CLINICAL INVESTIGATION PLAN

JNIR Trial

Multi-center study for evaluating the safety and efficacy of the Ridaforolimus Eluting Coronary Stent System (MedJ-01) In Coronary Stenosis Trial

CIP Number: JNIR01

Cooperating Investigator (CI)	Dr. Shigeru Saito Interventional Cardiologist Shonan Kamakura General Hospital
Investigational Sites	Approximately 10 sites in Japan will participate in the trial. An updated full site list is detailed in the trial's Site Binder.
Primary Investigators	See Appendix 1
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Core Laboratories (Angiographic, ECG) **Clinical Events Committee** **Data Safety Monitoring Board**	Cardiovascular Research Foundation 111 East 59th Street New York NY,USA Katharine Lymberis Administrative Director Clinical Trials Center klymberis@crf.org
Clinical Investigation Plan Version and Date	Version 2.0, 18-Sep-2016

This Clinical Investigation Plan has been written in accordance with Annex A of ISO 14155 (2011): Clinical investigations of medical devices for human subjects – Good Clinical Practice and ICH E6 Guidelines. In accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the standard stated in Japanese Drug Medical Device Law Act 23.2.5 Part 3 and Act 80.2, and MHLW Ministerial Ordinance No. 36, Mar 23, 2005 (GCP of Medical Device), Article 273 and Article 274, Part 2, 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 Japanese Drug Medical Device Law Act 23.2.5 Part 3 and Act 80.2, and MHLW Ministerial Ordinance No. 36, Mar 23, 2005 (GCP of Medical Device), Article 273 and Article 274, Part 2, Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), ISO 14155, ICH E6, and the applicable regulatory requirements.

Clinical Investigation Plan Review

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

Coordinating Investigator's Signature

Coordinating Investigator	Date

Sponsor Representative's Signature

Sponsor Representative Name	Date

CLINICAL INVESTIGATION PLAN REVISION SUMMARY

Version	Release Date	Summary of Changes
1.0 Initial release	03-Dec-2015	**N/A**
2.0 Revision per PMDA's comments	18-Sep-2016	**(In Bold –wording added)** • Site Monitoring & Data Analysis CRO replaced - Quintiles Transnational Japan K.K. instead of NAC-RA KK • Subject Population, Inc. 2, Exc. 1 (in the Synopsis) and sections 3.1, 5.3, Table 3, 6.3.1.1, 6.3.2.1 – the word "**subacute**" is added before the word "STEMI" • Angiographic inclusion 7 (in the Synopsis and on sec. 6.3.1.2) and 'Study Stent Use' sec. 6.4.6 – revised to reflect that "**Overlapping stents are allowed with the investigational device**" • Description of the investigational device, sec. 2.6 Figures 1-4 are added o 2.6.1 –Stent: wording updated for better accuracy of stent description o Table 1: Available Stent Lengths and Nominal Diameters – updated o 2.6.2 – Delivery System: correction was made as follows: "The catheter has a distal port approximately **30**~~25~~cm from the distal tip that accesses the guide wire lumen". o 2.6.3 – Polymer Coating: the word "matrix" is replaced with "**blend**", for better accuracy • BLAST Study –sec. 3.3.2 – wording updated to reflect study completion. • Pre-dilatation of target lesions, sec. 6.4.5 – revised to reflect that "**pre-dilatation should be performed, per local clinical practice**" • Pre-Procedure (Loading) Anti-Platelet Medication, sec. 6.4.9.1 – Table 6 - revised to adjust to the Japanese standard of care: A loading dose of clopidogrel **≤300** ~~to 600~~ mg must be administered at least 6 hours prior to PCI, as per standard of care. • Definitions and Acronyms – Protocol Deviations-Major – the following change was made to the 4th bullet: "who did not receive at least ~~6~~**12** months of DAPT post baseline procedure". • Change number of study participants, per PMDA request– instead of "a total of 86 subjects" – "a total of

		100 subjects" will be allocated in this study. Accordingly, the following sections are revised: Synopsis, 6.1.1, 6.1.6, 6.3, 6.3,7. • Wording added on section: synopsis and 6.3.1.2- angiographic inclusion # 6, and section 6.3 'Subjects' - to clarify as to rotational atherectomy: "Complex lesions are allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy **(e.g.: Rotablator System and Directional Coronary Atherectomy, DCA) are allowed)…"** • Sections 6.4.5 'Pre-Dilatation of Target Lesion', and 6.4.7 'Treatment Failures and Device Malfunctions of the MEDJ-01' - wording added to clarify that Pre-dilatation can **include DCA**. • Section 7 'Statistical Considerations' – revised to present the approach requested by PMDA. • Revisions per PMDA's comment as to de-registration, as follows: o Section 6.3.4 'Point of Enrollment', and section 21.1– 'Definitions' – Analysis Data Sets (FAS): "If the study stent **could not be implanted due to reasons that are not related to study device**, ~~is not advanced beyond the guiding catheter~~, the study subject will be de-registered from the trial and will not be analyzed as part of the full analysis set (FAS). Figure 5 – an **asterisk added** to refer to section 6.4.3 o Section 6.4.3 – 'Enrollment' –"A subject will be de-registered from the trial in case the study stent **could not be implanted due to reasons that are not related to study device** ~~If the study stent is not advanced beyond the guiding catheter~~ (for example, the lesion was not ~~successfully~~ **properly** ~~pre-dilated~~ **prepared for stenting)** ~~the subject will be de-registered from the trial.~~ • Appendix 1 – Primary Investigators in the JNIR Study – deletion of Dr. Takeshi Serikawa, as he will not take part in this study. • Minor editorial revisions. • Protocol version name and date- updated

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

MedJ-01 Ridaforolimus Eluting Stent System in Coronary Stenosis

JNIR Trial

CIP Number: JNIR01

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 Japanese Drug Medical Device Law Act 23.2.5 Part 3 and Act 80.2, and MHLW Ministerial Ordinance No. 36, Mar 23, 2005 (GCP of Medical Device), Article 273 and Article 274, Part 2, clinical investigation plan, Good Clinical Practice guidelines, 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

Institution Name/Location (print)

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1 OVERALL SYNOPSIS OF THE CLINICAL INVESTIGATION

JNIR Trial

Device	MedJ-01 Ridaforolimus Eluting Coronary Stent System (hereafter referred to as MedJ-01)
Objectives	Evaluating MedJ-01 safety and efficacy for de novo or restenosis lesion with target vessel diameter of 2.5mm to 4.25, for subjects undergoing coronary artery stent implantation
Trial Hypotheses	JNIR01 is aimed at assessing TLF at one year with the MedJ-01 stent in a Japanese patient population, to show non-inferiority of JNIR01 Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12}.
Subject Population	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), NSTEMI, and recent subacute STEMI (>72 hours from initial presentation and stable). Complex lesions are allowed. A maximum of two target vessels and two lesions per vessel may be treated (two lesions separated by up to 10 mm that can be covered by a single stent are considered as one lesion); the total planned study stenting in the coronary tree cannot exceed 100 mm.
Trial Design and Methods	This is a prospective, multi-center single- arm, open label clinical trial. Lesions planned to be treated must be declared and recorded at time of enrollment. Clinical follow-up will be performed at 30 days, 6 months, and 1, 2, 3, 4, and 5 years post enrollment.
Primary Endpoint	Target Lesion Failure (TLF) at 12 months defined as the composite of cardiac death, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization.
Secondary Endpoints	linical Secondary Endpoints to be evaluated at 30 days, 6 months, and 1, 2, 3, 4 and 5, except as noted: • Device, Lesion, and Procedure Success at time of baseline procedure • TLF at 30 days, 6 months, and 2, 3, 4 and 5 years defined as the composite of cardiac death, target vessel-related MI, or ischemia-driven TLR. • Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR) • Target vessel failure (TVF; the composite rate of death, target vessel related MI or ischemia-driven TVR) • 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	A total of 100 subjects will be allocated in this study.
Inclusion Criteria	**General Inclusion Criteria:** 1. Age ≥ 20 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 subacute STEMI. For subacute STEMI the time of presentation to the first treating hospital, whether a transfer facility or the study hospital, must be >72 hours prior to enrollment and enzyme levels (CK-MB or Troponin) demonstrating that either or both enzyme levels have peaked. 3. Non-target vessel PCI are allowed prior to enrollment depending on the time interval and conditions as follows: **a. During Baseline Procedure:** i. PCI of non-target vessels performed during the baseline procedure itself immediately prior to enrollment if <u>successful and uncomplicated</u> 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:** i. <u>Not allowed</u> (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 vessel 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: i. PCI of non-target vessels performed greater than 30 days prior to procedure whether or not successful and uncomplicated. 4. Patient is willing and able to provide informed written consent and comply with follow-up visits and testing schedule. **Angiographic inclusion criteria (visual estimate):** 5. Target lesion(s) must be located in a native coronary artery with visually estimated diameter of ≥2.5 mm to ≤4.25 mm. 6. Complex lesions are allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy (e.g.: Rotablator System) and Directional Coronary Atherectomy - DCA) are allowed), presence of thrombus that is non-occlusive and does not require thrombectomy, CTO, bifurcationlesions (except planned dual stent implantation), ostial RCA lesions, tortuous lesions, bare metal stent restenotic lesions, protected left main lesions. 7. Overlapping stents are allowed with the investigational device (MedJ-01).
Exclusion Criteria	**General Exclusion Criteria:** 1. STEMI within 72 hours (subacute) 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 12 months (including planned surgeries that cannot be delayed) 9. Subject has an indication for chronic oral anticoagulant treatment (with either vitamin K antagonists or novel anticoagulants – NOACs) 10. Calculated creatinine clearance <30 mL/min using Cockcroft-Gault equation. 11. Hemoglobin <10 g/dL.

	12. Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3. 13. White blood cell (WBC) count <3,000 cells/mm^3. 14. Clinically significant liver disease. 15. Active peptic ulcer or active bleeding from any site. 16. Bleeding from any site within the prior 8 weeks requiring active medical or surgical attention. 17. If femoral access is planned, significant peripheral arterial disease which precludes safe insertion of a 6F sheath. 18. History of bleeding diathesis or coagulopathy or will refuse blood transfusions. 19. Cerebrovascular accident or transient ischemic attack within the past 6 months, or any permanent neurologic defect attributed to CVA. 20. Known allergy to the study stent components e.g. cobalt, nickel, chromium, Carbosil®, PBMA, or limus drugs (ridaforolimus, zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative or similar compounds). 21. Known allergy to protocol-required concomitant medications such as aspirin, or DAPT (Drugs that inhibit P2Y12 such as clopidogrel and prasugrel), or heparin, or iodinated contrast that cannot be adequately pre-medicated. 22. 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). 23. Patient is participating in any other investigational drug or device clinical trial that has not reached its primary endpoint, or plans to participate in any clinical trial. 24. Women who are pregnant or breastfeeding (women of child-bearing potential, defined as females of childbearing potential if they have not undergone a permanent contraceptive operation or they are not postmenopausal, must have a negative pregnancy test within one week before treatment. Permanent contraceptive operation is defined as: hysterectomy, hysterosalpingectomy, or bilateral oophorectomy. The status of a female should be considered as postmenopausal when she has not had a period for 12 consecutive months without an alternative medical cause). 25. 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).

	26. Patient has received an organ transplant or is on a waiting list for an organ transplant. 27. Patient is receiving or scheduled to receive chemotherapy within 30 days before or any time after the baseline procedure. 28. 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):** 29. Target lesions in more than two (2) major coronary arteries (i.e., two of LAD, LCX, RCA) and their respective branches (the Ramus Intermedius is defined as a branch of the LCX). 30. More than two target lesions per target vessel are planned (two lesions separated by less than 10 mm that can be covered by a single stent are considered as one lesion). 31. More than 100 mm length of planned study stenting in the entire coronary tree. 32. Occlusive thrombus and/or a thrombus requiring thrombectomy in a target vessel. 33. Unprotected left main lesions ≥30%, or planned unprotected left main intervention. 34. Ostial LAD or LCX lesions (stenting of any diseased segment within 5 mm of the unprotected left main coronary artery). 35. Bifurcation lesions with planned dual stent implantation. 36. Stenting of lesions due to DES restenosis. 37. 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. 38. Target lesion exists in bypass graft vessels.

2 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

2.1 Summary Description of the Investigational Device and Its Intended Purpose

2.1.1 Summary Description of the Investigational Device

The MedJ-01 Ridaforolimus Eluting Coronary Stent System is a single use device/drug combination product comprising of:

- Stent - a mounted Cobalt Chromium (CoCr) alloy based stent
- 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 MedJ-01 Ridaforolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to lesions in vessels with reference diameters of 2.5 mm to 4.25 mm, including complex lesions.

2.2 Details Concerning the Manufacturer of the Investigational Device

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

2.3 Traceability of the Investigational 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 shipped, received, implanted in subjects, and returned if unused at the end of the trial.

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

See Section 2.1.2

2.5 Populations and Indications for Which the Investigational Device Is Intended

See Section 2.1.2

2.6 Description of the Investigational Device

2.6.1 Stent

The MedJ-01 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.

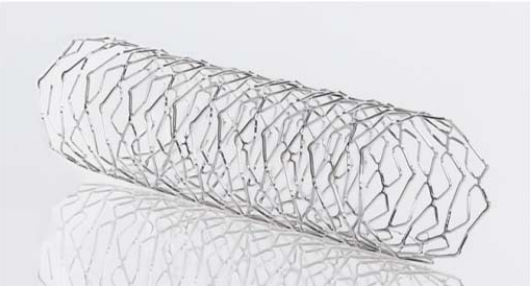


Figure 1: Closed cell design

The bare metal stent (implant) component of the MedJ-01 is equivalent to the stent of the CE Marked and PMA approved (P#110004 /S001) 'NIRxcell CoCr Coronary Stent on Rx System' and to the stent of the PMA approved (P#110004) and Health Canada licensed (HC 86087) Presillion Plus Coronary Stent System, (also known as the PIONIR™ bare metal stent).

Figure 2: Stent of the MedJ-01 mounted on balloon

Table 1: Available Stent Lengths and Nominal Diameters

	Stent Nominal Diameter (mm)				
Stent Length	**2.5**	**2.75**	**3.0**	**3.5**	**4.0**
8 mm	X	X	X	X	X
12 mm	X	X	X	X	X
17 mm	X	X	X	X	X
20 mm	X	X	X	X	X
24 mm	X	X	X	X	X
28 mm	X	X	X	X	X
33 mm	X	X	X	X	X

2.6.2 Delivery System

The delivery catheter for the MedJ-01 is a rapid exchange balloon catheter with a hydrophilic coating. The usable length of the delivery system is 140cm, with shaft profiles of 2.1F (0.69mm) / 2.6F (0.86mm), proximal and distal, respectively and for products up to 28 mm length, and 2.8F (0.94 mm) for products of 33mm.The catheter has a distal port approximately 30cm from the distal tip that accesses the guide wire lumen. The guide wire 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: 93cm; femoral: 103cm). The MedJ-01 delivery system design has a tapered tip to facilitate system deliverability and requires a 0.014" (0.36mm) diameter guide wire for navigation.

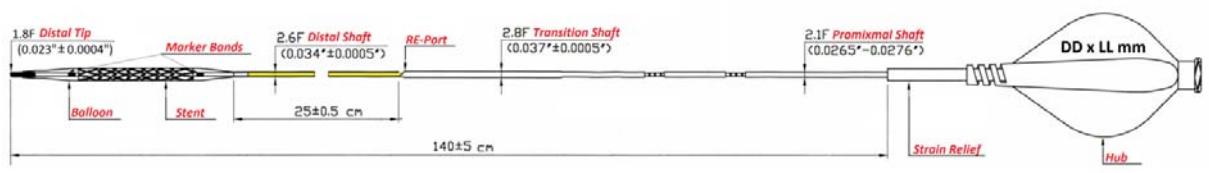


Figure 3: Stent Delivery System

2.6.3 Polymer Coating

The stent is coated with a polymer blend 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. The molecular structure of ridaforolimus is shown in Figure 4.

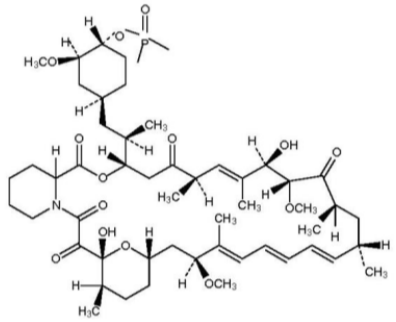


Figure 4: Molecular Structure of Ridaforolimus

Further detailed information on ridaforolimus can be found in the Investigator's Brochure (IB) # 900186023.

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

The MedJ-01 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.

The MedJ-01 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 assessing the safety and efficacy of the MedJ-01.

The trial will enroll a broad population including patients with ACS (unstable angina, NSTEMI, and subacute STEMI) as well as complex lesions. The inclusion of patients with AMI and particularly subacute 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 72 hours (subacute) 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.[6] 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. The methods and results of the bench testing and the pre-clinical testing are contained in the IB which clearly demonstrates the justification for use of the investigational device in this trial.

3.3 Evaluation of Clinical Data Relevant to the Proposed Clinical Investigation

Overall, clinical data for more than 900 patients are available to date for the use of the PIONIR™ stent (as part of the Presillion plus CoCr Coronary Stent on RX System device). See **Error! Reference source not found.**2 for a list of the clinical studies conducted, followed by a brief description of each study. These data have been presented to FDA in the PMA #P110004 submission and its annual update reports. There has been no previous clinical experience specifically with the MedJ-01.

Table 2: List of Previous Clinical Experience

Study	Number of Subjects	Countries
The PIONIR Study	278	Germany, Sweden, Belgium, Israel
The BLAST Study	57 (placebo group)	Israel
The Iberian Study	318	Spain, Portugal
The Belgium Study	101	Belgium, Luxembourg
The Vila Real Study	20	Portugal
The PREHAMI Registry	129	Italy

3.3.1 The PIONIR Study

This was the pivotal study conducted to demonstrate the safety and effectiveness of Presillion™ plus CoCr Coronary Stent on RX System (Presillion *plus* Stent System) in the treatment of *de novo* stenotic lesions in native coronary arteries. It was a post market study (for the EU, using an approved FDA protocol also supporting PMA submission) non-randomized, multi-center, prospective, single arm clinical study. Two hundred and seventy-eight (278) patients were enrolled to this study. Follow-up was performed at: discharge, 30 days, 180 days, 270 days, and 1 year.

The primary endpoint of the study was the incidence of target vessel failure (TVF) which was defined as the composite of cardiac death, target vessel myocardial infarction (Q-wave or

non Q-wave), or clinically-driven target vessel revascularization (TVR) by percutaneous or surgical methods, within 270 days of treatment with Presillion or Presillion *plus* Stent Systems.

Study results: The 270-day TVF rate was 8.9% and the upper bound of the exact one-sided 95% confidence interval was 12.3%. Since this upper bound is less than 16.46% (a performance goal derived using a meta-analysis of the standard-of-care therapy for coronary stenting with bare metal stents), the study stent is considered to have met the performance goal. Lesion success was achieved in 100.0% (280/280) of cases. Device success was achieved in 98.2% (275/280) of cases. Procedural success was achieved in 97.8% (272/278) of cases.

Conclusions: The 9-month results of the PIONIR study demonstrate Presillion Stent System and Presillion *Plus* Stent System to be safe and effective in the treatment of *de novo* stenotic lesions in native coronary arteries when compared to a performance goal derived using a meta-analysis of the standard-of-care therapy for coronary stenting with bare metal stents.[7]

3.3.2 The BLAST Study

The BLAST Study was a phase II, dose-finding, randomized, multi-center, prospective, double blind clinical study of Presillion Stent System in combination with Liposomal Alendronate, compared to Presillion Stent System alone.

The investigational product in this study was Liposomal Alendronate, a drug which was administered in a single dose, intravenously (IV) through a peripheral venous catheter. The study objective was to assess the safety and efficacy of the study drug in the treatment of *de novo* stenotic lesions in native coronary arteries in a population undergoing PCI, with implantation of a bare metal stent (Presillion stent).

The information relevant to the investigator's brochure focuses only on data from the placebo arm (57 out of 226 patients enrolled). Follow-up in this study includes: clinical follow-up at 30 days, clinical and angiographic (stent) follow-up at baseline and 6 months, including QCA, IVUS at baseline and 6 months for pre-specified patients, and yearly contact through 5 years.

The primary efficacy endpoint is the 6-month in-stent late lumen loss, as measured by QCA.

Six-month results: The mean (±SD) of in-stent late lumen loss for the 57 per-protocol (PP) placebo arm patients was 0.86mm (± 0.60 mm).

Conclusions: Despite the limited sample size, the outcomes of the placebo cohort (57 patients) analysis at 6 months post-procedure were presented to FDA in PMA #P110004. The Quantitative Angiographic Analysis provides complementary and supporting information on the safety and efficacy of the Presillion stent.

Medinol has continued to collect safety information on this study, per protocol. The study has been completed on Jan. 2015. None of the SAEs reported were adjudicated as related to the study drug or device.

3.3.3 The Iberian Study

The Iberian Study was a multi-center, post-market surveillance registry evaluating the performance and long term safety of the Presillion™ stent in de novo native coronary artery lesions, in routine clinical practice. It was completed on 18 Apr 2011, with 318 patients enrolled. Follow-up was performed at 30 days and 1 year post implantation. The registry objective was to assess the incidence of Major Adverse Cardiac Events defined as a composite of cardiac death, myocardial infarction (Q-wave and non Q-wave) and clinically-driven target lesion revascularization at the 12-month follow-up period. It was limited to subjects who had received Presillion Stent System. While no inclusion or exclusion criteria were specified, uniform, complete and accurate data was collected peri-procedurally, during the baseline hospitalization, and during follow-up. All subjects were treated according to the Instruction for Use (IFU), including conduct of the stenting procedure.

Study results: For the primary endpoint, a total of 9 subjects (2.9%) presented with MACE up to the 12-month FU, a figure significantly lower than the performance goal of 15% ($p<0.001$). For the secondary endpoint, device success was attained in 350 of the 354 lesions treated (98.9%); lesion success was present in 349 lesions (98.6%); and procedural success was reached for 344 lesions (97.2%).

Conclusions: The MACE rate at the 12 month follow-up (2.9%) was considerably lower than the performance goal (15.0%, $p<0.001$). Together with the good results for the secondary endpoints, this indicates adequate safety and performance of the Presillion™ stent. The possibility of underreporting of adverse events in this study cannot be ruled out.

3.3.4 The Belgian Study

The Belgian Study was a non-randomized single arm registry, evaluating the safety of Presillion Stent System in the treatment of *de novo* stenotic lesions in native coronary arteries. This registry was initiated as a 30-day follow-up after the procedure. At a later stage, the follow-up period was prolonged to include an additional data point (as close as possible to, but after, the 6-month post-procedure date). One hundred and one (101) patients were enrolled to the study.

The primary safety measure is a composite of MACE defined as the composite of cardiac death, myocardial infarction (Q-wave and non Q-wave) and clinically driven target lesion revascularization at 30 days and 6 months post procedure.

Study results: The MACE rate at the 30-day follow-up was 0.

Conclusions: Clinical endpoints at 30 days and beyond, up to 6-12 months, demonstrated the safety and efficacy of the Presillion stent for the treatment of *de novo* coronary artery stenosis. Presillion Stent System proved to be safe in this cohort of 101 patients studied in Belgium and Luxembourg.

3.3.5 The Vila Real Study

The Vila Real Study was a prospective study of the first 20 patients undergoing implantation of at least one Presillion™ stent in Vila Real, Portugal. After discharge, patients were followed and assessed clinically at 3 and 6 months for the occurrence of MACE defined as cardiovascular death, myocardial infarction, stroke, or revascularization.

Study results: The percentage of stenosis before and after angioplasty was 88.5+9.7% and 10.6+4.3%, respectively. The minimal luminal diameter (MLD) before and after angioplasty was 0.65+0.40 mm and MLD=2.58+0.36 mm, respectively. The success rate for Presillion implantation was 100%, with no significant drop in hemoglobin, no additional elevation of cardiac biomarkers or deterioration in renal function after the procedure. No MACE occurred before hospital discharge.

Conclusions: The success rate for Presillion stent implantation was 100%, despite 73% of the lesions being classified as B2 or C and 27% presenting moderate or severe calcification, which confirmed the excellent profile and deliverability of these stents. Evidence of the good performance of the stents was also seen during hospitalization, with no occurrence of MACE or elevation of markers of myocardial necrosis compared to pre-PCI values. This initial experience with Presillion stents in consecutive patients referred for BMS implantation showed a high efficacy rate at six months and an excellent safety profile, despite dual antiplatelet therapy being maintained for only two months.

3.3.6 The PREHAMI Registry

The prospective single-center PREHAMI (Presillion™ in High-risk Acute MI) Registry evaluated the in-hospital and 1-year outcomes of patients with high-risk acute myocardial infarction who underwent PCI with the bare-metal Presillion stent. One hundred and twenty-nine (129) patients were enrolled in the registry. The primary outcome of the registry was the occurrence of major adverse coronary events (MACE) defined as the composite of all-cause death, non-fatal acute myocardial re-infarction and target-vessel revascularization during initial hospitalization and at the 1-year follow-up. Stent thrombosis accounted in the MACE rate according to the clinical consequences of the thrombosis.

Study results: The device success rate was 98.8% (there were only 2 cases in which the lesion could not be reached due to severe coronary tortuosity). The hierarchical MACE rates were 7 (5.4%) during hospitalization, 17 (13.3%) at 6 months, and 22 (17.3%) at 1 year.

Conclusions: The use of the Presillion stents in patients with high-risk acute MI treated invasively appeared to be safe and efficacious with optimal deliverability and good long-term outcomes. The in-hospital and long-term event rates were limited, with similar outcomes to those of previous real world registries enrolling unselected patients (both low and high risk) with STEMI and NSTEMI.

3.3.7 The BIONICS and NIREUS Trials

The BIONICS and NIREUS clinical studies assessing the BioNIR (the same stent system as MedJ-01) were initiated in March 2014 and aim to assess the safety and efficacy of the BioNIR in comparison to a second generation DES, the Resolute Zotarolimus-Eluting Coronary Stent System (Medtronic).

BIONICS is a prospective, multi-center, single-blind, two-arm, 1:1 randomized clinical trial with a planned enrollment of approximately 1906 patients. The primary clinical endpoint is target lesion failure (TLF) at one year, with an additional angiographic endpoint of in-stent late lumen loss evaluated in approximately 200 patients at 13 months. Among the patients of this subset, at least 100 are also planned for intravascular ultrasound (IVUS) at baseline and 13 month follow up. The trial is conducted in the USA, Canada, Europe and Israel. 1919 patients have been enrolled to the BIONICS trial. Enrollment was completed on August 28, 2015.

NIREUS is a prospective, multi-center, single-blind, two-arm, 2:1 randomized clinical trial (2 BioNIR : 1 Resolute) encompassing approximately 300 patients with a wide spectrum of Percutaneous coronary intervention (PCI) indications (stable angina as well as Acute coronary syndrome [ACS], including subacute ST segment elevation myocardial infarction [STEMI]).

The primary endpoint is angiographic in-stent late loss at 6 months. Secondary clinical endpoints include target lesion failure (TLF) at 30 days, 6 months, 1 year and yearly thereafter until year 5. The trial is conducted in Europe and Israel. 302 patients have been enrolled to the NIREUS trial. Enrollment was completed on March, 24, 2015.

Both studies are supervised by an independent Data Safety Monitoring Board (DSMB). The DSMB has convened 4 times since trials initiation to review the safety data of both studies and did not find any concerns. The DSMB voted to continue the trials without any changes.

4 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

The risks and benefits of the MedJ-01 are summarized in the Investigator's Brochure.

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.

4.2 Anticipated Adverse Device Effects

It is expected that the adverse device effects for MedJ-01 would not differ from the anticipated adverse device effects based on years of clinical experience with rapid exchange DES implantations. Please refer to the IB for details.

4.3 Residual Risks Associated with Investigational Device

Foreseeable adverse events and device deficiencies that may result from stent intervention can be found in Section 14.6 and 14.7 as well as in the IB.

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

While formal drug interaction studies were not conducted with MedJ-01 due to expected negligible systemic exposure, since Ridaforolimus is a rapamycin analog, the possible interactions for rapamycin analogs (e.g. zotarolimus, everolimus, biolimus, tacrolimus) may apply to MedJ-01 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), or prasugrel (2.5-3.75 mg/day) for a minimum of 12 months following stent implantation according to national guidelines and standard of care unless an intervening medical necessity occurs such as severe bleeding, in accordance with the PCI recommendations from ACCF/AHA/SCAI [1] and the elective PCI guidelines from JCS [8]. If DAPT is discontinued before 12 months 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 MedJ-01 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, Xience and Promus stents. 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 novel MedJ-01 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. Therefore the risk of the JNIR Trial is expected to be similar to other DES trials. The risk to benefit relationship is therefore similar to other DES studies and reasonable.

5 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1 Objectives

Evaluating MedJ-01 safety and efficacy for de novo or restenosis lesion with target vessel diameter of 2.5 mm to 4.25 mm, for subjects undergoing coronary artery stent implantation.

5.2 Hypotheses to Be Accepted or Rejected by Statistical Data

JNIR01 is aimed at assessing TLF at one year with the MedJ-01 stent in a Japanese patient population to show non-inferiority of JNIR01 Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12}.

5.3 Claims and Intended Performance of the Investigational Device

The MedJ-01 Ridaforolimus Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with heart disease including angina (stable or unstable), silent ischemia, NSTEMI, or recent subacute STEMI due to lesions in vessels with reference diameters of 2.50 mm to 4.25 mm including complex lesions.

5.4 Risks and Anticipated Adverse Device Effects That Are to Be Assessed

The risks and anticipated adverse device effects (ADE) are summarized in Section 14.6 as well as the IB. All ADEs will be assessed by collection of adverse events which will be determined by the investigator as either being related to the device or not.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 General

6.1.1 Description of Trial

The JNIR Trial will enroll approximately 100 subjects with a wide spectrum of PCI indications (stable angina as well as ACS, including subacute STEMI (>72 hours since first hospital presentation).

This is a prospective, multi-center, single-arm, open label clinical trial. Lesions planned to be treated must be declared and recorded at time of enrollment.

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. 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 evaluate new stents.

The present trial is therefore aimed at assessing TLF at one year with the MedJ-01 stent in a Japanese patient population to show non-inferiority of JNIR01 Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12}.

The rationale for selection of TLF as the primary endpoint is based on recent US trials of best in class DES (Xience V, Promus Element and Resolute) including SPIRIT III, SPIRIT IV, PLATINUM, RESOLUTE US, RESOLUTE ALL-COMERS, TWENTE, COMPARE, and COMPARE II.

6.1.3 Primary and Secondary Endpoints

6.1.3.1 Primary Endpoint

The primary endpoint is Target Lesion Failure (TLF) at 12 months defined as the composite of cardiac death, target vessel-related myocardial infarction (MI), or ischemia-driven target lesion revascularization (TLR).

Definitions of terms and endpoints are located in Section 21.1. Acronyms and abbreviations are defined in Section **Error! Reference source not found.**.

6.1.3.2 Clinical Secondary Endpoints

The secondary endpoints are to be evaluated at 30 days, 6 months, and 1, 2, 3, 4, and 5 years except as noted:

- Device, Lesion, and Procedure Success at time of baseline procedure
- TLF at 30 days, 6 months, and 2, 3, 4, and 5 years defined as the composite of cardiac death, target vessel-related MI, or ischemia-driven TLR.
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR)
- Target vessel failure (TVF; the composite rate of death, target vessel related MI or ischemia-driven TVR)
- 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 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 3.
After discharge from the hospital, each subject will be followed with in-clinic or phone follow-up visits at 30 days, 6 months, and 1, 2, 3, 4, and 5 years. The 1-year follow-up will be conducted in-clinic unless the patient refuses to or cannot come to clinic.

Table 3: Schedule of Data Collection

TYPE OF DATA TO BE COLLECTED	Screening (within 7 days[1])	Pre-Procedure (within 24 hours)	Baseline Procedure	Post-Procedure	30 days (± 7 days)	6 Months (± 30 days)	1 year (-30 days / +14 days)[2]	2 years (± 60 days)	3 year (± 60 days)	4 year (± 60 days)	5 year (± 60 days)	Unscheduled visits
Patient Informed Consent	✓											
Patient Medical/Clinical History	✓											
Angina Status	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
General Eligibility Criteria	✓											
Angiographic Eligibility Criteria			✓									
Clinical Laboratory Tests:												
Pregnancy Test (childbearing potential women only)	✓											
CBC, Creatinine, BUN	✓											
Lipid profile[3]	✓											
CK, CK-MB or Troponin		✓[4]		✓[5]								✓[6]
12-Lead ECG		✓		✓			✓[2]					✓[6]
Coronary Angiogram & PCI			✓									
Enrollment and Study Stent Information			✓									
Per Protocol DAPT Medications[7]		✓	✓	✓	✓	✓	✓					
DAPT Medications								✓	✓	✓	✓	✓
Concomitant Cardiac Medications[8]		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Events Monitoring		✓[9]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

1. Subjects who undergo angiography following screening within 7 days but cannot proceed directly to enrollment (ie, undergo target PCI) can be enrolled within 30 days of the initial screening without reconsenting the patient and repeating screening procedures unless clinically indicated. 24 hr preprocedure angina status, cardiac enzymes, and ECG need to be repeated. In cases where target PCI is performed within 24-72 hrs. from non-target PCI, serial enzymes need to be obtained as detailed in inclusion criteria 3c.
2. In-clinic visit at 1-year follow-up and ECG may be waived if subject refuses to return to clinic or is unable to return. A telephone visit should then be conducted in lieu of a clinic visit.
3. Lipid profile is strongly recommended.

4. Within 24 hours pre-procedure. For subjects with ACS, enzyme levels need to be within 8 hours of the procedure or have already been shown to be decreasing. For subacute STEMI patients enzyme levels must have peaked for either CK-MB or Troponin (I or T) or both. High sensitivity troponin assays (hsTrop) are acceptable if non-hsTrop and CK-MB are not available at the local hospital.
5. 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
6. CK and CK-MB or Troponin (I or T) and ECG should be obtained for all suspected ischemic events. CK-MB is preferred but at sites where CK-MB is not available Troponin I or T may be used.
7. Clopidogrel 75 mg daily or prasugrel 2.5 to 3.75 mg daily must be given for a minimum of 12 months according to national guidelines and standard of care as well as aspirin 81 to 100 mg daily to be taken indefinitely.
8. 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).
9. Adverse events that occur after informed consent has been obtained will be recorded.

6.1.4.1 Screening and Pre-Procedure

Subject preparation will occur in accordance with standard hospital policy for the care of interventional cardiology patients. Once screening has determined that a patient meets the general inclusion and exclusion criteria, written informed consent will be obtained according to Section 13.

Subject information will include the following. Refer to Section 21.1 for definitions.

- Demographics (e.g., age, gender, height, weight)
- Risk factors (dyslipidemia, hypertension, family history of premature coronary disease, tobacco use, alcohol use and diabetes)
- Cardiac history (previous MI, intervention history, and past angina status according to CCS and Braunwald classifications)
- Current angina status
- General eligibility criteria
- Per-protocol DAPT medications
- Concomitant cardiac medication by category
- Adverse events that occur after informed consent has been obtained
- Assurance that informed consent has been obtained correctly

Subjects who undergo angiography following screening within 7 days but cannot proceed directly to enrollment (i.e., undergo target PCI) can be enrolled within 30 days of the initial screening without reconsenting the patient and per the following:

- Repeating screening procedures is not required, unless clinically indicated.
- 24 hr. pre-procedure angina status, cardiac enzymes, and ECG need to be repeated.
- In cases where target PCI is performed within 24-72 hrs. of non-target PCI, serial enzymes need to be obtained as detailed in inclusion criteria 3c.

6.1.4.2 Pre-Procedure Laboratory Assessments

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

Required within 7 days prior to procedure:

- Complete Blood Cell Count (CBC): RBC, WBC, hemoglobin, hematocrit, platelet
- Creatinine, BUN

  Calculated creatinine clearance <30 mL/min using Cockcroft-Gault equation:

  - Male: Ccr = {(140 – age) x weight (kg)}/{72 x serum creatinine level (mg/dL)}
  - Female: Ccr = 0.85 x {(140 – age) x weight (kg)}/{72 x serum creatinine level (mg/dL)}
- Pregnancy test (if applicable)

  If following angiography non-target PCI is performed but the subject cannot proceed directly to enrollment (ie, perform target PCI) the subject may be enrolled within 30 days of the initial screening without repeating the above tests.

Strongly recommended within 7 days prior to procedure:

- Lipid profile (total cholesterol, LDL, HDL, triglycerides)

  If following angiography non-target PCI is performed but the subject cannot proceed directly to enrollment (i.e., perform target PCI) the subject may be enrolled within 30 days of the initial screening without repeating the above tests.

Required within 24 hours pre-procedure:

- Electrocardiogram (ECG) (See the trial's Site Binder for ECG Core Lab Guidelines)
- Current angina status
- 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
- If following angiography non-target PCI is performed but the subject cannot proceed directly to enrollment (i.e., perform target PCI) the subject may be enrolled within 30 days of the initial screening BUT THE ABOVE WITHIN 24 HR PROCEDURES MUST BE REPEATED WITHIN 24 HRS. OF ENROLLMENT.

6.1.4.3 Baseline Procedure

- Angiographic eligibility criteria
- Enrollment and study stent information
- Target lesion location
- Non-target vessel treatment, if applicable
- Anticoagulation administration
- Procedural complications

- Per-protocol DAPT medications
- Adverse events

6.1.4.4 Post-Procedure and Discharge

- 12 lead ECG
- Angina status
- All adverse events, including related laboratory tests results and details of any subsequent repeat coronary angiography and results of such, if applicable
- Per-protocol DAPT medications
- 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 in Table 4 below:

Table 4: Patient Status as Indicated by Biomarker Levels post-PCI

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. 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 and/or	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 8.6 ng/L to 70 ng/L

6.1.4.5 30 Days (± 7 days) and 6 Months (± 30 days) Follow-up (in clinic or telephone visit)

- Angina status
- All adverse events including 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 1 year (- 30 Days / + 14 Days) Follow-up (in-clinic)

- Angina status
- All adverse events including 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
- 12 Lead ECG

Note: For subjects who refuse or cannot return to clinic for the 1 year visit, a telephone visit may be conducted in lieu of an in-clinic visit.

6.1.4.7 2, 3, 4, and 5 Year (± 60 days) Follow-up (in clinic or telephone visit)

- Angina status
- All adverse events including 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)
- Use and changes in chronic antiplatelet medications. Data are collected for the duration of the trial
- Concomitant cardiac medication by category

6.1.4.8 Additional (Unscheduled) Follow-up Visits

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

- Data regarding all adverse events including 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

The Angiographic Core Lab will perform a qualitative and quantitative coronary analysis (QCA) (Pie Medical CAAS Workstation v. 5.11.2 Software) assessment of all target lesions pre-procedure, post-procedure. 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.

6.1.6 Procedures for the Replacement of Subjects

Discontinued subjects will not be replaced. De-registered subjects will not count towards the sample size of approximately 100 subjects and will not be included in the FAS but will be included in the safety analysis set and will be followed until resolution of any adverse events related to study procedures.

6.2 Investigational Device

6.2.1 Description of the Exposure to the Investigational Device

All subjects will have a single treatment which is the study stent implantation at baseline procedure. The stent will remain implanted throughout the duration of the follow-up period.

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, contrast media, nitroglycerin, and relaxants are used. After the procedure, the subjects will receive DAPT for a minimum of 12 months (see Section 6.4.9.3) according to national guidelines and standard of care 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 Investigational Devices to Be Used

Each subject will receive at least one MedJ-01 stent. A subject can receive up to two stents per major coronary artery in a maximum of two major coronary arteries (A major coronary artery is defined as LAD, LCX, or RCA and their respective branches. The Ramus Intermedius is defined as a branch of the LCX). The total length of planned study stenting cannot exceed 100 mm.

6.3 Subjects

The Trial population will consist of approximately 100 male and female subjects undergoing PCI for angina (stable or unstable), silent ischemia, non ST elevation MI (NSTEMI), or recent ST elevation MI (STEMI >72 hours prior to enrollment and stable- subacute).

Complex lesions are allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy (e.g.: Rotablator System) and Directional Coronary Atherectomy, DCA) are allowed), presence of thrombus that is non-occlusive and does not require thrombectomy, CTO, bifurcation lesions (except planned dual stent implantation), ostial RCA lesions, tortuous lesions, bare metal stent restenotic lesions, protected left main lesions. A maximum of two target vessels, with a maximum of two study stents per vessel or individual lesion length are allowed.; however, the total planned study stenting in the coronary tree cannot exceed 100 mm .

Subjects must sign an IRB 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.

6.3.1.1 General Inclusion Criteria

1. Age ≥ 20 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 subacute STEMI. For subacute STEMI the time of presentation to the first treating hospital, whether a transfer facility or the study hospital, must be >72 hours prior to enrollment and enzyme levels (CK-MB or Troponin) demonstrating that either or both enzyme levels have peaked.
3. Non-target vessel PCI are allowed prior to enrollment depending on the time interval as follows:

    a. During Baseline Procedure:

        i. 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:

        i. 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 vessel 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:

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

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

6.3.1.2 Angiographic inclusion criteria (visual estimate)

5. Target lesion(s) must be located in a native coronary artery with visually estimated diameter of ≥2.5 mm to ≤4.25 mm.
6. Complex lesions are allowed including calcified lesions (lesion preparation with scoring/cutting and rotational atherectomy (e.g.: Rotablator System) and Directional Coronary Atherectomy, DCA) are allowed), presence of thrombus that is non-occlusive and does not require thrombectomy, CTO, bifurcation lesions (except for planned dual stent implantation), ostial RCA lesions, tortuous lesions, bare metal stent restenotic lesions, protected left main lesions.
7. Overlapping stents are allowed with the investigational device (MedJ-01).

6.3.2 Exclusion Criteria for Subject Selection

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

6.3.2.1 General Exclusion Criteria

1. STEMI within 72 hours (subacute) 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 12 months (including planned surgeries that cannot be delayed).
9. Subject has an indication for chronic oral anticoagulant treatment (with either vitamin K antagonists or novel anticoagulants-NOACs
10. Calculated creatinine clearance <30 mL/min using Cockcroft-Gault equation
11. Hemoglobin <10 g/dL.
12. Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3.
13. White blood cell (WBC) count <3,000 cells/mm^3.
14. Clinically significant liver disease.
15. Active peptic ulcer or active bleeding from any site.
16. Bleeding from any site within the prior 8 weeks requiring active medical or surgical attention.
17. If femoral access is planned, significant peripheral arterial disease which precludes safe insertion of a 6F sheath.
18. History of bleeding diathesis or coagulopathy or will refuse blood transfusions.
19. Cerebrovascular accident or transient ischemic attack within the past 6 months, or any permanent neurologic defect attributed to CVA.
20. Known allergy to the study stent components, whether in the MedJ-01 e.g. cobalt, nickel, chromium, Carbosil®, PBMA, or limus drugs (ridaforolimus, zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative or similar compounds).
21. Known allergy to protocol-required concomitant medications such as aspirin, or DAPT (drugs that inhibit P2Y12 such as clopidogrel, prasugrel), or heparin, or iodinated contrast that cannot be adequately pre-medicated.
22. 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).
23. Patient is participating in any other investigational drug or device clinical trial that has not reached its primary endpoint or plans to participate in any clinical trial.
24. Women who are pregnant or breastfeeding (women of child-bearing potential, defined as females of childbearing potential if they have not undergone a permanent contraceptive operation or they are not postmenopausal, must have a negative pregnancy test within one week before treatment. Permanent contraceptive operation is defined as: hysterectomy, hysterosalpingectomy, or bilateral oophorectomy. The status of a female should be

considered as postmenopausal when she has not had a period for 12 consecutive months without an alternative medical cause).

25. 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).
26. Patient has received an organ transplant or is on a waiting list for an organ transplant.
27. Patient is receiving or scheduled to receive chemotherapy within 30 days before or any time after the baseline procedure.
28. Patient is receiving oral or intravenous immunosuppressive therapy or has known life-limiting immunosuppressive or autoimmune disease (e.g., HIV). Corticosteroids are allowed.

6.3.2.2 Angiographic Exclusion Criteria (visual estimate)

29. Target lesions in more than two (2) major coronary arteries (ie, two of LAD, LCX, RCA) and their respective branches. (The Ramus Intermedius is defined as a branch of the LCX).
30. More than two target lesions per target vessel are planned (two lesions separated by less than 10 mm that can be covered by a single stent are considered as one lesion).
31. More than 100 mm length of planned study stenting in the entire coronary tree.
32. Occlusive thrombus and/or a thrombus requiring thrombectomy in a target vessel.
33. Unprotected left main lesions ≥30%, or planned unprotected left main intervention.
34. Ostial LAD or LCX lesions (stenting of any diseased segment within 5 mm of the unprotected left main coronary artery).
35. Bifurcation lesionswith planned dual stent implantation.
36. Stenting of lesions due to DES restenosis.
37. 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.
38. Target lesion exists in bypass graft vessels.

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 IRB 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.

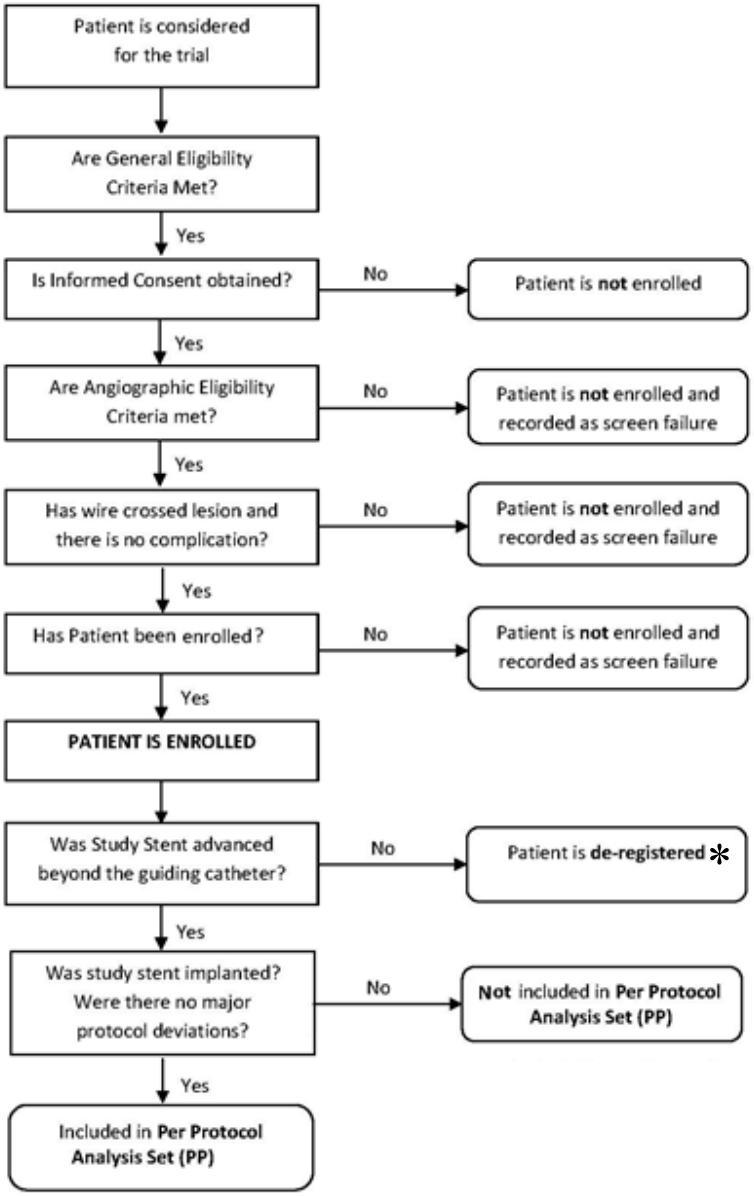
6.3.3.3 Follow-up for Withdrawn Subjects

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

Patients will be screened and consented for enrollment prior to any sedation. Patients may be consented prior to diagnostic angiography with possible PCI intervention as well as prior to a planned PCI procedure. **Once a patient has signed an informed consent, met all general and angiographic eligibility criteria, and a guidewire has successfully been passed beyond the target lesion, the patient will be considered enrolled in the trial** (refer to instructions for de-registration in the trial's Site Binder). If the study stent could not be implanted due to reasons that are not related to study device,, the study subject will be de-registered from the trial and will not be analyzed as part of the full analysis set (FAS).

The screening and enrollment process is displayed in Figure 5 **Error! Reference source not found.**.



*: refer to 6.4.3 Enrollment

Figure 5: Screening and Enrollment Flow Chart

The trial will enroll patients for whom a decision to undergo PCI has already been made. In the case CABG-eligible conditions, it is recommended that a heart team be consulted in the decision of whether the patient should undergo CABG or PCI.

6.3.5 Total Expected Duration of the Clinical Investigation

The clinical investigation will last from Q1 2016 until approximately Q3 2021.

6.3.6 Expected Duration of Each Subject's Participation

Each subject will remain in the clinical investigation for approximately 5 years from the time of the study stent implantation until the last follow-up office visit or 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

Based on the statistical assumptions described in section 7 enrollment of 100 subjects will provide **80% power** expecting a 5% loss to follow up.

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 trial's Site 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. A 6 French or larger guide catheter must be used 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 enrollment.

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:

During Baseline Procedure: The non-target vessel PCI must be successful and uncomplicated before enrollment of the subject into the trial and proceeding with enrollment. 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 vessel PCI can be performed 24 to 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. 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 enrollment 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 enrollment whether successful and uncomplicated or not.

Table 5: 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 Enrollment

Enrollment will occur after the angiographic eligibility criteria have been determined to be met and the lesion has been successfully crossed with the wire without complication.

A subject will be de-registered from the trial in case the study stent could not be implanted due to reasons that are not related to study device (for example, the lesion was not properly prepared for stenting).

6.4.3.1 De-registered Subjects

In case of de-registration, the de-registered subjects will be followed until resolution of any adverse event related to study procedures (refer to instructions for de-registration in the trial's Site Binder).

6.4.4 Staged Procedures

All target lesions must be planned to be treated during the baseline procedure. The investigator will declare which target lesions are intended for treatment at the time of enrollment. In the event all target lesions cannot be treated (for example, due to contrast load), planned

staged procedures of target lesions are allowed but must be declared immediately post baseline procedure. Staged procedures should be performed using the assigned stent. All staged procedures should be performed within six weeks of the baseline procedure. All follow-up visits are to be scheduled from the date of enrollment.

6.4.5 Pre-Dilation of Target Lesion(s)

Pre-dilation is recommended but not required. It should be performed, per local clinical practice. An angioplasty balloon, cutting balloon, angiosculpt scoring balloon, or atherectomy (including DCA) 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.

6.4.6 Study Stent Use

Prior to use, the study stent will be inspected and prepared according to the applicable Instructions for Use. **Note**: Refer to the MedJ-01 IFU in the trial's Site Binder.

- There is no limit to individual lesion length. However, the total planned stenting in the coronary tree cannot exceed 100 mm. A maximum of two target vessels may be treated with study stents with a maximum of two lesions per vessel. Two lesions separated by less than 10 mm that can be covered with a single stent are considered as one lesion
- If more than one target lesion is treated, all lesions must receive the study stent.
- 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 with the investigational device (MedJ-01). 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.

6.4.7 Treatment Failures and Device Malfunctions of the MedJ-01

In case of failure to deliver a 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 (including DCA) 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 MedJ-01 malfunctions will be documented on the appropriate CRF. The MedJ-01 should be returned to Medinol for analysis and be reported in the clinical results. Instructions for returning the MedJ-01 are included in the trial's Site Binder. Treatment failures or device malfunctions should be reported in the CRF within 24 hours, per the instructions of EDC completion.

6.4.8 Bail-out Stenting Procedures

Bailout stenting may be performed at the operator's discretion. If a bailout stent is required, a MedJ-01 stent of an appropriate diameter and length must be used. If a MedJ-01 stent of appropriate length and diameter is not available, an approved coronary stent should be used, preferably a second generation DES.

6.4.9 Concomitant Medications

6.4.9.1 Pre-Procedure (Loading) Anti-Platelet Medication

Loading doses of anti-platelet medications should be administered pre-procedure in all patients as shown in **Error! Reference source not found.**6.

Table 6: Pre-Procedure Anti-Platelet Medication Regimen

Agent	Instructions
Clopidogrel	A loading dose of clopidogrel ≤300 mg must be administered at least 6 hours prior to PCI, as per standard of care. For subjects who are already on chronic clopidogrel therapy of 75 mg (≥4 days), a loading dose should not be required at the investigator's discretion.
OR Prasugrel	Prasugrel can be used in place of clopidogrel at the investigator's discretion. A loading dose of prasugrel 20 mg must be administered on the day of PCI. For subjects already on chronic prasugrel therapy of 3.75 mg a day (or 2.5 mg if dose reduction is considered necessary for subjects) for ≥5 days a loading dose of prasugrel 20 mg should not be required at the investigator's discretion.
Aspirin	All subjects already taking daily chronic aspirin therapy should receive 81-162 mg or dose per standard hospital practice before the procedure. Subjects not already taking daily chronic aspirin therapy should receive 81-325 mg (or dose per standard hospital practice) preferably at least two hours before the procedure.

6.4.9.2 Anticoagulation during Baseline Procedure

PCI should be performed with adequate anticoagulation. Unfractionated heparin (UFH) may be used according to local standards.

6.4.9.3 Post-Procedure Anti-Platelet Medication

Dual anti-platelet therapy should be instituted post procedure in all patients as shown in **Error! Reference source not found.**7. **All subjects are required to have clopidogrel/prasugrel administration for a minimum of 12 months according to national guidelines (Guidelines for elective percutaneous coronary intervention in patients with stable coronary disease (JCS 2011)** [8]**) and standard of care as well as aspirin administration indefinitely unless an intervening medical necessity occurs such as severe bleeding.**

Table 7: Post-Procedure Anti-Platelet Medication Regimen

Agent	Instructions
Clopidogrel	All subjects who receive a study stent will be treated for a minimum of twelve months of clopidogrel (75 mg/day) according to national guidelines and standard of care. At least 12 months following stent implantation is recommended per the JCS guidelines for elective percutaneous coronary intervention [8].
OR Prasugrel	Prasugrel 3.75 mg/day can be used in place of clopidogrel at the investigator's discretion. In subjects considered to require dose reduction by their conditions (body weight (<50 kg), age, renal function, and other risks), prasugrel should be given at a dose of 2.5 mg/day.
Aspirin	Subjects with no aspirin resistance, allergy, or bleeding risk should continue on aspirin (minimum of 81 mg/day and up to 162 mg/day or dose per standard hospital practice) indefinitely, in accordance with the JCS PCI recommendations and the JCS guidelines. Low-dose aspirin (≤100 mg/day) is preferred in all patients.

6.4.10 Activities Performed by Sponsor Representatives

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

6.4.11 Known or Foreseeable Factors That May Compromise the Outcome

Factors that may compromise the outcome are lack of enrollment, 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 IRB 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, IRB 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, investigational device usage, clinical investigation plan requirements, 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 investigational 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

Overview of Statistical Approach

JNIR will be a single arm study enrolling Japanese patients with similar inclusion and exclusion criteria to the pivotal randomized BIONICS study. The primary endpoint of Target Lesion Failure will be the primary endpoint for the analysis. In order to ensure comparison of similar patients across these two populations a propensity-score matched analysis will be perfomed on both clinical and angiographic parameters. To maximize power and take advantage of the large BIONICS study, 4:1 matching will be done.

7.1 Target groups of Analysis

Target, ITT, and FAS population

Investigators will treat 100 Japanese patients (JNIR) with BIONIR, and compare event rates to a previous study population (BIONICS) carried out in Europe, Israel, and North America. The primary end point will be Target Lesion Failure (TLF) in the Full Analysis Set (FAS) population contains all enrolled Japanese patients regardless of whether they were given the BIONIR stent,

while the as-treated (AS) population contains only those Japanese patients who received the study stent. By definition, the (AS) population cannot be larger than (FAS).

7.2 Analysis of Efficacy

7.2.1 Primary Endpoint

Primary Endpoint hypothesis
This trial measures the non-inferiority of JNIR Target Lesion Failure at 12 months (TLF_{12}) to the BIONICS TLF_{12}.

The trial defines the statistical null hypothesis as

H_{Null}: TLF_{12} (JNIR) > TLF_{12} (BIONICS) + δ
$H_{Alternative}$: TLF_{12} (JNIR) ≤ TLF_{12} (BIONICS) + δ

or in terms of absolute event-rate difference

H_{Null}: TLF_{12} (JNIR) - TLF_{12} (BIONICS) > δ
$H_{Alternative}$: TLF_{12} (JNIR) - TLF_{12} (BIONICS) ≤ δ

where δ is the margin of non-inferiority.

Measured statistic
Farrington-Manning methodology estimates the difference in TLF_{12} as

$$\tau = \frac{\text{TLF12 (JNIR)} - \text{TLF12 (BIONICS)} - \delta}{\sqrt{\frac{\text{TLF12 (JNIR)}[1 - \text{TLF12 (JNIR)}]}{N(\text{JNIR})} + \frac{\text{TLF12 (BIONICS)}[1 - \text{TLF12 (BIONICS)}]}{N(\text{BIONICS})}}}$$

where $N(x)$ is the number of x patients.

Propensity-score matching
Propensity score matching will identify a covariate-unbiased population of patients between the JNIR and BIONICS patient population. The probability a patient (x) belongs to JNIR versus BIONICS, conditional on set of potential confounding covariates (C), defines the propensity score $\rho(x \mid C)$. Logistic regression will model this probability as

$$\rho(x \mid C) = \text{logit}^{-1}\left(\sum_{c \in C} c\right)$$

where $\text{logit}^{-1}(x) = \frac{1}{1+e^{-x}}$.

We will match patients from JNIR to patients from BIONICS using the following covariates known to confound the relationship between study-stent and outcome:

<u>Covariates considered in propensity-score matching:</u>
<u>Clinical Parameters</u>:
Age
Gender
Prior MI

Diabetes Mellitus
Prior Revascularization
Acute Coronary Syndrome
Angiographic Parameters:
Diameter Stenosis
Reference Vessel Diameter
Calcification
TIMI Flow (Pre-procedure)
Tortuosity
SYNTAX Score
Lesion located at LAD

After each patient in both JNIR and BIONICS has received a propensity score, these two groups will be combined and partitioned into propensity score quintiles.
Finally, we will match each JNIR patient in quintile x with a random BIONICS patient from the same quintile x. If no remaining BIONICS patients are left to match with JNIR patients in one of the five quintiles, we use the next closest quintile to choose a BIONICS patient.

7.2.2 Secondary Endpoint

Clinical Secondary Endpoints to be evaluated at 30 days, 6 months, and 1, 2, 3, 4 and 5, except as noted:

- Device, Lesion, and Procedure Success at time of baseline procedure
- TLF at 30 days, 6 months, and 2, 3, 4 and 5 years defined as the composite of cardiac death, target vessel-related MI, or ischemia-driven TLR.
- Major adverse cardiac events (MACE; the composite rate of cardiac death, any MI or ischemia-driven TLR)
- Target vessel failure (TVF; the composite rate of death, target vessel related MI or ischemia-driven TVR)
- All-cause mortality
- Cardiac death
- Myocardial Infarction
- Target Vessel Related MI
- Ischemia-driven TLR
- Ischemia-driven TVR
- Stent Thrombosis (ARC definite and probable)

Analyses of secondary clinical endpoints will be performed on the FAS group.

Data will be summarized with patient counts, percentages, and exact 95% confidence intervals. Treatment group differences will be summarized with 95% confidence intervals.

The secondary endpoints (with the exception of angiographic in-stent late loss) will not be formally tested for non-inferiority and testing will be considered descriptive.

See further details in the Statistical Analysis Plan.

7.3 Analysis of Safety

All adverse events collected will be coded using MedDRA, to preferred term and system organ class and summarized for the Safety Analysis Set and de-registered subjects. AEs will be summarized showing the number of events and the number of patients with each event.

A by-patient listing of (serious) adverse events / UADE, including identification of the event by investigator term, date and time started, intensity, relationship to study drug, action taken, and date and time resolved, will be presented in the data listings.

A by-patient listing of deaths will be presented.

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.

Device malfunction/deficiencies and any (serious) adverse events associated with device malfunction/deficiencies will be tabulated by treatment arm and overall. All randomized subjects, including de-registered subjects, will be included in the analysis.

7.4 Other subjects related to statistical analysis

1) Handling of Missing Values and Outlier

1. Missing values

   Handling of the missing values is indicated in the Statistical Analysis Plan. Final decision will be made at the Case Review Meeting.

2. Outlier

   Outlier is not expected in the plan. The effect of the outlier to the analysis will be reviewed when necessary.

2) Change of Data

If bias of data distribution is found, appropriate data will be used instead when necessary.

3) Interim Analysis

No interim analysis will be performed in this trial.

4) Handling of the bail-out lesion

Stents used for bail-out will be included in efficacy and safety analysis.

5) Others

When necessary, additional exploratory analysis will be performed.

7.5 Sample Size Considerations

Power

The Farrington-Manning test, with a TLF_{12} event-rate of 0.058, margin of 0.05, Type I error α of 0.10, and propensity-score matching 1 JNIR to 4 BIONIC patients provides enrollment of 100 subjects will provide 80% power expecting a 5% loss to follow up. We derive the 0.058 event rate from a sample-weighted average of the same 8 related trials used to design BIONICS: SPIRIT (III/IV), PLATINUM, RESOLUT (All Comers / US), TWENTE, and COMPARE (I/II). A margin of 0.05 (5%) , 1.5 times that of BIONICS, leverages a reasonable clinical threshold with safety concerns over sample size. Likewise, propensity-score matching every one JNIR patient to 4 BIONICS patients allows higher power without a higher burden on enrollment.

8 DATA MANAGEMENT

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

Medidata will provide Rave electronic data capture (EDC) system for the trial. The sites are responsible for completing the clinical electronic CRF (eCRF) from Rave. The data cleaning routines are performed during data entry through automatic edit checks that occur during data entry by the sites into Rave. The auto-queries are generated by Rave 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 can create manual queries on data as well for the sites to review. Rave 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 standard reports from Rave. Data listings needed for data review are created outside of Rave. Please see the separate Data Management Plan for specific details.

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

Rave EDC system hosted by Medidata will be programmed and maintained by Quintiles DM. Rave EDC system will enforce restricted access control mechanisms under the management of Quintiles CPM. 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 via SAS on Demand function in Rave 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 IRB, or other regulatory agencies.

The Investigator will be notified by the Sponsor of the date of marketing approval or discontinuation of the trial. 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 21.1.

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

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

In accordance with the investigational site IRB requirements, the Investigator will (a) advise the IRB of the progress of this trial on a regular basis until trial completion. The head of medical institution will (b) obtain written IRB 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 IRB 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 IRB 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. 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 IRB of the clinical investigational plan amendment. For changes involving subject care or safety the Primary Investigator is responsible for obtaining IRB 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 IRB 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 IRB 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 IRB 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 IRB of clinical investigational plan deviations in accordance with their specific IRB 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 Investigational Product Accountability

The Sponsor will ship the MedJ-01 to the Primary Investigator (or designee) at each site. The Primary Investigator will maintain adequate records of the receipt and disposition of the MedJ-01 on the device inventory log or case report form (CRF), including stent size/dimensions; date implanted; subject identification number; and implanting Investigator. The Inventory Accountability Report must document the disposition of all investigational devices including those that have been returned to the Sponsor. Use of any investigational device outside of the clinical investigation plan (e.g. compassionate use) is strictly forbidden and may constitute grounds for removal of the Investigator/Site from the trial.

11.2 Investigational Product Return

Investigators will be notified in writing of enrollment completion. All unused MedJ-01 products must be returned to the Sponsor when enrollment is complete according to the returned goods process. All MedJ-01 or any remaining components that are associated with a device malfunction must be returned to the Sponsor.

12 STATEMENTS OF COMPLIANCE

The trial will be conducted in compliance with the Japanese Drug Medical Device Law Act 23.2.5 Part 3 and Act 80.2, and MHLW Ministerial Ordinance No. 36, Mar 23, 2005 (GCP of Medical Device), Article 273 and Article 274, Part 2, 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/favorable opinions from the respective regulatory authority and IRB have been obtained. Any additional requirements imposed by the respective regulatory authority and/or IRB will also be followed, where specified.

All subjects must provide written informed consent in accordance with the site's IRB, using an IRB-approved informed consent form. The final eligibility for the trial will be 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 the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the patient. If the patient agrees to participate, the informed consent form must be signed and personally dated by the patient or legally authorized representative. The Investigator/designee must also sign the informed consent form prior to patient enrollment. Any

additional persons required by the site's IRB 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

CIP-specific procedures or alterations of patient care must not be performed until the prospective subject has provided a signed informed consent. The informed consent will be in the prospective subject's native language and will contain non-technical language to describe the investigational 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 to determine general eligibility, 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. Local IRB regulations regarding obtaining informed consent must be followed. 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 IRB requirements, using an IRB-approved informed consent form. **Error! Reference source not found.** 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.

In case that study coordinators are involved in obtaining the informed consent, the study coordinators must co-sign on the informed consent form.

14 ADVERSE EVENTS, ADVERSE DEVICE/DRUG EFFECTS, AND DEVICE DEFICIENCIES

All definitions for adverse events, adverse device effects, and device deficiencies are taken from Ministerial Ordinance on Good Clinical Practice for Medical Devices (MHW Ordinance No. 36, 2005, Devices-GCP), and Pharmaceutical and Medical Device Act, Enforcement Regulations. A summary of adverse events and adverse device effects is shown in **Error! Reference source not found.**8.

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 and drug constituting the medical device.

This definition includes events related to the investigational medical device and drug constituting the 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.

However, symptoms that are not associated with aggravation of primary disease or complications prior to usage of medical device and hospitalization that is planned prior to usage of medical device are not defined as adverse events.

14.1.2 Adverse Device/Drug Effect (ADE)

An ADE is an adverse event (untoward medical occurrence) that is related to the investigational device and drug constituting the medical 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/Drug 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/Drug 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/Drug 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 8: Categories of Adverse Events

<table>
<tr><th>Adverse Events</th><th>Non-device related</th><th colspan="2">Device-, Drug- or procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)[a]</td><td colspan="2">Adverse Device/Drug Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)[b]</td><td colspan="2">Serious Adverse Device/Drug Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device/Drug Effect (ASADE)</td><td>Unanticipated Serious Adverse Device/Drug Effect (USADE)</td></tr>
<tr><td colspan="4">a Includes all categories
b Includes all categories that are serious</td></tr>
</table>

14.4 Time Period in Which the Investigator Shall Report All AE and Device Deficiencies to the ICCC (Quintiles)

Each complication meeting the definition for SAE or device deficiency will be reported upon discovery to the ICCC (Quintiles) and within 24 hours of the Investigator's knowledge of the event. The Investigator will further report the event or device deficiency to the IRB according to the institution's IRB 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 and drug constituting the 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/drug effects and cardiac related serious adverse events will be collected and monitored throughout the entire course of the trial. Non-cardiac SAEs and AEs will be collected and monitored throughout the trial, i.e. until 5 years from enrollment.

14.5.2 Reporting USADE

If the Investigator determines that an adverse event meets the definition of an unanticipated adverse device/drug 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 IRB according to the institution's IRB reporting requirements. If the relationship of the unanticipated effect to the investigational device/drug 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 investigational device.

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

- NOT RELATED: The event is clearly not related to the investigational device/procedure/drug.
- UNLIKELY RELATED: The event is unlikely to be related to the investigational device/ procedure/drug.

- POSSIBLY RE LATED: The event is possibly related to the investigational device/ procedure/drug.
- RELATED: The event is clearly related to the investigational device/ procedure/drug.

AEs that were classified as "RELATED" and "POSSIBLY RELATED", or undetermined relationship to the study device / drug are considered "related", and are classified as adverse reactions. "UNLIKELY RELATED" and "NOT RELATED" events are regarded as AEs that can be denied a causal relationship to the study device / drug, that will be handled as "not related to study device / drug" for reporting purposes.

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 **Error! Reference source not found.**9. These events as well as mitigation or treatment are also included in the IB.

Table 9: 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 **Error! Reference source not found.**10. 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 MedJ-01. The Aes are included here for completeness.

Table 10: Foreseeable AE and ADE for Ridaforolimus

Anemia	Hypertriglyceridemia	Pyrexia
Dehydration	Mucosal inflammation	Renal failure acute
Diarrhea	Nausea	Stomatitis
Febrile neutropenia	Pneumonia	Thrombocytopenia
Hyperglycemia	Pneumonitis	Vomiting

14.7 List of Foreseeable Device Deficiencies

Foreseeable device deficiencies based on years of clinical experience with rapid exchange DES implantation are summarized in **Error! Reference source not found.**11. These events as well as mitigation or treatment are also included in the IB.

Table 11: Foreseeable Device Deficiencies for DES Implantation

Failure to deliver the stent to the intended site	Balloon burst, tear
Stent deform, migration, dropout, tear	Balloon expansion defect, deflation defect
Stent expansion defect	Shaft breakage, damage
Stent compression	Failure to insert the catheter or pull it out
Stent misplacement	

14.8 Emergency Contact Details for Reporting SAE and SADE

When sites encounter trouble related to SAE reporting (e.g. when having trouble entering/submitting SAE related information on EDC or having trouble sending SAE form by fax while EDC is down due to technical trouble) please use the following methods to contact Quintiles Safety:

* Please note that the contact information below should not be used to report the actual SAE.

Contact Quintiles Safety by phone during business hours from Monday through Friday from 9AM to 5PM.

- Phone: 03-6859-9603

Contact Quintiles Safety by e-mail out of business hours.

- Email: qjpnsafety@quintiles.com

14.9 Information Regarding the DSMB

The Data Safety Monitoring Board (DSMB) is comprised of at least three 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.

14.10 Adjudication of Clinical Endpoints

The Clinical Event 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 21.1.

14.10.1 Death

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

14.10.2 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.

14.10.3 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.

14.10.4 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.

14.10.5 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.

14.10.6 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.

14.10.7 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 JNIR Trial.

16 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

There is no expectation that the JNIR 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.

18 COMPENSATION FOR HEALTH HAZARD

1) Sponsor will compensate the subject based on the clinical trial insurance policy set when any kind of health hazard occurred due to the trial, except the case where the cause of the health hazard can be proved to be totally unrelated to the trial.

2) When health hazard occurred due to the trial which lead to the subject to dispute with a third party, or likely lead to a dispute, clinical site and sponsor will discuss to support the subject to find a solution.

3) The clinical trial insurance of the sponsor will be responsible for the indemnity liability caused by the health hazard of the trial except the case where the clinical site is found to be responsible.

4) Sponsor will be responsible according to applicable law and regulation for the compensation caused by the health hazard of the trial according to the clinical trial insurance.

5) Sponsor has to take measures such as preparing insurance to ensure sponsors legal liability.

19 PRIVACY POLICY

Identifying code will be assigned to each subject in the Case Report Form in order to protect the privacy of the subject. For monitoring, audit and other operation, privacy of the subject will be protected. All data collected in the Case Report Form will be used only for this trial. For the publication of the trial result, privacy of subject will also be protected.

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21 DEFINITIONS AND ACRONYMS

21.1 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 angina 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 <50% (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 <50% (by QCA) using any percutaneous method.
- Procedure Success
  Procedure success is defined as achievement of a final in-stent diameter stenosis of <50% (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/DRUG EFFECTS

See Section 14 for definitions of adverse device/drug 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)

Patients are considered enrolled after the guidewire has successfully been passed beyond the target lesion. If the study stent could not be implanted due to reasons that are not related to study device, 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 7.1 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 (post infarction 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 or 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 RESTENOSIS - MEHRAN CLASSIFICATION [20]

- 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 [21] as follows:

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[20] Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of In-stent restenosis: Classification and implications for long-term outcome. Circulation. 1999. **100:** p. 1872-78.

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 Universal Definition of MI definition (JACC Vol. 60, 2012)
- 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 [22] 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

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[21] Moussa, ID, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization an expert consensus document from the society for cardiovascular angiography and interventions (SCAI). Catheter Cardiovasc Interv, 2013.

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

- 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 the study stent
- who did not receive at least 12 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/DRUG EFFECT

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

SERIOUS ADVERSE EVENT (SAE)

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

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.

21.1.1 Acronyms

Acronym	Term
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ADE / SADE	Adverse Device/Drug Effect / Serious Adverse Device/Drug 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
CoCr	Cobalt Chromium
CRF / eCRF	Case Report Form / electronic Case Report Form
cTn	Cardiac **troponin**
CTO	Chronic Total Occlusion
DAPT	Dual Antiplatelet Therapy
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
EES	Everolimus-eluting Stent
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
IB	Investigator's Brochure
IFU	Instructions for Use
IRB	Institutional Review Board
IVUS	Intravascular Ultrasound

Acronym	Term
LAD	**Left Anterior Descending Artery**
LCX	Left Circumflex
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
MLD	Minimum Luminal Diameter
mTOR	Mammalian Target of Rapamycin
NIH	Neointimal Hyperplasia (IVUS)
NSTEMI	Non ST Elevation Myocardial Infarction
PBMA	poly n-butyl methacrylate
PCI	Percutaneous Coronary Intervention
PMA	Premarket Approval
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/Drug Effect
ZES	Zotarolimus-eluting Stent

21.1.2 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)
JAAC	Journal of the American College of Cardiology
JCS	Japanese Circulation Society
MHLW	Ministry of Health, Labour and Welfare (Japan)
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)

Appendix 1: Primary Investigators in JNIR Study

Primary Investigator	Specialty	Institution	Institution's Address
Dr. Shigeru Saito	Interventional Cardiologist	Shonan Kamakura General Hospital	1370-1 Okamoto, Kamakura-City, Kanagawa
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