVESTIGATION

BIONICS (*EluNIR Ridaforolimus Eluting Coronary Stent System In Coronary Stenosis*) 38 mm Trial

Device	EluNIR Ridaforolimus Eluting Coronary Stent System - (hereafter referred to as EluNIR) 38 mm length (2.75 mm, 3.00 mm,3.5 mm,4 mm diameter)
Objectives	To further assess the safety and efficacy of long (38 mm) Ridaforolimus Eluting Stent - EluNIR.
Subject Population	Subjects who underwent PCI for angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present), NSTEMI, and recent STEMI (>24 hours from initial presentation and stable) with attempted implantation of 38 mm EluNIR stent.
Trial Design and Methods	This is a prospective, multi-center, single-arm, open-label clinical trial. Clinical follow-up will be performed at 30 days. Follow-up by phone will be performed at 6 months, and 1 year after the procedure
Primary Endpoint	Combined efficacy and safety endpoint: **Device success as determined by the Angiographic Core Lab (ACL) with no 30 day MACE**. Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the EluNIR 38 mm stent only and without a device malfunction. MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR.
Secondary Endpoints	• Device success • Lesion success • Procedure success As determined by the Angiographic Core Laboratory at time of baseline procedure. Secondary endpoints to be evaluated at 30 days, 6 months, and 1 year: • Target lesion failure (TLF; the composite rate of cardiac death, target vessel related MI, or ischemia-driven TLR) • Target vessel failure (TVF; the composite rate of death, target vessel related MI or ischemia-driven TVR) • Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR) • All-cause mortality • Cardiac death • Myocardial infarction • Target vessel related MI

	• Ischemia-driven TLR • Ischemia-driven TVR • Stent thrombosis (ARC definite and probable)
Sample Size	Approximately 50 subjects will be enrolled in this study.
Inclusion Criteria (Inclusion and Exclusion Criteria refer to patient's baseline condition prior to index PCI)	**General Inclusion Criteria:** 1. Age ≥ 18 years. 2. Patient with an indication for PCI including angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present), NSTEMI, or recent STEMI. For STEMI the time of presentation to the first treating hospital, whether a transfer facility or the study hospital, must be >24 hours prior to enrollment and enzyme levels (CK-MB or Troponin) demonstrating that either or both enzyme levels have peaked. 3. An attempt (whether successful or not) was made to implant a 38 mm EluNIR stent (Stent was advanced beyond the guiding catheter). 4. Non-target vessel PCI are allowed prior to the screening for eligibility depending on the time interval and conditions as follows: **a. During Baseline Procedure:** PCI of non-target vessels performed during the baseline procedure itself immediately prior to screening for eligibility, if successful and uncomplicated defined as: <50% visually estimated residual diameter stenosis, TIMI Grade 3 flow, no dissection ≥ NHLBI type C, no perforation, no persistent ST segment changes, no prolonged chest pain, no TIMI major or BARC type 3 bleeding. **b. Less than 24 hours prior to Baseline Procedure:** Not allowed (see exclusion criteria #2). **c. 24 hours-30 days prior to Baseline Procedure:** i. PCI of non-target vessels 24 hours to 30 days prior to the baseline procedure if successful and uncomplicated as defined above. ii. In addition, in cases where non-target lesion PCI has occurred 24-72 hours prior to the baseline procedure, at least 2 sets of cardiac biomarkers must have been drawn at least 6 and 12 hours after the non-target vessel PCI.

	iii. If cardiac biomarkers are initially elevated above the local laboratory upper limit of normal, serial measurements must demonstrate that the biomarkers are falling. **d. Over 30 days prior to Baseline Procedure:** PCI of non-target vessels performed greater than 30 days prior to baseline procedure whether or not successful and uncomplicated. 5. Patient or legal guardian is willing and able to provide informed written consent and comply with follow-up visits and testing schedule. **Angiographic inclusion criteria (visual estimate):** 6. Target lesion(s) must be located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.75 mm to ≤4.25 mm. 7. Complex lesions are allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy are allowed), presence of thrombus, CTO, bifurcation lesions, ostial RCA lesions, tortuous lesions, bare metal stent restenotic lesions, protected left main lesions, and saphenous vein graft lesions. 8. Overlapping stents are allowed as long as the first stent implanted is the EluNIR 38 mm long stent
Exclusion Criteria	**General Exclusion Criteria:** 1. STEMI within 24 hours of initial time of presentation to the first treating hospital, whether at a transfer facility or the study hospital or in whom enzyme levels (either CK-MB or Troponin) have not peaked. 2. PCI within the 24 hours preceding the baseline procedure. 3. Non-target lesion PCI in the target vessel within 12 months of the baseline procedure. 4. History of stent thrombosis. 5. Cardiogenic shock (defined as persistent hypotension (systolic blood pressure <90 mm/Hg for more than 30 minutes) or requiring pressors or hemodynamic support, including IABP. 6. Subject is intubated. 7. Known LVEF <30%. 8. Relative or absolute contraindication to DAPT for 6 months in non-ACS patients and 12 months in ACS patients (including planned surgeries that cannot be delayed, or subject is indicated for chronic oral anticoagulant treatment). 9. eGFR <30 mL/min

	10. Hemoglobin <10 g/dL. 11. Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3. 12. White blood cell (WBC) count <3,000 cells/mm^3. 13. Clinically significant liver disease. 14. Active peptic ulcer or active bleeding from any site. 15. Bleeding from any site within the prior 8 weeks requiring active medical or surgical attention. 16. If femoral access is planned, significant peripheral arterial disease which precludes safe insertion of a 6F sheath. 17. History of bleeding diathesis or coagulopathy or will refuse blood transfusions. 18. Cerebrovascular accident or transient ischemic attack within the past 6 months, or any permanent neurologic defect attributed to CVA. 19. Known allergy to the study stent components cobalt, nickel, chromium, molybdenum, Carbosil®, PBMA, or limus drugs (ridaforolimus, zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative or similar compounds). 20. Known allergy to protocol-required concomitant medications such as aspirin, or DAPT (clopidogrel, prasugrel, ticagrelor), or heparin and bivalirudin, or iodinated contrast that cannot be adequately pre-medicated. 21. Any co-morbid condition that may cause non-compliance with the protocol (e.g. dementia, substance abuse, etc.) or reduced life expectancy to <24 months (e.g. cancer, severe heart failure, severe lung disease). 22. Patient is participating in or plans to participate in any other investigational drug or device clinical trial that has not reached its primary endpoint. 23. Women who are pregnant or breastfeeding. 24. Women who intend to become pregnant within 12 months after the baseline procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the baseline procedure). 25. Patient has received an organ transplant or is on a waiting list for an organ transplant. 26. Patient is receiving or scheduled to receive chemotherapy within 30 days before or any time after the baseline procedure.

	27. Patient is receiving oral or intravenous immunosuppressive therapy or has known life-limiting immunosuppressive or autoimmune disease (e.g., HIV). Corticosteroids are allowed. **Angiographic Exclusion Criteria (visual estimate):** 28. Unprotected left main lesions ≥30%, or planned left main intervention. 29. Bifurcation lesions with planned dual stent implantation. 30. Stenting of lesions due to DES restenosis. 31. Occlusive thrombus and/or a thrombus requiring thrombectomy in a target vessel 32. Another lesion in a target or non-target vessel (including all side branches) is present that requires or has a high probability of requiring PCI within 12 months after the baseline procedure.

2 IDENTIFICATION AND DESCRIPTION OF THE STUDY DEVICE

2.1 Summary Description of the Study Device and Its Intended Purpose

2.1.1 Summary Description of the Study Device

The EluNIR Ridaforolimus Eluting Coronary Stent System is a single use device/drug combination product comprising of:

- Stent - a mounted Cobalt Chromium (CoCr) alloy based stent – 38 mm length and 2.75mm, 3.0 mm, 3.5mm, 4.0mm diameter
- Delivery System - Rapid Exchange (RX) Coronary System
- Polymer matrix coating - Poly n-butyl methacrylate (PBMA) and CarboSil®
- Ridaforolimus drug - CAS Registry Number: 572924-54-0

2.1.2 Intended Purpose

The EluNIR Ridaforolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to de novo lesions of length ≤42mm in native coronary arteries with reference diameters of 2.5* mm to 4.25 mm.

2.2 Details Concerning the Manufacturer of the Study Device

Medinol Ltd.
Beck Tech Building
Har Hotzvim B, Hartom Street 8
PO Box 45026
Jerusalem, 9777508, Israel

* The 2.5mm diameter stent for EluNIR Stent System is available for up to 33mm stent length.

2.3 Traceability of the Study Device

Each device will be traced using the lot number that is affixed to the label of the device. Both the Sponsor (or designee) and the investigational site will maintain a log of the devices that have been implanted (or attempted to be implanted) in subjects.

2.4 Intended Purpose of the Study Device in the Proposed Clinical Investigation

See Section 2.1.2.

2.5 Populations and Indications for Which the Study Device Is Intended

See Section 2.1.2.

2.6 Description of the Study Device

2.6.1 Stent

The EluNIR (formerly named BioNIR™) is comprised of the CoCr Coronary Stent coated with a polymer matrix and ridaforolimus drug, mounted on RX System.

The bare metal substrate CoCr stent is a continuous "closed cell" design with adaptive cells capable of differential lengthening, thereby enabling the stent to be flexible in the unexpanded state and to support the vessel, while conforming to its curvature, in the expanded state.

The EluNIR 38mm stent is available in 2.75mm, 3.0mm. 3.5mm and 4.0mm diameters.
The EluNIR stent was approved both in the US and in the EU in 2017, and in Israel in 2018.

2.6.2 Delivery System

The D-catheter is a rapid exchange (Rx) balloon catheter with a hydrophilic coating.
The usable length of the delivery system is 140cm, with a shaft proximal profile of 2.1F (0.69mm) and a distal shaft profile of 2.7F (0.90mm) for products of up to 28mm length, and 2.9F (0.97mm) for products of 33mm and up to 44mm length. The catheter has a distal port approximately 30 cm from the distal tip that accesses the guidewire lumen. The guidewire lumen begins at the distal port and terminates at the distal tip. The catheter has two (2) markers on the proximal catheter shaft that indicate approximately the exit of the balloon catheter tip from the guiding catheter (brachial: 93 cm; femoral: 103 cm). The D-catheter requires a 0.014" (0.36 mm) diameter guidewire for navigation.

2.6.3 Polymer Coating

The stent is coated with a polymer matrix coating consisting of poly n-butyl methacrylate (PBMA) and CarboSil® 20 55D polymer.

2.6.4 Ridaforolimus

Ridaforolimus (CAS Registry Number: 572924-54-0; formerly deforolimus) is a member of the limus family of drugs. It is a unique, non-prodrug analog of rapamycin (sirolimus), a macrocyclic

lactone produced by *Streptomyces hygroscopicus*. Ridaforolimus is manufactured by CARBOGEN AMCIS AG (Hauptstrasse 171, CH-4416 Bubendorf, Switzerland; FDA Registration Number: 3000998501). It is utilized on the stent system at a dose of 1.1 µg/mm^2 (with a drug load of 100 µg per 2.75/3.00 x 17 mm stent).

The drug ridaforolimus, like rapamycin, is expected to permeate the cell membrane, bind to cytosolic FKBP12 and then to mTOR, a P13K-related protein kinase. Treatment of cultured tumor cell lines with Rapamycin *in vitro* has been shown to slow the rate of tumor proliferation. These effects are attributable to the inhibition of the multiple downstream effects of mTOR's activity: synthesis of components required for macromolecular synthesis (such as ribosomes), cell size increase, and progression through the G1 phase of the cell cycle. In the *in vitro* studies, Ridaforolimus demonstrated anti-proliferative activity on a broad range of human tumor cell lines.

2.7 Summary of Necessary Training and Experience Needed to Use the Study Device

The EluNIR Ridaforolimus Eluting Coronary Stent System is similar to existing stent systems currently on the market so there will not be any additional training required for experienced interventionalists to implant the stents. Investigator training is described in Section 6.5.4.1.

2.8 Description of the Specific Medical or Surgical Procedures

Subjects in this trial will undergo coronary angiography and percutaneous coronary intervention (PCI) with stent implantation for narrowings (stenoses) in the coronary arteries using standard angiographic and stenting techniques. Both radial and femoral approaches are acceptable. Adherence to PCI guidelines issued by professional societies such as the ACCF/AHA/SCAI 2011 Guideline for Percutaneous Intervention (1) is recommended.

3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1 Background

Percutaneous Intervention (PCI) is part of the standard treatment for coronary artery stenoses and has been shown to relieve ischemia and angina in stable coronary disease and improve outcomes in acute coronary syndromes particularly in patients with ST elevation myocardial infarction (STEMI). Stents, originally developed in the 1980s, have almost entirely replaced balloon angioplasty with the advantage of greater procedural success with reduced risk of abrupt closure as well as reduced rates of restenosis.(2) Bare metal stents, however, were still limited by up to 30% restenosis rate due to neointimal proliferation. The advent of drug eluting stents (DES) which released anti-proliferative medications into the stented region markedly reduced the restenosis rate, thereby reducing the rate of repeat revascularization. Concern emerged, however, over late and very late stent thrombosis with the use of DES.(3) Stent thrombosis has been linked to delayed and incomplete endothelialization as well as stent mal-apposition and strut breakage. Additional issues

with DES include a local inflammatory reaction, allergic reactions to the stent components, and impairment of endothelial function.(4)

Different DES have been shown to have differing rates of angiographic late loss as well as different rates of clinical events such as target lesion failure (TLF) and stent thrombosis.(5) Different stent design, polymer features, and anti-proliferative drug used may impact these important clinical endpoints. The overall low event rate, however, has necessitated large scale clinical trials to evaluate new stents. Registration studies have also been limited by strict enrollment criteria which have excluded many patient and lesion types which are typically treated in clinical practice including complex lesions and patients with acute coronary syndromes.

Long-length stenting has particularly poor outcomes when bare metal stents are used. (6) Moreover, treatment of a long coronary lesion with multiple stents, has been associated with serious complications such as significantly increased risk of stent thrombosis or restenosis at the gap between adjacent stents (7), as the vessel is exposed to more stent's struts, polymer, and larger drug dose is delivered to the to the intima at the site of the stent's overlap.(8) As such, implanting long DES, could potentially reduce the need to use multiple stents in long coronary lesions.

The EluNIR is a new DES which uses a closed-cell design and an improved delivery system and therefore may improve outcomes compared to other drug eluting stents. The present trial is aimed at further assessing the safety and efficacy of the long (38 mm) EluNIR stent which is approved and marketed OUS. The trial will include a diverse population representative of contemporary stent use. The trial will enroll a broad population including patients with ACS (unstable angina, NSTEMI, and STEMI) as well as complex lesions. The inclusion of patients with AMI and particularly STEMI is justified given that the majority of PCIs are in patients with ACS with STEMI accounting for up to 30% of ACS cases. In order to reduce the potential for confounding, patients with STEMI will be enrolled only after 24 hours have elapsed from their initial hospital presentation. Typically, such patients will have already undergone primary PCI of the culprit lesion. Stent thrombosis is increased in the setting of primary PCI mostly in the first 24 hours.(9) Therefore, confounding is unlikely and furthermore subjects will be stratified in the trial by ACS vs. non-ACS status.

3.2 Evaluation of the Results of the Relevant Pre-Clinical Testing

A broad range of bench testing, stability, and shelf life studies as well as pre-clinical testing including biocompatibility, animal pharmacokinetic, and safety studies (single and overlapping configuration) in swine coronary arteries have been completed without any pertinent findings.

3.3 Evaluation of Clinical Data Relevant to the Proposed Clinical Investigation

The present trial is a companion study to the NIREUS (BioNIR Ridaforolimus Eluting Coronary Stent System (BioNIR) EUropean Angiography Study) and the BIONICS (BioNIR in Coronary Stenosis) studies, as detailed below:

- NIREUS is a prospective, multicenter, single blind, randomized study, randomized 2:1, BioNIR vs Medtronic Resolute. The trial population included 302 subjects undergoing PCI for angina (stable or unstable), silent ischemia (in absence of symptoms was required to have a visually estimated target lesion diameter stenosis of ≥ 70% or positive non-invasive stress test, or FFR ≤0.80), NSTEMI, or recent STEMI (>24 hours prior to enrollment and stable). Treatment of up to three de novo target lesions was allowed, with a maximum of one de novo target lesion per epicardial vessel. Randomization was stratified by the presence of medically treated diabetes vs. no medically treated diabetes and by site. Angiographic follow-up was performed at 6 months. Clinical follow-up was performed at 30 days, 6 months and 1 year. Main results were published (11) and the trial is ongoing with planned follow up at 2, 3, 4, and 5 years post randomization.

  The BioNIR stent demonstrated a low late lumen loss result of 0.04 ±0.30 mm (n=201) compared with 0.03 ± 0.31 mm for Resolute Integrity (n=101) and met the non-inferiority definition with a high degree of statistical significance (p<0.0001). In addition, the BioNIR stent demonstrated a target lesion failure (TLF) rate of 3.4% at six months compared with 5.9% for Resolute Integrity (p=0.22). Rates of MACE (cardiac death, any MI, and clinically-driven target lesion revascularization) were similar between the BioNIR and Resolute Integrity (4.3% vs 5.9%, respectively, p=0.45).

- The BIONICS is a prospective single blind trial with 1:1 randomization of the BioNIR stent vs. the Medtronic Resolute stent and was powered to demonstrate non-inferiority (n=1919 subjects). The trial population is similar to that of NIREUS, but there was no limit on the number of denovo lesions allowed per vessel.

  The 12-month primary end point of target lesion failure (composite of cardiac death, target vessel-related myocardial infarction, and target lesion revascularization) was 5.4% for both devices (upper bound of 1-sided 95% confidence interval 1.8%, $P_{noninferiority}$=0.001). Definite/probable stent thrombosis rates were low in both groups (0.4% BioNIR versus 0.6% Resolute, P=0.75); 13-month angiographic in-stent late lumen loss was 0.22±0.41 mm and 0.23±0.39 mm ($P_{noninferiority}$=0.004) for the BioNIR and Resolute, respectively, and intravascular ultrasound (IVUS) percent neointimal hyperplasia was 8.10±5.81 and 8.85±7.77, respectively ($P_{noninferiority}$=0.01)(10).

  In addition, in a post-hoc analysis from BIONICS Trial, 277 (out of 1,919) patients had at least one long lesion (exceeding 30 mm), overall 287 lesions. Of these, 136 lesions were treated with Ridaforolimus Eluting stents (RES) and 151 lesions were treated with Zotarolimus Eluting stent (ZES). Mean (± standard deviation, SD) lesion lengths were 40.3 ± 11.8 mm and 39.9 ± 9.7 mm for the RES and ZES groups, respectively. The 12-month TLF (a composite of cardiac death, target vessel-related MI and target lesion revascularization), for patients with long lesions who were treated either by RES (available in length up to 33 mm) or ZES (available in length up to 38 mm), were 6.3% and 6.8% respectively (P=0.84). The rates of clinically-driven target lesion revascularization were

4.0% for the RES group and 3.4% for the ZES (P=0.83). Definite/probable stent thrombosis rates were low in both groups (0.8% RES vs. 0.7% ZES, P=0.92). These findings support the safety and efficacy of RES in patients with complex long lesions.

An independent DSMB convened by the Cardiovascular Research Foundation has been monitoring both the on-going NIREUS and BIONICS and has not identified any safety issues.

4 RISKS AND BENEFITS OF THE STUDY DEVICE AND CLINICAL INVESTIGATION

The risks and benefits of the EluNIR are summarized in the IFU.

4.1 Anticipated Clinical Benefits

The study stent is expected to provide the same radial support as other coronary stents which maximize the lumen size of a stenosed artery, as is commonly indicated for coronary stenting. Additionally, the potential benefit of the study stent is its effectiveness in inhibition of neointimal growth while enhancing endothelial coverage. The study stent has the potential to reduce rates of restenosis without increasing rates of late and very late stent thrombosis compared to other commercially available DES In addition, as it reduces the need for using multiple stents for long coronary lesions, it can potentially decrease thrombotic complications and restenosis in two overlapping stents or in the gaps between adjacent stents.

4.2 Anticipated Adverse Device Effects

It is expected that the adverse device effects for EluNIR would not differ from the anticipated adverse device effects of approved DES as well as other approved EluNIR stents based on years of clinical experience with rapid exchange DES implantations.

4.3 Residual Risks Associated with the Device

Foreseeable adverse events that may result from stent intervention can be found in Section 14.6 as well as the IFU.

4.4 Risks Associated with Participation in the Clinical Investigation

There is extensive clinical and commercial experience worldwide with cardiac catheterization and interventional procedures, and it is expected that the surgical and procedural risks will not be significantly different in this clinical trial.

4.5 Possible Interactions with Concomitant Medical Treatments

Strong inhibitors of CYP3A4 (e.g. Ketoconazole) might cause increased rapamycin analog exposure to levels associated with systemic effects, especially if multiple stents are deployed. Systemic exposure of rapamycin analog should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

While formal drug interaction studies were not conducted with EluNIR due to expected negligible systemic exposure, since Ridaforolimus is also a rapamycin analog, the aforementioned possible interactions apply to EluNIR as well.

4.6 Steps to Control or Mitigate Risks

Subjects with no aspirin resistance, allergy, or bleeding risk will continue on aspirin indefinitely and either clopidogrel (75 mg/day), prasugrel (5-10 mg/day), or ticagrelor (90 mg bid) for at least six months following stent implantation. In accordance with the PCI recommendations from ACCF/AHA/SCAI, it is recommended that dual anti platelet therapy (DAPT) be continued for 6 months (12 months in ACS patients) following stent implantation (1) unless an intervening medical necessity, such as severe bleeding, occurs. If DAPT is discontinued before 6 months (or 12 months in ACS patients) due to medical necessity (for example, severe bleeding), the reason should be documented.

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

In addition, an independent Data Safety Monitoring Board (DSMB) will monitor safety of the subjects throughout the trial.

4.7 Risk-to-Benefit Rationale

The EluNIR represents a potential advance in both stent and delivery system design and is expected to be noninferior to second generation DES such as the Resolute. Subjects enrolled in this trial have an indication for PCI due to significant coronary stenosis. The majority of risk associated with the trial is inherent to standard of care PCI and is not likely to be increased by participation in this trial. While there may be unknown risks associated with the long EluNIR stent these are mitigated by the use of an approved stent platform and delivery system with a polymer coating (Carbosil) which is biocompatible and thrombo-resistant. Ridaforolimus is part of the rapamycin analog family of drugs for which there is extensive experience on DES.

5 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 Objectives

To further assess the safety and efficacy of the long (38 mm) Ridaforolimus Eluting Stent – EluNIR.

5.2 Claims and Intended Performance of the Study Device

The EluNIR Ridaforolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with heart disease including angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a

positive non-invasive stress test, or FFR ≤0.80 must be present), NSTEMI, or recent STEMI due to de novo lesions in vessels with reference diameters of 2.75 mm to 4.25 mm.

5.3 Risks and Anticipated Adverse Device Effects That Are To Be Assessed

The risks and anticipated adverse device effects are summarized in Section 14.6 as well as in the IB. All Adverse Device Effects (ADE) will be collected and assessed as such, based on initial assessment of the Investigator, as well as the appointed Medical Monitor, whether the adverse event is or is not related to the device.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 General

6.1.1 Description of Trial

The BIONICS 38 mm Trial will enroll approximately 50 subjects with a wide spectrum of PCI indications (stable angina as well as ACS, including subacute STEMI (>24 hours since first hospital presentation) as well as complexity.

This is a prospective, multi-center, single-arm, open-label clinical trial.

6.1.2 Rationale for Trial

Drug eluting stents have significantly lowered the restenosis rate following PCI. Because of delayed re-endothelization, however, prolonged (current recommendations are for 12 months) dual anti-platelet therapy (DAPT) is indicated, but has not completely eliminated stent thrombosis, a serious complication with potential mortality. Rates for stent thrombosis with second generation DES have been in the range of 1-3% at one year after stent implantation.

Long-length stenting has particularly poor outcomes when bare metal stents are used (6). Moreover, treatment of a long coronary lesion with multiple stents, has been associated with serious complications such as significantly increased risk of stent thrombosis or restenosis at the gap between adjacent stents (7), as the vessel is exposed to more stent's struts, polymer, and larger drug dose is delivered to the to the intima at the site of the stent's overlap (8). As such, implanting long DES, could potentially reduce the need to use multiple stents in long coronary lesions. The maximum stent length available for current stent platform is 38 mm and thus overlapping stents are often required to cover longer segments (8). In addition, in a post-hoc analysis from the BIONICS Trial, the 12-month target lesion failure (TLF) outcomes, for patients with long lesions -exceeding 30 mm- who were treated either by Ridaforolimus-Eluting stent or Zotarolimus-Eluting stent, were similar supporting the safety and efficacy of Ridaforolimus-Eluting stent in patients with complex long lesions

Rates for restenosis as well as ST vary between stents and depend on a myriad of factors including stent design (for example, open- vs. closed-cell), strut thickness, stent material, flexibility of the stent, and degree of mal-apposition. It is therefore important to examine the safety and efficacy of the long (38 mm) EluNIR stents. Comparisons focus on clinical events, primarily target lesion

failure (TLF), defined as the composite of cardiac death, target vessel related MI, or ischemia driven target lesion revascularization.

The present trial is a companion trial to the BIONICS and NIREUS trials aimed at further assessing the safety and efficacy of the long (38 mm) EluNIR stent.

6.1.3 Primary and Secondary Endpoints

Definitions of terms and endpoints are located in Section 19.1. Acronyms and abbreviations are defined in Section 19.2.

6.1.3.1 Primary Endpoint

Combined efficacy and safety endpoint:
Device success as determined by the Angiographic Core Lab (ACL) with no 30 day MACE.

Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the EluNIR 38 mm stent only and without a device malfunction.
MACE is defined as the composite of cardiac death, any MI, or ischemia-driven TLR.

6.1.3.2 Secondary Endpoints

- Device success
- Lesion success
- Procedure success

As determined by the Angiographic Core Laboratory at the time of the baseline procedure.
Secondary endpoints to be evaluated at 30 days, 6 months and 1 year:

- Target lesion failure (TLF; the composite cardiac death, target vessel related MI, or ischemia-driven TLR)
- Target vessel failure (TVF; the composite rate of death, target vessel related MI or ischemia-driven TVR)
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR)
- All-cause mortality
- Cardiac death
- Myocardial infarction
- Target vessel related MI
- Ischemia-driven TLR
- Ischemia-driven TVR
- Stent thrombosis (ARC definite and probable)

6.1.4 Methods and Timing for Assessing, Recording, and Analyzing Variables

Data collection commences after the subject has provided an informed consent. Data collection including subject demographic information, laboratory tests, and procedural data as well as follow-up visits or telephone contacts will be conducted by an Investigator or site coordinator who has been trained on the CIP and Case Report Forms (CRF).

Data required for analysis will be obtained as outlined in Table 1. After discharge from the hospital, each subject will be followed with an in-clinic follow-up visit at 30 days, and follow-up by phone at 6 months and 1year post procedure.

Table 1: Schedule of Data Collection

TYPE OF DATA TO BE COLLECTED	Pre-Procedure[1] (within 30 days)	Pre-Procedure[1] (within 24 hours)	Baseline Procedure	Post-Procedure	30 days (± 7 days)	6 Months (± 30 days) by phone	1 year (-30 days / +14 days) by phone	Unscheduled visits
Patient Informed Consent				✓				
Patient Medical/Clinical History				✓[1]				
Angina Status		✓[1]		✓[1]	✓	✓	✓	✓
General Eligibility Criteria			✓[1]					
Angiographic Eligibility Criteria			✓[1]					
Clinical Laboratory Tests:								
CBC, Creatinine, BUN	✓[1,2]							
Lipid profile	✓[1,2]							
CK, CK-MB or Troponin		✓[1-3]		✓[4]				
12-Lead ECG		✓[1]		✓				
Coronary Angiogram & PCI			✓[1]					
Study Stent Information			✓[1]					
Per Protocol DAPT Medications[5]		✓[1]	✓[1]	✓	✓	✓	✓	✓
Concomitant Cardiac Medications[6]		✓[1]		✓	✓	✓	✓	✓
Adverse Events Monitoring			✓[1,7]	✓	✓	✓	✓	✓

1. Data will be collected only after post-procedural informed consent has been obtained.
2. Should be collected at time of enrollment if not collected at baseline as part of routine SOC.
3. Within 24 hours pre-procedure if collected per site protocol. For subjects with ACS, it is recommended that enzyme levels be within 8 hours of the procedure or have already been shown to be decreasing. For STEMI patients enzyme levels should have peaked for either CK-MB or Troponin (I or T) or both.
4. If Troponin is elevated or CK-MB is elevated ≥ upper limit of normal, serial measurements of CK and CK-MB (preferred) or Troponin (I or T) must be done until a decline is noted
5. Clopidogrel 75 mg daily or prasugrel 5 to 10 mg daily or ticagrelor (90 mg bid) must be given for a minimum of 6 months (12 months in ACS patients) as well as aspirin 75 to 100 mg daily to be taken indefinitely.
6. Concomitant cardiac medications will be recorded by categories (e.g., statin, non-statin lipid lowering, ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, other anti-anginals).
7. All adverse events that occur after EluNIR stent was inserted into the patient's target artery (beyond the guiding catheter) will be recorded.

6.1.4.1 Pre-Procedure

Subject preparation will occur in accordance with standard hospital policy for the care of interventional cardiology patients. Written informed consent will be obtained according to Section 13, post- procedure. Pre-procedural data will be collected after informed consent has been obtained.

6.1.4.2 Pre-Procedure Laboratory Assessments

The following laboratory assessments are to be performed (having been done as part of routine clinical care) prior to the baseline procedure.

Within 30 days prior to procedure:

- Complete Blood Cell Count (CBC)
- Creatinine, BUN
- Lipid profile (total cholesterol, LDL, HDL, triglycerides)

Within 24 hours pre-procedure:

- Electrocardiogram (ECG)
- Creatine kinase (CK) and creatine kinase muscle-brain isoenzyme (CK-MB) (For subjects with ACS, enzyme levels need to be within 8 hours of the procedure or have already been shown to be decreasing.)
- Troponin (T or I) where CK-MB is not available

  Note: If any of the baseline tests were not obtained prior to the PCI procedure they may be obtained (including baseline biomarkers) as soon as possible after enrollment.

6.1.4.3 Baseline Procedure

Diagnostic angiography and PCI will be performed in accordance with standard hospital routine. Procedural data will be collected only after informed consent has been obtained.

- Angiographic eligibility criteria

Once it has been determined that a patient meets the angiographic eligibility criteria and a 38 mm EluNIR stent has been implanted or an attempt was made to implant a 38 mm EluNIR stent (ie, stent has advanced beyond the guide catheter), the patient will be screened for general eligibility criteria.

6.1.4.4 Post-Procedure and Discharge

- Enrollment and study stent information

Subject information will include the following. Refer to Section 19.1 for definitions.

- Demographics (e.g., age, gender, height, weight)

- Risk factors (dyslipidemia, hypertension, family history of premature coronary disease, tobacco use, and diabetes)
- Cardiac history (previous MI, intervention history, and past angina status according to CCS and Braunwald classifications)
- Baseline (pre-procedure) angina status
- DAPT medications (pre-procedure)
- Concomitant cardiac medication by category
- Assurance that informed consent has been obtained correctly

Collection of pre-procedure laboratory assessments and ECG data (if were done; if missing can be obtained as soon as possible after enrollment).

Angiographic data:

- Target lesion location
- Non-target vessel treatment, if applicable
- Anticoagulation administration
- Procedural complications that occur after the long EluNIR stent was advanced beyond the guiding catheter.
- Per-protocol DAPT medications
- Adverse events that occur after the long EluNIR stent was advanced beyond the guiding catheter.

Subjects who undergo PCI with a long EluNIR stent but do not consent to be enrolled in the study will not be included in the study and their data will not be collected.

- Post-PCI 12 lead ECG
- Post-PCI angina status
- Post-PCI adverse events with related laboratory tests results and details of any subsequent repeat coronary angiography and results of such, if applicable
- Post-PCI per-protocol DAPT medications
- Post-PCI concomitant cardiac medication by category
- CK and CK-MB or Troponin (I or T). Two post-PCI measures are recommended, but if early discharge is contemplated, at least one post procedure measurement 6-10 hours post-PCI is mandatory with the results known before discharge. The need for further cardiac biomarker measurement will be determined by the biomarker level, as detailed below in Table 2:

Table 2: Patient Status as Indicated by Biomarker Levels

Biomarker Level	Patient Status	Action
<ULN CK-MB or Troponin* <7X ULN and	Clinically stable**	The patient may be discharged without additional levels.
1-3x ULN CK-MB or Troponin* 7-20X ULN and	Clinically stable**	The patient may be discharged but a second level is required at 12-18 hours prior to discharge. If the patient had an elevated troponin level immediately prior to study PCI and post-PCI level is lower than the immediate pre-PCI level, a second level is not required.
≥3x ULN CK-MB or Troponin* >20 X ULN	Not clinically stable	The patient may not be discharged until serial CK-MB or Troponin levels are decreasing and the patient is stable. If the patient had an elevated troponin level immediately prior to study PCI and post-PCI level is lower than the immediate pre-PCI level, a second level is not required.

*using conventional or hs-troponin assays with 99th percentile cutoff of 14 ng/L to 70 ng/L

** clinically stable- no chest pain, no ECG changes, no hypotension and no overt bleeding

6.1.4.5 30 Days (± 7 days)

- Angina status
- Adverse events with related laboratory tests results, ECGs, details of any subsequent myocardial infarction, hospitalization, or repeat coronary angiography and results of such, if applicable
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)
- Compliance to protocol-required DAPT medications
- Use and changes in chronic antiplatelet medication regimen. Data are collected for the duration of the trial
- Concomitant cardiac medication by category

6.1.4.6 6 months (± 30 Days) & 1 year (±30 Days) Follow-up (by phone)

- Angina status
- Adverse events with related laboratory tests results, ECGs, details of any subsequent myocardial infarction, hospitalization, or repeat coronary angiography and results of such, if applicable
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)
- Compliance to protocol-required DAPT medications
- Use and changes in chronic antiplatelet medications. Data are collected for the duration of the trial
- Concomitant cardiac medication by category

6.1.4.7 Additional (Unscheduled) Follow-up Visits

Additional subject visits may occur as clinically warranted. The following information will be collected at such visits:

- Data regarding adverse events with related laboratory tests results, ECG, details of any subsequent myocardial infarction, hospitalization, or repeat coronary angiography and results of such, if applicable. For suspected ischemic events, CK and CK-MB or Troponin (I or T) must be measured and 12 lead ECG obtained.
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG)
- Use and changes in chronic antiplatelet medication regimen. Data are collected for the duration of the trial
- Concomitant cardiac medication by category

6.1.5 Equipment to Be Used for Assessing the Clinical Variables and Arrangements for Monitoring Maintenance and Calibration

The Angiographic Core Lab will perform a qualitative coronary analysis (Pie Medical CAAS Workstation v. 5.11.2 Software) assessment of all target lesions pre-procedure, post-procedure. In-segment and in-stent target lesion minimal lumen diameter (MLD) and diameter stenosis (DS) will be determined by the angiographic core lab. Morphological characteristics (calcification, tortuosity, bifurcation, presence of thrombus), TIMI flow and blush will be assessed at baseline. Complications (no reflow, slow reflow, abrupt closure, new or worsening thrombus, distal embolization, perforation and dissection by NHLBI criteria) will be assessed intra-procedurally and at the end of the baseline procedure.

The Angiographic Core Lab will carry out intra- and inter-observer variability testing in accordance with the Standard Operating Procedures (SOP) of the Cardiovascular Research Foundation.

6.1.6 Procedures for the Replacement of Subjects

Discontinued subjects will not be replaced. Patients who do not consent to be enrolled in the study will not count towards the sample size of approximately 50 subjects and will not be included in the FAS.

Patients who are consented but do not meet eligibility and are not in the FAS will be in the Safety Analysis Set which will also include all FAS patients. Safety Analysis Set patients will be followed until resolution of any adverse events related to study procedures.

6.2 Study Device

6.2.1 Description of the Exposure to the Study Device

All subjects will have a single treatment with the (38 mm) EluNIR study stent which is approved and marketed in Israel.

6.2.2 List of Any Other Medical Devices or Medication to Be Used During the Clinical Investigation

The stent implantation will be part of a standard cardiac intervention which includes accessory medical devices such as arterial sheaths, guidewires, guiding catheters, inflation devices, and other accessories. Standard medications such as heparin, bivalirudin, contrast media, nitroglycerin, and relaxants are used. After the procedure, the subjects will receive DAPT for a minimum of 6 months, 12 months in ACS patients (see Section 6.4.8.3) as well as other medications as prescribed to control other co-morbidities such as hypertension, hypercholesterolemia, and heart failure. All of these accessory medical devices and medications are approved to be on the market.

6.2.3 Number of Study Devices to Be Used

Each subject will receive one study stent.

6.3 Subjects

The trial population will consist of approximately 50 male and female subjects undergoing PCI for angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present), non ST elevation MI (NSTEMI), or recent ST elevation MI (STEMI >24 hours prior to enrollment and stable).

Complex lesions are allowed (enrolled after successful pre-dilatation or aspiration thrombectomy). There is no limit to the number of lesions per vessel or individual lesion length.

Subjects must sign an EC approved Subject Informed Consent Form, and meet all the general and angiographic eligibility criteria before being enrolled to the trial.

6.3.1 Inclusion Criteria for Subject Selection

All inclusion criteria must be present for the patient to be eligible for enrollment.

Note: the I/E criteria refer to the patient's baseline condition prior to PCI.

General Inclusion Criteria

1. Age ≥ 18 years.
2. Patient with an indication for PCI including angina (stable or unstable), silent ischemia (in absence of symptoms a visually estimated target lesion diameter stenosis of ≥70%, a positive non-invasive stress test, or FFR ≤0.80 must be present), NSTEMI, or recent STEMI. For STEMI the time of presentation to the first treating hospital, whether a transfer facility or the study hospital, must be >24 hours prior to enrollment and enzyme levels (CK-MB or Troponin) demonstrating that either or both enzyme levels have peaked.
3. An attempt (whether successful or not) was made to implant a 38 mm EluNIR stent (Stent was advanced beyond the guiding catheter).

4. Non-target vessel PCI are allowed prior to enrollment depending on the time interval as follows:

   a. During Baseline Procedure:

   PCI of non-target vessels performed during the baseline procedure itself immediately prior to enrollment if successful and uncomplicated defined as: <50% visually estimated residual diameter stenosis, TIMI Grade 3 flow, no dissection ≥ NHLBI type C, no perforation, no persistent ST segment changes, no prolonged chest pain, no TIMI major or BARC type 3 bleeding.

   b. Less than 24 hours prior to Baseline Procedure:

   Not allowed (see exclusion criteria #2).

   c. 24 hours-30 days prior to Baseline Procedure:

   i. PCI of non-target vessels 24 hours to 30 days prior to enrollment if successful and uncomplicated as defined above.

   ii. In addition, in cases where non-target lesion PCI has occurred 24-72 hours prior to the baseline procedure, at least 2 sets of cardiac biomarkers must be drawn at least 6 and 12 hours after the non-target vessel PCI.

   iii. If cardiac biomarkers are initially elevated above the local laboratory upper limit of normal, serial measurements must demonstrate that the biomarkers are falling.

   d. Over 30 days prior to Baseline Procedure:

   PCI of non-target vessels performed greater than 30 days prior to procedure whether or not successful and uncomplicated.

5. Patient or legal guardian is willing and able to provide informed written consent and comply with follow-up visits and testing schedule.

Angiographic inclusion criteria (visual estimate)

6. Target lesion(s) must be located in a native coronary artery or bypass graft conduit with visually estimated diameter of ≥2.75 mm to ≤4.25 mm.
7. Complex lesions are allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy are allowed), presence of thrombus, CTO, bifurcation lesions, ostial RCA lesions, tortuous lesions, bare metal stent restenotic lesions, protected left main lesions, and saphenous vein graft lesions.
8. Overlapping stents are allowed as long as the first stent implanted is the EluNIR 38 mm long stent

6.3.2 Exclusion Criteria for Subject Selection

All exclusion criteria must be absent for the patient to be eligible for enrollment.

General Exclusion Criteria

1. STEMI within 24 hours of initial time of presentation to the first treating hospital, whether at a transfer facility or the study hospital or patients in whom enzyme levels (either CK-MB or Troponin) have not peaked.

2. PCI within the 24 hours preceding the baseline procedure.
3. Non-target lesion PCI in the target vessel within 12 months of the baseline procedure.
4. History of stent thrombosis.
5. Cardiogenic shock (defined as persistent hypotension (systolic blood pressure <90 mm/Hg for more than 30 minutes) or requiring pressors or hemodynamic support, including IABP.
6. Subject is intubated.
7. Known LVEF <30%.
8. Relative or absolute contraindication to DAPT for 6 months in non-ACS patients and 12 months in ACS patients (including planned surgeries that cannot be delayed, or on or indicated for chronic oral anticoagulant treatment).
9. eGFR<30 ml/min/1.72 m^2
10. Hemoglobin <10 g/dL.
11. Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3.
12. White blood cell (WBC) count <3,000 cells/mm^3.
13. Clinically significant liver disease.
14. Active peptic ulcer or active bleeding from any site.
15. Bleeding from any site within the prior 8 weeks requiring active medical or surgical attention.
16. If femoral access is planned, significant peripheral arterial disease which precludes safe insertion of a 6F sheath.
17. History of bleeding diathesis or coagulopathy or will refuse blood transfusions.
18. Cerebrovascular accident or transient ischemic attack within the past 6 months, or any permanent neurologic defect attributed to CVA.
19. Known allergy to the study stent components cobalt, nickel, chromium, molybdenum, Carbosil®, PBMA, or limus drugs (ridaforolimus, zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative or similar compounds).
20. Known allergy to protocol-required concomitant medications such as aspirin, or DAPT (clopidogrel, prasugrel, ticagrelor), or heparin and bivalirudin, or iodinated contrast that cannot be adequately pre-medicated.
21. Any co-morbid condition that may cause non-compliance with the protocol (e.g. dementia, substance abuse, etc.) or reduced life expectancy to <24 months (e.g. cancer, severe heart failure, severe lung disease).

22. Patient is participating in or plans to participate in any other investigational drug or device clinical trial that has not reached its primary endpoint.
23. Women who are pregnant or breastfeeding.
24. Women who intend to procreate within 12 months after the baseline procedure (women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the baseline procedure).
25. Patient has received an organ transplant or is on a waiting list for an organ transplant.
26. Patient is receiving or scheduled to receive chemotherapy within 30 days before or any time after the baseline procedure.
27. Patient is receiving oral or intravenous immunosuppressive therapy or has known life-limiting immunosuppressive or autoimmune disease (e.g., HIV). Corticosteroids are allowed.

Angiographic Exclusion Criteria (visual estimate)

28. Unprotected left main lesions ≥30%, or planned left main intervention.
29. Bifurcation lesions with planned dual stent implantation.
30. Stenting of lesions due to DES restenosis.
31. Occlusive thrombus and/or a thrombus requiring thrombectomy in a target vessel
32. Another lesion in a target or non-target vessel (including all side branches) is present that requires or has a high probability of requiring PCI within 12 months after the baseline procedure.

6.3.3 Criteria and Procedures for Subject Withdrawal or Discontinuation

6.3.3.1 When and How to Withdraw Subjects

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

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

The reason for subject discontinuation must be documented on the CRF and source documents. The Primary Investigators must also report all subject discontinuations to their EC as defined by their institution's procedure.

6.3.3.2 Data to Be Collected from Withdrawn Subjects

All data from evaluations and treatments performed prior to the withdrawal should be documented on the CRFs. Source documents and angiograms that pre-date the withdrawal should be submitted

as required by the clinical investigation plan. No data that post-dates the withdrawal will be collected.

6.3.3.3 Follow-up for Withdrawn Subjects

Once a subject has withdrawn from the trial, no further follow-up contact will be performed. However, vital status will be obtained from public records.

6.3.4 Point of Enrollment

Given the relatively low incidence of PCI to long lesion (8.4% in the ADAPT-DES trial), and the fact that the EluNIR 38 mm stent is approved and marketed in Israel, patients will be consented after PCI. Once a patient has met all general and angiographic eligibility criteria, a 38 mm long EluNIR stent been passed beyond the guiding catheter, and the patient has signed an informed consent (post-procedure), the patient will be enrolled into the trial. If the study stent is not advanced into the guiding catheter, the subject will not be consented and not be enrolled.

In order to minimize selection bias, all eligible patients (meeting I/E criteria and in whom a 38 mm long EluNIR stent was advanced beyond the guiding catheter) will be approached for participation in the study, regardless of final procedure outcome.

The sites will maintain a screening log of all 38 mm EluNIR stents advanced beyond the guiding catheter and document eligibility and patient consent versus refusal to participate in the study.

The screening and enrollment process is displayed in Figure 1.

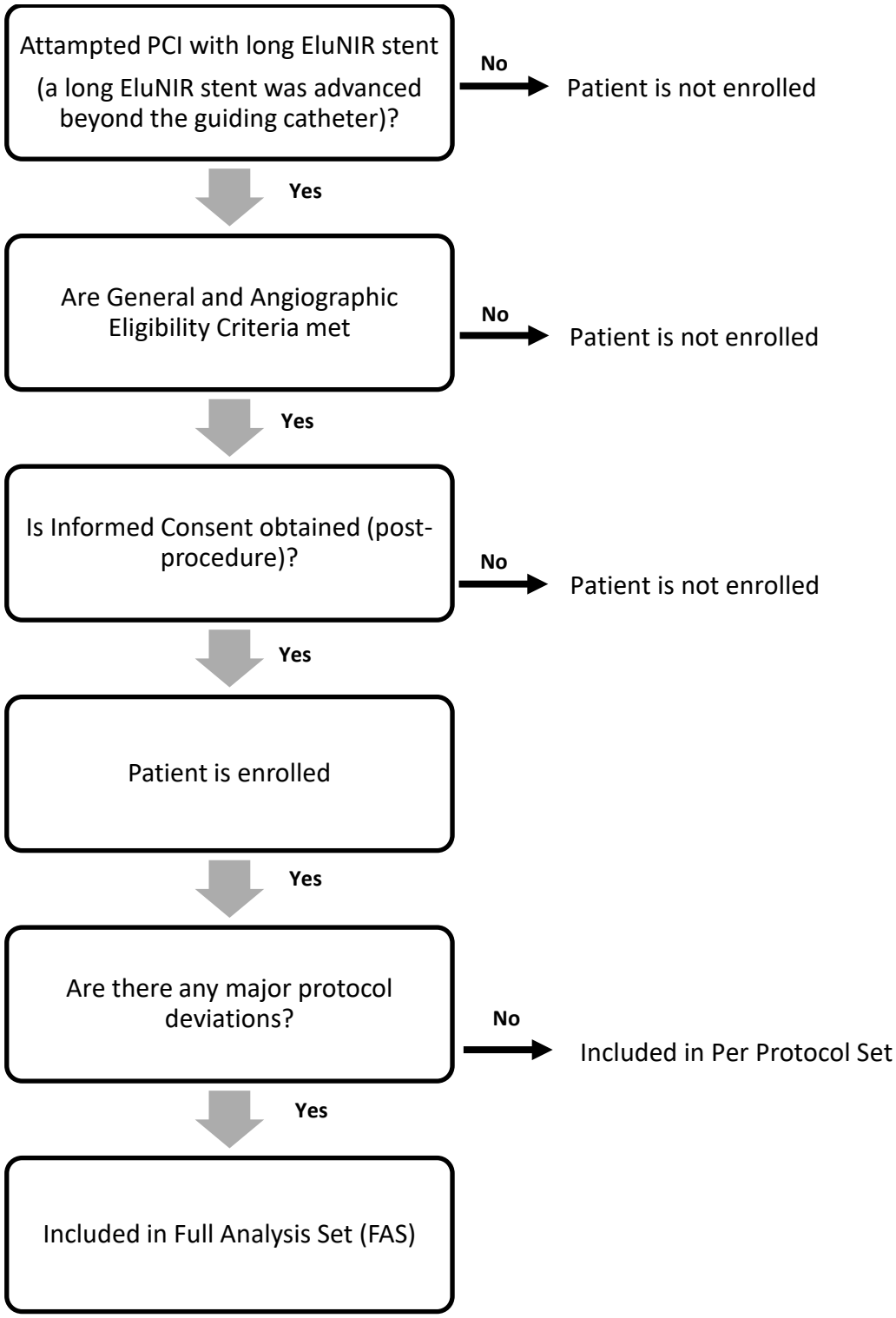

Figure 1: Screening and Enrollment Flow Chart

6.3.5 Total Expected Duration of the Clinical Investigation

The clinical investigation will last from Q3 2018 until approximately Q4 2019.

6.3.6 Expected Duration of Each Subject's Participation

Each subject will remain in the clinical investigation for approximately 1 year from the time of the study stent implantation until the last follow-up telephone contact.

The subjects will not be provided any follow-up contact or medical care related to the trial after the clinical investigation has been completed.

6.3.7 Number of Subjects Required to Be Included in the Clinical Investigation

Approximately 50 subjects will be enrolled in this study. This sample size (n=50) provides 80% power to observe at least one device-related AE if occurring with an incidence of 3.2%. (see statistical considerations section for additional details).

6.3.8 Estimated Time Needed to Complete Study Enrollment

The enrollment period is expected to last one year.

6.4 Procedures

6.4.1 Baseline Angiography

Baseline angiography of the target vessel will be completed as per the Angiographic Core Laboratory Protocol contained in the Study Binder. Angiography of non-target vessels (if required) may be performed per site standard.

Assessment of angiographic eligibility is based on a visual assessment of the immediate pre-procedure angiogram obtained by the Investigator. Use of a 6 French or larger guide catheter is recommended for accurate QCA measurements. Following intra-coronary injection of nitroglycerin (50-200 mcg IC nitroglycerin or per standard hospital practice), baseline angiography of the involved vessel will be performed for at least two orthogonal views showing the target lesion free of foreshortening or vessel overlap according to the Angiographic Core Laboratory Guidelines. Angiographic images of the target lesion must be sent to the Angiographic Core Laboratory per specified shipping method.

6.4.2 Non-Target Vessel PCI and Non-Target Lesion PCI in Target Vessel

- All non-target vessel PCI must be treated prior to the screening for eligibility.
- Non-target lesion PCI in the target vessel is allowed but must have occurred ≥12 months prior to the baseline procedure.

The following are the criteria for non-target vessel PCI (as summarized in Table 3):
During Baseline Procedure: The non-target vessel PCI must be successful and uncomplicated before screening of the subject for eligability. Successful and uncomplicated is defined as <50% visually estimated residual diameter stenosis, TIMI Grade 3 flow, no dissection ≥ NHLBI type C,

no perforation, no persistent ST segment changes, no prolonged chest pain, no TIMI major or BARC type 3 bleeding.

Within 24 hours prior to Baseline Procedure: PCI of non-target vessels are NOT allowed within the 24 hours immediately preceding the baseline procedure and enrollment.

24 hours to 72 hours prior to Baseline Procedure: Non-target lesion PCI can be performed 24 to 72 hours prior to the baseline procedure. In this case, at least 2 sets of cardiac biomarkers must have been drawn at least 6 and 12 hours after the non-target vessel PCI, according to the local standards. If the biomarkers are initially elevated above the local laboratory upper limit of normal, the serial measurements must demonstrate that the biomarkers are falling.

72 hours to 30 days prior to Baseline Procedure: PCI of non-target vessels can be performed 72 hours to 30 days prior to baseline procedure if PCI was successful and uncomplicated.

More than 30 days prior to Baseline Procedure: PCI of non-target vessels may be performed more than 30 days prior to baseline procedure whether successful and uncomplicated or not.

Table 3: Summary of Timing of Non-Target Vessel According to PCI Rules

Non-Target Vessel PCI Decision Matrix	During Baseline Procedure	Time prior to Baseline Procedure			
		<24 hours	24 hours to 72 hours	72 hours to 30 days	>30 days
Is PCI of a non-target vessel allowed?	Yes	No	Yes	Yes	Yes
Is procedural success required?	Yes	N/A	Yes	Yes	No
Must the procedure be uncomplicated?	Yes	N/A	Yes	Yes	No
Are serial biomarkers required?	No	N/A	Biomarkers must be negative post procedure or falling (at least 2 sets of measurements)	No	No

N/A = not applicable

6.4.3 Staged Procedures

6.4.4 Planned staged procedures are not allowed. All non-target lesions should be treated prior to target lesion treatment; as specified in section 6.4.2 Pre-Dilation of Target Lesion(s)

Pre-dilation is recommended but not required. Pre-dilation can be performed per study stent labeling and per local standards. An angioplasty balloon, cutting balloon, angiosculpt scoring balloon, or atherectomy can be utilized for pre-dilation. The pre-dilation balloon should be shorter than the planned stent(s) length to limit pre-dilation injury within the area to be stented. It is recommended that a pre-dilation catheter that is 0.5 mm smaller in diameter than the reference vessel is used.

6.4.5 Study Stent Use

Prior to use, the study stent will be inspected and prepared according to the applicable Instructions for Use.

- There is no limit to the number of lesions per vessel or individual lesion length.
- If more than one lesion in the same epicardial vessel is treated, it is recommended that stenting be initiated distally and progress proximally.
- Overlapping stents are allowed as long as the first stent implanted is the EluNIR 38 mm long stent. It is recommended that the distal stent should be deployed first, followed by deployment of the proximal stent, to reduce the risk of dislodging the proximal stent.
- Stent sizing should follow a stent: artery ratio of 1.1:1 per operator's visual estimate.
- Brachytherapy must NOT be performed in conjunction with the baseline procedure.
- Post-dilation is strongly recommended, and when performed should only be performed with balloon lengths that fit within the boundaries of the stent. Do not exceed the rated burst pressure as indicated in the product labeling of the study stents. The vessel size and lesion length should be assessed after post-dilation. An optimal stent result is final diameter stenosis of <20% by operator's visual estimate.

6.4.6 Treatment Failures and Device Malfunctions

In case of failure to deliver the study stent, typical measures should be undertaken to ensure the lesion has been adequately prepared, such as use of appropriately sized pre-dilatation balloons, cutting or scoring balloons, and/or rotational atherectomy as appropriate. Guide catheter support should be optimized using standardized techniques, including use of buddy wires and/or guide extension devices as appropriate. If the study stent can still not be delivered, any commercially available stent may be used to successfully and safely complete the procedure.

All failures and EluNIR malfunctions will be documented on the appropriate CRF if the patient has been enrolled to the study. The EluNIR should be returned to Medinol for analysis and be reported in the clinical results. Instructions for returning the EluNIR are included in the trial's operations manual. Treatment failures or device malfunctions should be reported in the CRF within 24 hours, per the instructions of EDC completion.

6.4.7 Bail-out Stenting Procedures

Bailout stenting may be performed at the operator's discretion. If a bailout stent is required, EluNIR stent of an appropriate diameter and length must be used. If EluNIR of appropriate length and diameter is not available, an approved coronary stent should be used, preferably a second generation DES.

6.4.8 Concomitant Medications

6.4.8.1 Pre-Procedure (Loading) Anti-Platelet Medication

Loading doses of anti-platelet medications should be administered pre-procedure in all patients as shown in Table 4 and according to the local standards.

Table 4: Recommended Pre-Procedure Anti-Platelet Medication Regimen

Agent	Instructions
Clopidogrel	A loading dose of clopidogrel 600mg must be administered between 0 to 24 hours prior to PCI or immediately post PCI (administration prior to PCI is preferred in all patients). For subjects who are already on chronic clopidogrel therapy of 75 mg (≥5 days), a loading dose of 300 mg is required in all patients between 0 to 24 hours prior to PCI or immediately post PCI (administration prior to PCI is preferred in all patients).
OR Prasugrel	At sites in countries where prasugrel is approved and is commercially available, a loading dose of prasugrel 60 mg can be used in place of clopidogrel at the investigator's discretion. For subjects already on chronic prasugrel therapy of 10mg a day (5mg if >75 years old or <60kg weight) for ≥5 days a loading dose of prasugrel 60mg is recommended at the investigator's discretion.
OR Ticagrelor	At sites in countries where ticagrelor is approved and commercially available, a loading dose of ticagrelor 180 mg can be used in place of clopidogrel at the investigator's discretion. For subjects already on chronic ticagrelor therapy of 90mg twice daily for ≥5 days a loading dose of ticagrelor 180mg is recommended at the investigator's discretion.
Aspirin	All subjects already taking daily chronic aspirin therapy will receive 75-325mg or dose per standard hospital practice before the procedure. Subjects not already taking daily chronic aspirin therapy will receive 300 to 325mg (or dose per standard hospital practice) at least two hours and preferably 24 hours before the procedure.

6.4.8.2 Anticoagulation during Baseline Procedure

PCI should be performed with adequate anticoagulation. Unfractionated heparin (UFH), low-molecular weight heparin (LMWH) or bivalirudin may be used with additional glycoprotein inhibitor (GPI) according to local standards.

6.4.8.3 Post-Procedure Anti-Platelet Medication

Dual anti-platelet therapy should be instituted post procedure in all patients as shown in Table 5.

All subjects are required to have clopidogrel/prasugrel/ticagrelor administration for a minimum of 6 months (12 months in ACS patients) as well as aspirin administration indefinitely unless an intervening medical necessity occurs such as severe bleeding.

Table 5: Post-Procedure Anti-Platelet Medication Regimen

Agent	Instructions
Clopidogrel	All subjects who receive a study stent will be treated for a minimum of six months of clopidogrel (75 mg/day) and up to 12 months following stent implantation, per the AHA/ACCF/SCAI joint guidelines for percutaneous coronary intervention.(1)
OR Prasugrel	At sites in countries where prasugrel is approved and is commercially available, prasugrel 10 mg/day can be used in place of clopidogrel at the investigator's discretion. In subjects weighing less than 60 kg or who are over 75 years old, prasugrel should be given at a dose of 5 mg/day.
OR Ticagrelor	At sites in countries where ticagrelor is approved and is commercially available, ticagrelor 90 mg bid can be used in place of clopidogrel at the investigator's discretion.
Aspirin	Subjects with no aspirin resistance, allergy, or bleeding risk should continue on aspirin (minimum of 75 mg/day and up to 162 mg/day or dose per standard hospital practice) indefinitely, in accordance with the AHA/ACC/SCAI PCI recommendations. Low-dose aspirin (<100 mg/day) is preferred in all patients. Higher doses should not be used with ticagrelor.

6.4.9 Activities Performed by Sponsor Representatives

No activities other than monitoring will be performed by the Sponsor representatives.

6.4.10 Known or Foreseeable Factors That May Compromise the Outcome

Factors that may compromise the outcome are lack of enrollment and poor data collection.

6.5 Monitoring Plan

6.5.1 Monitoring

Sponsor and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. The trial monitor will visit each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the clinical investigation plan. The trial monitor may inspect all documents and required records that are maintained by the Investigator/Site, including medical records (office, clinic, or hospital) for the subjects in this trial. Source documentation must be available to substantiate proper informed consent procedures, adherence to clinical investigation plan procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information. A monitoring visit sign-in log will be maintained at the site. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator/Site will provide the trial monitor with a suitable working environment for review of study-related documents.

6.5.2 Identification of Data Recorded on CRF and Considered Source Data

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, device accountability records, correspondence with the EC as well as trial monitors and sponsor, adverse event reports, and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject's medical records which documents and corroborates data entered in the case report forms. As a minimum the subject record should contain:

- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Documentation of subject's consent and subject ID number in the trial
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, ECGs, etc.
- Record of clinical investigation plan required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial

6.5.3 Direct Access to Source Data/Documents

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

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

6.5.4 Training

6.5.4.1 Site Training

All Investigators and trial personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions including training utilizing electronic media. Training of Investigators and trial personnel will include, but is not limited to, the investigational plan, study device, case report form completion and trial personnel responsibilities. All Investigators and trial personnel who are trained must sign a training log (or an equivalent) upon completion of the training. Investigator and trial personnel must not perform any study-related procedures prior to being trained. All Investigators must be trained to the clinical investigation plan and trial procedures prior to enrolling subjects.

6.5.4.2 Training of Sponsor's Monitors

The Sponsor's monitors or designee will be trained to the clinical investigational plan, case report forms, and study device usage. The Sponsor or designee is responsible for the training. Training will be conducted in accordance with the Sponsor's and/or designee's standard procedures.

6.5.5 Quality Assurance Assessments

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

6.5.6 Regulatory Agency Inspection

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

7 STATISTICAL CONSIDERATIONS

7.1 Statistical Design

This is a prospective, multi-center, single arm, open label, clinical trial that is descriptive in nature. The Trial will enroll approximately 50 subjects with a wide spectrum of PCI indications (stable angina as well as ACS, including subacute STEMI (>24 hours since first hospital presentation) as well as complexity. This sample size (n=50) provides 80% power to observe at least one device related AE if occurring with an incidence of 3.2%.

Among 50 patients, we will have > 80% probability to detect at least one event from any events with a rate above 3.2% . Mathematically, we compute the probability (assuming Binomially distributed events) as

$$p(\text{Event} > 0) = 1 - p(\text{Event} = 0)$$
$$0.80 = 1 - (1 - p)^{50}$$
$$p = 1 - \ (1 - 0.80)^{1/50}$$

7.2 Analysis and Reporting of Results

7.2.1 Methods

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

Descriptive statistics will be used to generate an overall summary of the study endpoints, baseline and procedural variables, and clinical outcomes. Continuous variables will be presented as means, standard deviations, medians, first and third quartiles, minimums, maximums, and 95% confidence intervals for the means. For categorical variables, the number within each category and the percentage out of the total number of available observations will be summarized.

7.2.2 Analysis of Primary Endpoint

The primary endpoint of device success as determined by the Angiographic Core Lab (ACL) with no 30 day MACE will be summarized descriptively with patient counts, percentages, and 95% exact Binomial confidence intervals. This analysis will be performed using the Full Analysis Set (FAS) as the primary analysis set; however, an analysis in the per-protocol (PP) population will also be performed.

The following additional definitions will be used to assess peri-procedural MIs for the purpose of sensitivity analyses for the primary 30 day MACE endpoint:

- The 3rd Universal Definition of MI definition
- A modification of the SCAI definition of periprocedural MI that utilizes a threshold CK-MB of ≥5x ULN (rather than ≥10x) in subjects with a normal baseline CK-MB without a requirement for associated clinical signs or symptoms
- A modification of the SCAI definition of periprocedural MI that utilizes a threshold CK-MB of ≥3x (rather than ≥10x) in subjects with a normal baseline CK-MB without a requirement for associated clinical signs or symptoms

7.2.3 Analysis of Secondary Endpoints

Analysis of the secondary endpoints will be performed on the FAS population. Data for all categorical endpoints will be summarized with patient counts, percentages, and exact 95% confidence intervals. Data for all continuous endpoints will be summarized with descriptive statistics (means, medians, standard deviations, minimums, maximums, and 95% confidence intervals for the means).

7.2.4 Poolability of Data

No adjustment for multiple centers is necessary, as this study is descriptive in nature.

7.2.5 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons/multiplicity are necessary, as this study is descriptive in nature.

There are no planned interim analyses prior to the primary endpoint.

7.3 Criteria for Termination of the Clinical Investigation

There are no stopping rules for the trial. The EluNIR Program (BIONICS and NIREUS Trials) DSMB will review data from this study.

7.4 Procedures for Reporting Any Deviation(s) from the Original Statistical Plan

Details of the statistical analysis will be outlined in a trial-specific Statistical Analysis Plan (SAP). Any changes to planned analyses will be described and justified in the SAP and noted in the final trial report.

7.5 Specification of Subgroups for Analysis

No subgroups analysis will be performed for the primary endpoint of Device Success.

7.6 Procedures That Take into Account All the Data

The analysis of the primary endpoint will be performed using the following datasets, as appropriate:

- **Full Analysis Set (FAS):** All subjects who have been enrolled into the trial, regardless of whether they received the study stent or not. Subjects are included in the FAS once the stent has been advanced beyond the guide catheter. If the study stent is not advanced beyond the guiding catheter, the patient will be de-registered and will not be considered part of the full analysis set.
- **Per-Protocol (PP) Analysis Set:** All subjects in the Full Analysis Set (FAS) with no major protocol deviations will be included in the Per-Protocol Analysis Set. Major protocol deviations include, but are not limited to, enrollment of a subject:
  - ✓ whose informed consent was not properly obtained
  - ✓ who did not meet all of the inclusion or exclusion criteria
  - ✓ who did not receive at least 6 months of DAPT post baseline procedure
- **Safety Analysis Set:** The safety analysis set will include all subjects, including de-registered subjects, who signed an informed consent and who had any trial-related activities.

7.7 Treatment of Missing, Unused, or Spurious Data, Including Drop-Outs and Withdrawals

Only available data will be analyzed. No imputations will be performed for missing data.

7.8 Minimum and Maximum Number of Subjects to Be Included for Each Center

Sites that anticipate enrolling a minimum of 5 subjects in the trial will be recruited. The maximum number of subjects to be included for each center will be 20.

8 DATA MANAGEMENT

8.1 Procedures Used for Data Review, Database Cleaning, and Issuing and Resolving Data Queries

The Cardiovascular Research Foundation will provide the electronic data capture (EDC) for the trial. The sites are responsible for completing the clinical electronic CRF (eCRF) from the EDC

clinical database. The database data cleaning routines are performed during data entry through automatic edit checks that occur during data entry by the sites into the EDC system. The auto-queries are generated by the EDC system and are resolved by the site. Those auto-queries will be cleared when the revised data entry meets the edit check criteria or the monitor accepts the revised entry. The manual queries are created by the site monitors. The Data Manager from the Cardiovascular Research Foundation can create manual queries on data as well for the sites to review. The EDC system flags the records with data queries which are resolved by the site, and the manual queries are cleared by the originating personnel. Tracking of data cleaning query status is facilitated by listings from the EDC system. Data listings needed for data review are also created within the EDC system. Please see the separate Data Management Plan for specific details.

8.2 Procedures for Verification, Validation, and Securing of Electronic Clinical Data Systems

The trial website will be programmed and maintained by the Cardiovascular Research Foundation which will meet patient confidentiality requirements consistent with applicable regulations such as the US HIPAA (Health Insurance Portability and Accountability Act). The trial website will enforce restricted access control mechanisms under the management of the Cardiovascular Research Foundation and will incorporate encrypted point-to-point data transfer via secure HTTP protocols. Trial Investigators/sites will enter data online; data will be stored at a secure and confidential location, and will be downloaded by The Cardiovascular Research Foundation for review and analyses on a regular basis. Further details of verification, validation, and securing of electronic clinical data systems can be found in the trial specific Data Management Plan.

8.3 Procedures for Data Retention and Specified Retention Period

All core laboratories and clinical sites will maintain study records pertaining to this trial for 15 years following trial completion, or as otherwise instructed by the Sponsor, or per local requirements whichever is longer.

ICH guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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

The Investigator will be notified by the Sponsor on discontinuation of the trial, if relevant. The Investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any trial records.

8.4 Other Aspects of Clinical Quality Assurance

8.4.1 Clinical Events Committee

The Clinical Events Committee (CEC) will be comprised of cardiologists who are not participants in the trial and who have no conflict of interest with the trial or the trial sponsor. All members of the CEC will be blinded to the primary results of the trial.

The CEC will be responsible for the adjudication of the clinical trial endpoint events. At the onset of the trial, the CEC will establish explicit rules outlining the process for adjudication and the algorithms followed in order to classify a clinical endpoint event. The CEC will also review and rule on all deaths that occur throughout the trial. In addition, the CEC will review and adjudicate device non-success. Definitions are provided in Section 19.1.

Once the specific criteria for clinical endpoints are established by the CEC, Cardiovascular Research Foundation will be responsible for preparing all clinical endpoint event dossiers and for the conduct of the CEC meetings.

8.4.2 Selection of Clinical Sites and Investigators

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

8.4.3 Clinical Investigational Plan and Informed Consent Approval at Investigative Sites

Ethics Committee (EC) approval for the clinical investigation plan (CIP), informed consent form and other trial related documents should be obtained by the Primary Investigator at each investigational site prior to the start of the trial. The approval letter must be signed by the EC chairperson or authorized representative prior to the start of this trial and a copy must be provided to the Sponsor. In addition, the Investigator or designee will provide the Sponsor with all required documentation necessary for initial and ongoing trial approval at their site.

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

8.4.4 Source Documents

For the duration of the trial, the Investigator will maintain complete and accurate documentation including but not limited to medical records, trial progress records, laboratory reports, case report forms, signed informed consent forms, device accountability records, and correspondence with the EC and Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the trial.

Source documents are defined as original documents, data, and records. Regulations require that the Investigator maintain source documents in the subject's medical records, which confirm the data entered on the case report forms. All data provided to the Sponsor on the CRFs must be also part of the subject's medical record as noted in Section 6.5.2.

8.4.5 Case Report Form (CRF) Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the clinical investigation plan and CRF completion guidelines. The Sponsor or designee will provide clinical monitoring as specified in Section 6.5.1.

9 AMENDMENTS TO CIP

If the clinical investigational plan needs an amendment, the Sponsor is required to submit such amendment to the Regulatory Agencies and/or other regulating body in each participating country for approval. Approved clinical investigational plan amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. For administrative changes the Primary Investigator is responsible for notifying the EC of the clinical investigational plan amendment. For changes involving subject care or safety the Primary Investigator is responsible for obtaining EC approval of the clinical investigational plan amendment according to the instructions provided by the Sponsor with the clinical investigational plan amendment.

Acknowledgement/approval by the EC of the clinical investigational plan amendment must be documented in writing prior to implementation of the clinical investigation plan amendment. Copies of this documentation must also be provided to the Sponsor.

10 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

10.1 Statement Specifying That the Investigator Is Not Allowed to Deviate from the CIP

No investigative procedures other than those defined in this clinical investigational plan will be undertaken on the enrolled subjects without the written agreement of the EC and Sponsor.

It is the Investigator's responsibility to ensure that there are no deviations from the clinical investigational plan and full compliance with all established procedures of the EC is maintained. The Investigator will not deviate from the clinical investigational plan for any reason except in

cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject.

10.2 Procedures for Recording, Reporting, and Analyzing CIP Deviations

A deviation is an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the Clinical Investigation Plan. All deviations must be reported to the Sponsor. The occurrence of clinical investigational plan deviations will be monitored by the Sponsor or designee. It is the Investigator's responsibility to inform their EC of clinical investigational plan deviations in accordance with their specific EC reporting policies and procedures.

In the event that an investigative site does not comply with the Investigator Agreement or clinical investigational plan, the Sponsor will notify the Investigator of the site's non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor's standard procedures.

10.3 Notification Requirements and Time Frames

Major protocol deviations shall be notified to the trial Sponsor and Ethics Committee. Sponsor nominated personnel will also observe and record any protocol deviations during routine monitoring visits and follow up accordingly.

10.4 Corrective and Preventative Actions and Principal Investigator Disqualification Criteria

Protocol deviations and site/PI non-compliance will be closely monitored by the Sponsor and appointed study personnel. Identifying deviations and taking corrective actions at the earliest possible stage increases the potential for clinical trial success and reduces patient risk. The initiation of a corrective and preventative action (CAPA) to investigate and establish corrective actions may be required in some cases. The Sponsor reserves the right to close a clinical study site or replace a PI if non-compliance is observed

11 DEVICE ACCOUNTABILITY

11.1 Product Accountability

Off the shelf commercial devices will be used for this study. Device deficiencies and/or malfunctions will be reported to Medinol in accordance with local regulations.

12 STATEMENTS OF COMPLIANCE

The trial will be conducted in compliance with the clinical investigation plan, ISO 14155:2011 (Clinical investigation of medical devices for human subjects - good clinical practice), and the ethical principles of the Declaration of Helsinki as well as local regulations, and applicable regional regulatory requirements.

The clinical investigation shall not begin until the required approvals from the respective regulatory authority and ethics committee have been obtained. Any additional requirements imposed by the respective regulatory authority and/or ethics committee will also be followed, where specified.

All subjects must provide written informed consent in accordance with the site's EC, using an EC-approved informed consent form. The final eligibility for the trial will be confirmed based on the final pre-stenting angiographic qualification.

Trial-specific procedures must not be performed until a signed informed consent has been obtained. The Investigator/designee, who has been trained on the clinical investigation plan, will explain to the candidate subject the nature and scope of the trial, potential risks and benefits of participation, and answer questions post by the candidate subject. If the candidate subject agrees to participate, the informed consent form must be signed and personally dated by the candidate subject or legally authorized representative. The Investigator/designee must also sign the informed consent form prior to subject enrollment. Any additional persons required by the site's EC to sign the informed consent form must also comply.

All subjects are to be fully informed and trial conduct must be in accordance to the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

The trial Sponsor has taken out appropriate insurance for this clinical investigation.

13 INFORMED CONSENT PROCESS

13.1 General Process for Obtaining Informed Consent

Written informed consent will be obtained post- procedure. Pre-procedural data will be collected after informed consent has been obtained.

The informed consent will be in the prospective subject's native language and will contain non-technical language to describe the study procedures. The informed consent should also include a clause that ensures important new information will be provided to the subject throughout the clinical investigation.

After a review of the prospective subject's medical records, the investigator or authorized designee who has been trained on the CIP, will approach the prospective subject to explain the purpose and scope of the clinical trial, prospective risks, and benefits of participation. The prospective subject must be given the opportunity to ask questions about the trial and must be given sufficient time to decide to participate in the trial or not. Additional information requested by the prospective subject should be provided. Any coercion or undue improper influence on the prospective subject is to be avoided.

If the prospective subject agrees to participate, the informed consent form must be signed and personally dated by the prospective subject. The investigator or an authorized member of the

research team who has witness the prospective subject's signature must also sign and date the informed consent, prior to enrollment of the prospective subject. A copy of the completed informed consent form must be provided to the subject. The subject's medical record should have a notation regarding the signing of the informed consent.

The subject is to be made aware that their participation in the trial is voluntary, their legal rights will not be waived, and that they may withdraw from the trial at any time, without giving specific reason for doing so. The subject must also be informed that withdrawal from the trial will not affect their future treatment.

The investigator is responsible for the achievement of written consent from the prospective subject before they are included in the trial. All subjects must provide informed consent in accordance with the local EC requirements, using an EC-approved informed consent form. Figure 1 outlines the screening process and illustrates the point where informed consent should be obtained. The final eligibility for the clinical trial will be confirmed based on the pre-intervention angiography.

13.2 Informed Consent Process in Circumstances Where the Subject Is Unable to Give It

It is anticipated that the subjects enrolled in this trial will not be requiring emergency treatments as part of the clinical investigation. Therefore there will be sufficient time to obtain written informed consent without emergency measures being taken.

It is possible that a prospective subject will be unable to provide written consent due to limitations in ability to read or write. In this case, informed consent shall be obtained through a supervised oral process of a prospective subject. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject and, whenever possible, the subject shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

14 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

All definitions for adverse events, adverse device effects, and device deficiencies are taken from EN ISO 14155:2011 (12). A summary of adverse events and adverse device effects is shown in Table 6.

14.1 Definition of AE and ADE

14.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events related to the investigational medical device or the comparator. It also includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the investigational medical device.

14.1.2 Adverse Device Effect (ADE)

An ADE is an adverse event (untoward medical occurrence) that is related to the Study Device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

14.2 Definition of Device Deficiencies

Device deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

14.3 Definition of SAE, SADE, and USADE

14.3.1 Serious Adverse Event (SAE)

An adverse event that:

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

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

For the purpose of this trial, all myocardial infarctions, unscheduled revascularizations, and stent thromboses are classified as SAEs.

14.3.2 Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

14.3.3 Anticipated Serious Adverse Device Effect (ASADE)

An SADE is an effect which by its nature, incidence, severity, or outcome has been previously identified in the risk analysis report or IB.

14.3.4 Unanticipated Serious Adverse Device Effect (USADE)

An SADE is an effect which, by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report, IB, or labeling.

Table 6: Categories of Adverse Events

Adverse Events	Non-device related	Device- or procedure-related	
Non-serious	Adverse Event (AE)[a]	Adverse Device Effect (ADE)	
Serious	Serious Adverse Event (SAE)[b]	Serious Adverse Device Effect (SADE)	
		Anticipated	**Unanticipated**
		Anticipated Serious Adverse Device Effect (ASADE)	Unanticipated Serious Adverse Device Effect (USADE)
a Includes all categories b Includes all categories that are serious			

Source: EN ISO 14155:2011, Annex F, Table F-1.

14.4 Time Period in Which the PI Shall Report All AE and Device Deficiencies to the Sponsor

Each complication meeting the definition for SAE or device deficiency will be reported upon discovery to the Sponsor and within 24 hours of the Investigator's knowledge of the event. The Investigator will further report the event or device deficiency to the EC according to the institution's EC reporting requirements. The subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

14.5 Details of Process for Reporting AE and Device Deficiencies

14.5.1 Reporting AE and Device Deficiencies

The Investigator will monitor the occurrence of adverse events or device deficiencies for each subject during the course of the trial. All adverse events (AEs) reported by the subject, observed by the Investigator, or documented in medical records will be recorded on the adverse event CRF, whether believed by the Investigator to be related or unrelated to the study stent. Starting with the trial enrollment, any new event/experience that was not present at screening, or worsening of an event presents at baseline, is considered an adverse event. All adverse events will be monitored until they are adequately resolved or stabilized.

Unchanged, chronic conditions are not adverse events and should not be recorded on the adverse event CRF. All unanticipated adverse device effects and cardiac related serious adverse events will be collected and monitored throughout the entire course of the trial. All SAEs and AEs will be collected and monitored through the 1 year follow-up.

14.5.2 Reporting USADE

If the Investigator determines that an adverse event meets the definition of an unanticipated adverse device effect, the Investigator must report the event to the Sponsor, preferably within 24 hours of the Investigators' knowledge of the effect. The Primary Investigator must report the effect to the reviewing EC according to the institution's EC reporting requirements. If the relationship of the unanticipated effect to the study device is unknown, the Investigator is also required to follow these reporting obligations.

The Sponsor will ensure that all reported USADEs and product experience handling reporting requirements are followed for the study device.

RELATIONSHIP TO STUDY Device / Procedure should be reported with the following categories:

- NOT RELATED: The event is clearly not related to the study device/procedure.
- UNLIKELY RELATED: The event is unlikely to be related to the study device/ procedure.
- POSSIBLY RELATED: The event is possibly related to the study device/ procedure.
- RELATED: The event is clearly related to the study device/ procedure.

14.6 List of Foreseeable AE and ADE

Foreseeable adverse events and adverse device effects based on years of clinical experience with rapid exchange DES implantation are summarized in Table 7.

These events, as well as mitigation or treatment, are also included in the IB.

Table 7: Foreseeable AE and ADE for DES Implantation

Access site complications*	Failure to deliver stent to intended site
Acute myocardial infarction	Fever or pyrogenic reactions
Allergic reaction or hypersensitivity to stent components or contrast media	Hypertension
	Hypotension
Aneurysm	Infections
Angina pectoris	Myocardial ischemia
Anxiety	Nausea and vomiting
Bleeding complications which may require transfusions or surgical repair	Palpitations
	Perforation of the heart or great vessels
Need for CABG - emergent or non-emergent	Pericardial effusion
Cardiac arrhythmias	Pulmonary failure
Cardiac failure	Renal failure
Cardiac tamponade	Stent compression
Cardiac shock	Stent misplacement / migration / embolization
Coronary artery complications**	Stent thrombosis
Death	Stroke / CVA / TIA

Delayed endothelialization	Vasovagal reaction
Distal emboli	Ventricular fibrillation
Endocarditis	Volume overload

* includes arteriovenous fistula, hematoma, infection, nerve injury, pain, peripheral ischemia, phlebitis, pseudoaneurysm

** includes abrupt closure, dissection, embolism, injury, perforation, plaque rupture/shift, restenosis, rupture, spasm, thrombosis, total occlusion

Foreseeable adverse events for ridaforolimus are summarized in Table 8.

These events as well as mitigation or treatment are also included in the IB. Note: These AEs are based on experience with ridaforolimus in cancer trials where there is systemic exposure in concentrations that are many fold greater than foreseeable with the EluNIR. The AEs are included here for completeness.

Table 8: Foreseeable AE and ADE for Ridaforolimus*

Anemia	Febrile neutropenia	Pneumonia
Anorexia	Fatigue	Pneumonitis
Alopecia	Hyperglycemia	Pyrexia
Aspartate Aminotransferase increased	Hypertriglyceridemia	Pruritus
Blood Creatine phosphokinase	Hypokalaemia	Paraesthesia
Blood Alkaline Phosphatase increased	Hypercholesterolaemia	Renal failure acute
Constipation	Hypophosphataemia	Rash
Dehydration	Leukopenia	Stomatitis
Diarrhea	Mucosal inflammation	Thrombocytopenia
Dysgeusia	Nausea	Vomiting
Dermatitis acneiform	Nail disorder	Weight decrease

*There may be other potential adverse events that are unforeseen at this time.

14.7 Emergency Contact Details for Reporting SAE and SADE

Sites should contact Medinol Ltd. by one of the following methods:

- Fax: 972-3-6474323
- Email: Lilachz@medinol.com

For medical consulting, contact Ori Ben-Yehuda: obenyehuda@crf.org

14.8 Information Regarding the DSMB

The Data Safety Monitoring Board (DSMB) for the EluNIR program (BIONICS and NIREUS studies) will review the safety data from this study. The DSMB is comprised of at least five members who are not directly involved in the conduct of the trial. The DSMB will review the trial on a periodic basis to be defined at their first meeting.

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the DSMB charter to ensure the safety of subjects enrolled in this trial. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Committee modify or discontinue the trial. All final decisions, regarding trial modifications, however, rest with the Executive Committee.

14.9 Adjudication of Clinical Endpoints

The Clinical End-point Committee (CEC) will review and adjudicate all clinical endpoint events. The CEC will as appropriate determine if the event occurred, (in the case of procedures) whether the procedure was clinically indicated vs. non-clinically indicated, if the event was cardiac or non-cardiac related, and if the event is target lesion/vessel related and if primary and/or secondary endpoints have occurred. Definitions are provided in Section 19.1.

14.9.1 Death

The Clinical Events Committee (CEC) will adjudicate all subject deaths.

14.9.2 Myocardial Infarction

The CEC will adjudicate all cases of myocardial infarction (MI) and the relationship of the event to the target vessel. If an angiogram is available for these events, the Angiographic Core Laboratory will provide information to the CEC as to the culprit lesions. All infarcts that cannot be clearly attributed to a vessel other than the target vessel will be considered related to the target vessel. The CEC will also adjudicate whether the MI was spontaneous or procedure-related.

14.9.3 Revascularization

The Angiographic Core Laboratory will be responsible for reviewing all baseline procedure angiograms, as well as clinically indicated and protocol-required angiograms during the follow-up period, to characterize the target lesion. The Angiographic Core Laboratory will be responsible for adjudication of revascularization type (TLR, TVR, non-TVR) as well as angiographic evidence of stent thrombosis. The CEC will determine whether any revascularization event was ischemia driven.

14.9.4 Stent Thrombosis

The CEC will adjudicate all cases of stent thromboses according to the ARC definitions for confirmation and outcomes. If an angiogram is available, the Angiographic Core Laboratory will provide their evaluation to the CEC.

14.9.5 Vascular and Bleeding Complications

All vascular and bleeding complications that are reported as serious adverse events and/or require transfusion or surgical intervention will be adjudicated by the CEC.

14.9.6 Other Adverse Events

The Sponsor will submit other cases for CEC adjudication as necessary. Non-safety endpoint adverse events (including events associated with any standard usage of contrast agents) will not be provided to the CEC for adjudication.

14.9.7 Follow-up of Subjects after Adverse Events

Subjects should be followed after adverse events until resolution or until end of trial, whichever comes first. Additional trial visits may be scheduled, as necessary, to allow for adequate follow-up.

15 VULNERABLE POPULATION

There is no expectation that any individuals from a vulnerable population will be approached for enrollment in the BIONICS 38 mm Trial.

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

There is no expectation that the BIONICS 38 mm Trial will encounter events or trial conduct that will lead the DMC or the Executive Committee to recommend termination.

16.1 Criteria and Arrangements for Suspension or Premature Termination of the Clinical Investigation or of the Clinical Investigation in One or More Sites

In case one or more sites are incapable of continuing to follow the patients in accordance with GCP (for example due to lack of staff), the site may be suspended or terminated by the Sponsor. Arrangements will then be made to reassign subjects to a nearby site, conditional to consent by the affected subjects.

16.2 Requirements for Subject Follow-Up

All patients will continue to receive standard of care follow-up in the event of suspension or premature termination of the clinical investigation.

17 PUBLICATION POLICY

17.1 Statement Indicating Whether the Results of the Clinical Investigation Will Be Submitted for Publication

The Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results and tertiary analyses. At the conclusion of the trial, a multicenter abstract reporting the primary results will be prepared by the Principal Investigators (in collaboration with the Executive Committee) and presented at an annual scientific meeting. A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any

single center experience within the trial is not allowed until both the publication of the multicenter results.

17.2 Statement Indicating the Conditions under Which the Results of the Clinical Investigation Will Be Offered for Publication

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

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19 DEFINITIONS AND ACRONYMS

19.1 Definitions

ABRUPT CLOSURE

- Abrupt closure is defined as the occurrence of new (during the baseline procedure) severely reduced flow (TIMI grade 0-1) within the target vessel that persisted and required rescue by stenting or other treatment, or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not connote "no reflow" due to microvascular flow limitation, in which the epicardial artery is paten but had reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the baseline treatment application reverses the closure.
- Sub-abrupt closure is defined as abrupt closure that occurred after the baseline procedure is completed and the patient left the catheterization laboratory and before the 30-day follow-up evaluation.
- Threatened abrupt closure is defined as a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. For the purpose of this CIP, ACS will be defined as hospitalization for anginal pain or discomfort within the previous 24 hours to their hospitalization with any one (or more) of the following criteria:

- Elevated troponin or creatine kinase-MB (CK-MB) consistent with MI, as reported by local laboratory and measured prior to baseline PCI
- Electrocardiographic changes (including transient changes) comprising new or presumably new ST segment depression ≥ 0.1 mV (≥ 1 mm), or ST segment elevation ≥ 0.1 mV (≥ 1 mm) in at least 2 contiguous leads, or new or presumably new Left Bundle Branch Block

ACUTE SUCCESS

Acute Success is classified according to the following definitions:

- Device Success

Device success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA), using the assigned device only and without a device malfunction.

- Lesion Success

Lesion success is defined as achievement of a final in-stent residual diameter stenosis of <30% (by QCA) using any percutaneous method.

- Procedure Success

Procedure success is defined as achievement of a final in-stent diameter stenosis of <30% (by QCA) using the assigned device and/or with any adjunctive devices, without the occurrence of cardiac death, Q wave or non-Q wave MI, or repeat revascularization of the target lesion during the hospital stay.

ADVERSE DEVICE EFFECTS

See Section 14 for definitions of adverse device effects (serious, anticipated, and unanticipated)

ADVERSE EVENTS

See Section 14 for definitions of adverse events (non-serious and serious)

ANALYSIS DATA SETS

Full Analysis Set (FAS)

If the study stent is not advanced beyond the guiding catheter, the patient will be de-registered and will not be considered part of the full analysis set. Patients not receiving the study stent after it has been advanced beyond the guiding catheter will be analyzed in the full analysis set. Patients enrolled in the trial with major deviations will also be analyzed in the full analysis set.

Per Protocol (PP Population)

Patients who receive the study stent with no major protocol deviations as detailed in Section 7.6 will be included in the Per Protocol Analysis Set.

Safety Analysis Set

The safety analysis set will include all subjects who signed an informed consent and have had any trial related activities including de-registered subjects.

ANGINA PECTORIS

CCS Classification of Stable Angina

I. Ordinary physical activity does not cause angina, such as walking or climbing stairs. Angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

II. Slight limitation of ordinary activity. Angina occurs upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs if walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

III. Marked limitation of ordinary activity. Angina occurs upon walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

IV. Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.

Braunwald Classification of Unstable Angina

Severity		Clinical Circumstances		
		A	**B**	**C**
		Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extracardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (postinfarction UA)
I	New onset of severe angina or accelerated angina; no rest pain[1]	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)	IIA	IIB	IIC
III	Angina at rest within 48 hours (angina at rest, acute)	IIIA	IIIB	IIIC

[1] Subjects with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (>3 episodes/day) or subjects with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

BLEEDING (HEMORRHAGIC) COMPLICATIONS

Bleeding will be classified and reported by both the TIMI bleeding classification and the BARC classification.

TIMI Bleeding Classification

Major:	Intracranial or clinically significant overt signs of hemorrhage associated with a hemoglobin decrease greater than 5g/L*.The diagnosis of intracranial bleeding requires confirmation by computed tomography or magnetic resonance imaging of the head.
Minor:	Observed blood loss and a decrease in hemoglobin level of 3 to 5 g/dL*

Bleeding Academic Research Consortium (BARC) Classification:

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that **does not** fit the criteria for Types 3, 4, or 5 but **does** meet at least one of the following criteria: • Requiring non-surgical, medical intervention by a health care professional • Leading to hospitalization of increased level of care • Prompting evaluation
Type 3a	• Overt bleeding plus hemoglobin drop of 3 to <5** g/dL (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding
Type 3b	• Overt bleeding plus hemoglobin drop ≥5** g/dL (provided hemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid) • Bleeding requiring intravenous vasoactive agents
Type 3c	• Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal) o Subcategories: confirmed by autopsy or imaging or LP • Intra-ocular bleed compromising vision
Type 4	CABG-related bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period* • Chest tube output ≥ 2 L within a 24 hour period
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes.
* Cell saver products will not be counted.
** Corrected for transfusion (1 unit PRBC or 1 unit of whole blood = 1 g/dL Hgb)

CEREBROVASCULAR ACCIDENT (CVA) (See STROKE)

- Ischemic stroke (cerebral infarction); or
- Hemorrhagic stroke (intracerebral hemorrhage or subarachnoid hemorrhage).

CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)

Acute CABG is defined as immediate transfer from the cath lab to the operative room for emergent bypass surgery during the initial treatment phase.

CABG during follow-up is only considered as a clinical-indicated Target Lesion Revascularization if coronary angiography indicates a diameter of stenosis greater than 50% of the stented coronary segment associated with one of the following conditions:

- A positive history of recurrent angina pectoris presumably related to the target vessel.
- Objective signs of ischemia (exercise test or equivalent) presumably related to the target vessel.
- Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve).

DEATH (per ARC definition, Circulation 2007;115:2344-51)

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (e.g. cancer, infection) should be classified as cardiac.

Cardiac death:

Any death due to proximate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure related deaths including those related to concomitant treatment.

Vascular death:

Death due to non-coronary vascular causes such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-cardiovascular death:

Any death not covered by the above definitions such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma.

DEVICE DEFICIENCY

See Section 14 for definition of device deficiency.

DIABETES MELLITUS (DM)

History of diabetes mellitus. The condition will be further categorized as treated by diet, oral hypoglycemic medications, or insulin.

DISSECTION

NHLBI Dissection Classification System:

- Grade A: Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance.
- Grade B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance.
- Grade C: Extraluminal cap with persistence of contrast after dye clearance from the lumen.
- Grade D: Spiral luminal filling defects.
- Grade E: New persistent filling defects.
- Grade F: Non-A-E types that lead to impaired flow or total occlusion.

Note: Grade E and F dissections may represent thrombus.

DISTAL EMBLOIZATION

Distal embolization is defined as new abrupt cut off or filling defect distal to the treated lesion.

IN-STENT PERCENT NEOINTIMAL HYPERPLASIA

In-stent percent neointimal hyperplasia will be calculated as neointimal hyperplasia (NIH) divided by stent volume. Volumetric analysis will include measurement every 1mm of the stent and lumen cross-sectional areas (CSA). NIH will be calculated as stent minus lumen. Once a complete set of CSA measurements will be obtained, stent and NIH volumes will be calculated using Simpson's rule. Volumetric analysis will be performed only for lesions in which motorized pullback was consistent and reliable.

IN-STENT RESTENOSIS - MEHRAN CLASSIFICATION (13)

- Class I: Focal ISR group. Lesions are ≤10 mm in length and are positioned at the unscaffolded segment (i.e., articulation or gap), the body of the stent, the proximal or distal margin (but not both), or a combination of these sites (multifocal ISR);
- Class II: "Diffuse intra-stent" ISR. Lesions are >10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s).
- Class III: "Diffuse proliferative" ISR. Lesions are >10 mm in length and extend beyond the margin(s) of the stent(s).
- Class IV: ISR with "total occlusion." Lesions have a TIMI flow grade of 0.

MAJOR EPICARDIAL VESSELS

- Left anterior descending artery (LAD) with septal and diagonal branches;
- Left circumflex artery (LCX) with obtuse marginal and/or ramus intermedius branches;
- Right coronary artery (RCA) and any of its branches.

MAJOR ADVERSE CARDIAC EVENTS (MACE)

The composite rate of cardiac death, any MI or ischemia-driven TLR

MINIMUM LUMEN DIAMETER (MLD)

MLD is defined the average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. MLD is visually estimated during angiography by the Investigator; it is measured during QCA by the Angiographic Core Laboratory.

MYOCARDIAL INFARCTION (MI)

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

Periprocedural MIs will be defined based on the SCAI definitions (14) as follows:

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

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

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

In addition, the following additional definitions will be used to assess peri-procedural MIs for the purpose of sensitivity analyses:

- The 3rd Universal Definition of MI definition
- A modification of the SCAI definition of periprocedural MI that utilizes a threshold CK-MB of ≥5x ULN (rather than ≥10x) in subjects with a normal baseline CK-MB without a requirement for associated clinical signs or symptoms
- A modification of the SCAI definition of periprocedural MI that utilizes a threshold CK-MB of ≥3x (rather than ≥10x) in subjects with a normal baseline CK-MB without a requirement for associated clinical signs or symptoms

Spontaneous MI (MI Type I):

Spontaneous MI (MI Type I) will be defined based on the Universal Definition of Myocardial Infarction (15) as follows:

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB
- Development of new Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a *target* or *non-target vessel or lesion* in most cases.

NO-REFLOW

An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion. Also see 'Acute Closure'.

PERCENT DIAMETER STENOSIS (%DS)

The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by QCA.

PERCUTANEOUS CORONARY INTERVENTION (PCI)

Refers to all interventional cardiology methods for treatment of coronary artery disease.

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 hemorrhage/tamponade: perforation resulting in cardiac tamponade.

PERSISTING DISSECTION

Dissection at follow-up that was present post baseline procedure.

PRIMARY INVESTIGATOR

The physician responsible for conducting the clinical trial at each investigational site.

PRINCIPAL INVESTIGATOR

A physician-specialist, related to the trial, who is responsible for the overall conduct of the trial at all sites and compliance with clinical investigation plan and relevant regulations.

PROTOCOL DEVIATIONS - MAJOR

Major protocol deviations include, but are not limited to, enrollment of a subject:

- Whose informed consent was not properly obtained
- Who did not meet all of the inclusion or exclusion criteria
- Who did not receive at least 6 months of DAPT post baseline procedure

REFERENCE VESSEL DIAMETER (RVD)

Average diameter of proximal and distal healthy segments by QCA. 10 mm "normal" reference segments are selected proximal and distal to the stenosis and averaged to define the reference vessel diameter. A computer-defined interpolated normal segment will be used to calculate percent diameter stenosis.

RESTENOSIS

Re-narrowing of the artery following the removal or reduction of a previous narrowing.

REVASCULARIZATION (per ARC definition, Circulation 2007;115:2344-51)

Target Lesion Revascularization (TLR)

TLR is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLR should be classified prospectively as clinically indicated (CI) or not clinically indicated by the investigator prior to repeat angiography. An independent Angiographic Core Laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement. The target lesion is defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

Target Vessel Revascularization (TVR)

TVR is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel). The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches, and the target lesion itself.

Non Target Lesion Revascularization (Non-TLR)

Any revascularization in the target vessel for a lesion other than the target lesion is considered a non-TLR.

Non Target Vessel Revascularization (Non-TVR)

Any revascularization in a vessel other than the target vessel is considered a non-TVR.

Clinically Driven Revascularization (TLR/TVR)

Revascularization at the target site (TLR) or in the target vessel (TVR) that is associated with:

- A positive functional ischemia study or ischemic symptoms; AND angiographic lumen minimal lumen diameter stenosis ≥50% by QCA; OR
- A TLR or TVR with a diameter stenosis ≥ 70% by QCA without either angina or a positive functional study.

SERIOUS ADVERSE DEVICE EFFECT

See Section 14 for definitions of adverse device effects (serious, anticipated, and unanticipated)

SERIOUS ADVERSE EVENT (SAE)

See Section 14 for definitions of adverse events (non-serious and serious)

STENT MAL-APPOSITION

Stent mal-apposition is defined as blood speckle behind stent struts, and categorized as persistent (visible both at baseline and follow-up), resolved (only visible at baseline), and late-acquired (only visible at follow-up) by comparing baseline and follow-up IVUS images.

STENT THROMBOSIS (per ARC definition, Circulation 2007;115:2344-51)

Stent Thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the patient left the catheterization lab after the baseline procedure.

Timing	Acute Subacute Late Very late	≤ 24 hours post stent implantation > 24 hours to 30 days post stent implantation > 30 days to 1 year post stent implantation > 1 year post stent implantation
Type	Primary	Occurs in target lesion or margins after baseline procedure
	Secondary	Occurs after revascularization (TLR, TVR, or non-TVR)
Category	Definite	Definite stent thrombosis is confirmed by either angiographic* or pathologic† analysis
	Probable	Probable stent thrombosis is considered to have occurred after intracoronary stenting for either: • any unexplained death within the first 30 days unless that patient had baseline procedure for ST elevation MI • any MI, irrespective of time after baseline procedure, that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
	Possible	Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up

***Angiographic confirmation of stent thrombosis**

The presence of an intracoronary thrombus that originates in the stent or in the segments 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest – The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)
- New ischemic ECG changes that suggest acute ischemic
- Typical rise and fall in cardiac biomarkers (refer to spontaneous MI definition)

- Intracoronary thrombus is defined as a spheric, ovoid, or irregular noncalcified filling defect or lucency surrounded by contrast material on 3 sides or within a coronary stenosis seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
- Nonocclusive or occlusive thrombus
- TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch if originates from the side branch.

[†]**Pathological confirmation of stent thrombosis**
Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

STROKE

Stroke is defined as the sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria, or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists >24 hours.

SUBINVESTIGATOR

A physician-member of a clinical study team who administers investigational products, used in the clinical trial, to a subject.

SUCCESSFUL PRE-DILATION

Pre-dilation has been successfully completed without complications if all of the following apply:

- Diameter stenosis < 50%
- TIMI Grade III flow
- Lesion length still within the requirements of the protocol
- No angiographic complications or prolonged chest pain

TARGET LESION

Lesion that has met the angiographic inclusion and exclusion criteria and that is to be treated during the baseline procedure.

TARGET LESION FAILURE (TLF)

The composite rate of cardiac death, target-vessel MI or ischemia-driven TLR

TARGET VESSEL

The entire epicardial vessel in which the treated lesion is located.

TARGET VESSEL FAILURE (TVF)

The composite rate of death, target vessel-related MI or ischemia-driven TVR

TIMI FLOW GRADES

0. No contrast flow through the stenosis.
1. A small amount of contrast flows through the stenosis but fails to fully opacify the artery beyond.
2. Contrast material flows through the stenosis to opacify the terminal artery segment. However, contrast enters the terminal segment perceptibly more slowly than more proximal segments. Alternatively, contrast material clears from a segment distal to a stenosis noticeably more slowly than from a comparable segment not preceded by a significant stenosis.
3. Anterograde flow into the terminal coronary artery segment through a stenosis is as prompt as anterograde flow into a comparable segment proximal to the stenosis. Contrast material clears as rapidly from the distal segment as from an uninvolved, more proximal segment.

VASCULAR COMPLICATIONS

These may include access-site hematoma, pseudoaneurysm, arteriovenous fistula, peripheral ischemia or nerve injury.

19.2 Acronyms and Abbreviations

19.2.1 Acronyms

Acronym	Term
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ADE / SADE	Adverse Device Effect / Serious Adverse Device Effect
AE / SAE	Adverse Event / Serious Adverse Event
ARB	Angiotensin Receptor Blocker
ASADE / USADE	Anticipated Serious Adverse Device Effect / Unanticipated Serious Adverse Device Effect
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CAPA	Corrective and Preventative Action
CEC	Clinical Events Committee
CK	Creatine Kinase
CK-MB	Creatine Kinase Muscle-Brain Isoenzyme
CRF / eCRF	Case Report Form / electronic Case Report Form
CSA	Cross Sectional Area (IVUS)
CTO	Chronic Total Occlusion
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EES	Everolimus-eluting Stent
FAS	Full Analysis Set
FFR	Fractional Flow Reserve
GEE	Generalized estimating equation
IB	Investigator's Brochure
IFU	Instructions for Use

Acronym	Term
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
MLD	Minimum Luminal Diameter
NIH	Neointimal Hyperplasia (IVUS)
NSTEMI	Non ST Elevation Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel-eluting Stent
PP	Per Protocol Analysis Dataset
PTCA	Percutaneous Transluminal Coronary Angioplasty
QCA	Quantitative Coronary Angiography
RCA	Right Coronary Artery
RES	Ridaforolimus-eluting Stent
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STEMI	ST Elevation Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect
ZES	Zotarolimus-eluting Stent

19.2.2 Abbreviations from Clinical Trials, Academic Bodies, or Regulations

Abbreviation	Term
ACC / AHA / SCAI	American College of Cardiology / American Heart Association / Society for Cardiovascular Angiography and Interventions (dual anti-platelet therapy guideline)
ARC	Academic Research Consortium (definitions for bleeding, death, myocardial infarction, and stent thrombosis)
BARC	Bleeding Academic Research Consortium (BARC) (classification for bleeding)
CCS	Canadian Cardiovascular Society (angina grading scale)
HIPAA	Health Insurance Portability and Accountability Act (U.S. privacy rule for protected health information)
NHLBI	National Heart, Lung, and Blood Institute (coronary artery dissection scale)
NYHA	New York Heart Association (heart failure classification)
TIMI	Thrombolysis In Myocardial Infarction (bleeding definition and coronary artery blood flow scale)