NIRTRAKS – (NIRxcell TRial for a post mArKet Study)

Clinical Protocol
NIRxcell™ Stent System

Study Number: CV103-02

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Amended:
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The protocol was developed in collaboration between Harvard Clinical Research Institute and Medinol.

NIRTRAKS –(NIRxcell TRial for a post mArKet Study)– Protocol Signature Page

Site Name: _____

Investigator's Responsibility

Prior to enrolling subjects in the NIRTRAKS Post-Market Study, the principal investigator must obtain written approval from his/her Institutional Review Board (IRB). This approval must be in the principal investigator's name and a copy sent to Medinol, among other essential documents, along with the IRB-approved informed consent and the signed clinical trial agreement. Additionally, the principal investigator must sign the declaration below:

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to all site personnel involved in this study. I will discuss this material with them and ensure they are fully informed regarding the investigational product and the conduct of the study.

_____ Date: _____
Principal Investigator's Signature

_____
Principal Investigator's Printed Name

_____ Date: _____
Sub- Investigator's Signature

_____
Principal Investigator's Printed Name

_____ _____
Site Name Site #

CLINICAL INVESTIGATION PLAN REVISION SUMMARY

Version	Release Date	Summary of Changes
1.0 To the FDA	30-Oct-2014	Initial Release
1.1 To the FDA	12-Jan-2015	Revisions made per FDA's requirements, as well as few corrections/clarifications added to the previous protocol version. See detailed list of changes below.
1.2 To the FDA	03-Mar-2015	Revisions made per FDA's requirements presented in the letter dated 3 Feb, 2015. See detailed list of changes below.

List of major changes versus Protocol ver. 1.1:

Section (in 1.1 version)	Revisions	Rationale
4.2 – Secondary Endpoints	Addition of a secondary endpoint of TVF at 9 months	Medinol's answer to Q1 FDA letter dated Feb. 3, 2015
4.2.4 – All Cause MI at 30 Days, and 1, 2 and 3 Years	Deletion of wording due to change of MI definition	Medinol's answer to Q3 FDA letter dated Feb. 3, 2015
5.0 – Study Design	Addition of 9 months follow-up (FU)	Medinol's answer to Q1 FDA letter dated Feb. 3, 2015
7.0 – Treatment Methodology	Clarification that post procedure cardiac biomarkers will be routinely measured in all subjects	Medinol's answer to Q2 FDA letter dated Feb. 3, 2015
9.0 – Follow-Up Assessments	Addition of a follow-up telephone contact at 9 months	Medinol's answer to Q1 FDA letter dated Feb. 3, 2015
9.0 – Follow-Up Assessments	Clarification that post procedure cardiac biomarkers will be routinely measured in all subjects	Medinol's answer to Q2 FDA letter dated Feb. 3, 2015
12.1 – Determination of Performance Metrics	Removal of the adjustment for non-clinically relevant periprocedural MI	Medinol's answer to Q3 FDA letter dated Feb. 3, 2015 Post-procedure cardiac biomarkers will be routinely collected in all subjects as was done in the reference studies. Therefore, there is no need to adjust the periprocedural MI rates in the reference studies.

12.1 – Determination of Performance Metrics Table 5	Updating the adjusted TVF rates in Table 5 to reflect the removal of the adjustment for non-clinically relevant periprocedural MI	Medinol's answer to Q3 FDA letter dated Feb. 3, 2015
12.1 – Determination of Performance Metrics	Updating the meta-analysis rate of 3-year TVF to 23.2%	Medinol's answer to Q3 FDA letter dated Feb. 3, 2015 Following the removal of the adjustment for non-clinically relevant periprocedural MI and the updated TVF rates in Table 5.
12.2 – Performance Goal	Updating the performance goal to 34.8%	Medinol's answer to Q1 FDA letter dated Feb. 3, 2015 To reflect the updated meta-analysis rate
12.3 – Primary Endpoint and Sample Size Calculation	Updating the power to 83%	Medinol's answer to Q1 FDA letter dated Feb. 3, 2015 To reflect the updated meta-analysis rate and updated performance goal
12.7 – Analysis of Primary Endpoint	Updating the performance goal to 34.8%	Medinol's answer to Q1 FDA letter dated Feb. 3, 2015
12.9 – Analysis of secondary endpoint	Addition of TVF at 9 months	Per Medinol's response to FDA's Q1
16.2 – Sponsor's Responsibilities for Preparing and Submitting Reports	Updating the timelines for submission of PAS Progress Reports	Medinol's answer to Q4 FDA letter dated Feb. 3, 2015
Appendix 1-P Study Definitions – MI definition	Updating the definition of periprocedural MI to follow the ARC definition rather than the new definition of clinically relevant MI	Medinol's answer to Q3 FDA letter dated Feb. 3, 2015
Editorial/minor corrections throughout the protocol		

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Protocol Summary

STUDY TITLE	NIRTRAKS Post-Market Study
DEVICE(S)	NIRxcell™ CoCr Coronary Stent on RX System (NIRxcell™ Stent System)
REGULATORY STATUS	Approved device: FDA approved (PMA# P110004/S001); CE marking since May 31, 2013; Israeli registration number 7840404 since March 11, 2014.
STUDY DESIGN	This is a prospective, post-marketing, non-randomized, multi-center, single-arm clinical study that will be conducted at up to 15 sites in the United States (US). All subjects will be treated with the NIRxcell Stent System and followed at 30 days, 9 months and 1, 2 and 3 years post–index stenting procedure. An unscheduled follow up may be conducted as clinically warranted.
OBJECTIVE	The main objective of this study is to collect and analyze additional information about the safety and effectiveness of the NIRxcell Stent System in the treatment of *de novo* stenotic lesions in native coronary arteries in the US population. The primary endpoint will be the rate of target vessel failure (TVF) at 3 years of treatment with the NIRxcell Stent System. This rate will be compared with a performance goal derived from a meta-analysis of coronary stenting with bare metal stents (BMS).
STUDY HYPOTHESIS	Medinol NIRTRAKS Post-Market Study will have a primary endpoint (TVF) rate less than 34.8% at 3 years, and by that will meet the performance goal for BMS.
NUMBER OF SUBJECTS	131 subjects will be enrolled to account for loss to follow-up, which is conservatively estimated at approximately 7.0% per year (resulting in 105 evaluable subjects), at up to 15 sites in the US.
PRIMARY ENDPOINT	**Target vessel failure**, defined as a composite of cardiac death, target vessel myocardial infarction (MI), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods within 3 years post-procedure.
SECONDARY ENDPOINTS	1. **TVF** at 9 months

SECONDARY ENDPOINTS (CONT.)	2. **All-cause death** at 30 days, and 1, 2 and 3 years. 3. **Cardiac death** at 30 days, and 1, 2 and 3 years. 4. **All cause MI** at 30 days, and 1, 2 and 3 years. 5. **Target vessel MI** at 30 days, and 1, 2 and 3 years. 6. **Clinically driven target lesion revascularization (TLR)** at 30 days, and 1, 2 and 3 years. 7. **Clinically driven TVR** at 30 days, and 1, 2 and 3 years. 8. **Acute success rates** *a.* *Device success*: Attainment of <50% final residual stenosis of the target lesion using *only* the NIRxcell Stent System. *b.* *Lesion Success*: Attainment of <50% final residual stenosis of the target lesion using any percutaneous method. *c.* *Procedure Success*: Attainment of <50% residual stenosis of the target lesion and no in-hospital death, MI, or TLR. 9. **Stent thrombosis** at hospital discharge, 30 days, and 1, 2 and 3 years.
SUBJECT POPULATION	Subjects with symptomatic ischemic heart disease due to a single *de novo* stenotic lesion contained within a native coronary artery with a reference vessel diameter between 2.5 mm and 4.0 mm and lesion length ≤30 mm that is amenable to percutaneous revascularization with stent deployment.
SAMPLE SIZE CONSIDERATIONS	• 3-year TVF rate for BMS derived from the meta-analysis is 23.2% (95% CI 19.8%, 26.7%). • Performance goal for BMS = 34.8%. • Type I error (α) = 0.05 (one-sided). • Statistical power ($1 - \beta$) = 83%%. • Expected 3-year TVF rate for NIRxcell Stent System = 23.2%. An evaluable sample size of 105 provides 83% power to demonstrate that NIRxcell Stent System meets the performance goal for TVF. Thus, 131 subjects will be enrolled to account for loss to follow-up, which is conservatively estimated at approximately 7% per year.

INCLUSION CRITERIA	*General Inclusion Criteria* 1. Subject is ≥18 years old. 2. Subject is eligible for percutaneous coronary intervention (PCI). 3. Subject is eligible for dual anti-platelet therapy (DAPT) with aspirin plus either clopidogrel, prasugrel or ticagrelor for a minimum of 1 month. 4. Subject understands the nature of the procedure and provides written informed consent **prior** to the catheterization procedure. 5. Subject is willing to comply with specified follow-up evaluation and can be contacted by telephone. 6. Subject is an acceptable candidate for coronary artery bypass graft (CABG) surgery. 7. Subject has stable angina pectoris (Canadian Cardiovascular Society Classification [CCSC] 1, 2, 3 or 4) or unstable angina pectoris (Braunwald Class 1-3, B-C) or a positive functional ischemia study (e.g. exercise tolerance test [ETT], single-photon emission computerized tomography [SPECT], stress echocardiography or cardiac computerized tomography [CT]). 8. Female subjects of child bearing potential must have a negative pregnancy test within 7 days prior to enrollment in the study. *Angiographic Inclusion Criteria* 1. Subject is indicated for elective stenting of a single stenotic lesion in a native coronary artery. 2. Reference vessel ≥2.5 mm and ≤4.0 mm in diameter by visual estimate. 3. Target lesion ≤30 mm in length by visual estimate (the intention should be to cover the whole lesion with 1 stent of adequate length). 4. Target lesion stenosis ≥50% and <100% by visual estimate.

EXCLUSION CRITERIA	*General Exclusion Criteria* 1. Subject is currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints. 2. Subject was enrolled in another stent trial within 2 years prior to the index procedure. 3. Any planned elective surgery or percutaneous intervention within 9 months post- procedure. 4. A previous coronary interventional procedure of any kind within 30 days prior to the procedure. 5. The subject requires staged procedure of either the target vessel or any non-target vessel within 9 months post-procedure. 6. The target lesion requires treatment with a device other than percutaneous transluminal coronary angioplasty (PTCA) prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.). 7. Previous drug-eluting stent (DES) deployment anywhere in the target vessel. 8. Any previous DES deployment within the past 12 months. 9. Any previous stent placement within 15 mm proximal or distal to the target lesion. 10. Co-morbid condition(s) that could limit the subject's ability to participate in the trial or to comply with follow-up requirements, or impact the scientific integrity of the trial. 11. Concurrent medical condition with a life expectancy of <3 years. 12. Documented left ventricular ejection fraction (LVEF) <25% at the most recent evaluation. 13. Evidence of an acute MI within 72 hours of the intended index procedure. 14. History of cerebrovascular accident or transient ischemic attack within 6 months prior to the index procedure. 15. Leukopenia (leukocytes $<3.5 \times 10^9$/liter). 16. Neutropenia (absolute neutrophil count $<1{,}000/mm^3$) ≤ within 7 days prior to enrollment. 17. Thrombocytopenia (platelets $<100{,}000/mm^3$) pre-procedure (within 7 days prior to enrollment). 18. Active peptic ulcer or active gastrointestinal (GI) bleeding.

EXCLUSION CRITERIA (CONT.)	19. Subjects who are ineligible for ≥1 month of DAPT because of bleeding diathesis or any other reason. 20. Known hypersensitivity or contraindication to aspirin, thienopyridine, both heparin and bivalirudin, cobalt, nickel, L-605 cobalt chromium alloy or sensitivity to contrast media which cannot be adequately pre-medicated. 21. Serum creatinine level >2.5 mg/dL within 7 days prior to the index procedure. 22. Subject was previously enrolled in the PIONIR Study or the NIRTRAKS Post-Market Study. *Angiographic Exclusion Criteria* 1. Unprotected left main coronary artery disease (obstruction >50% in the left main coronary artery that is not protected by ≥1 non-obstructed bypass graft to the left anterior descending [LAD] or left circumflex [LCX] artery or a branch thereof). 2. Target vessel exhibiting multiple lesions with >60% diameter stenosis outside of a range of 5 mm proximal and distal to the target lesion based on visual estimate or on-line quantitative coronary angiography (QCA). 3. Target lesion exhibiting an intraluminal thrombus (occupying >50% of the true lumen diameter) at any time prior to the start of the intervention. 4. Lesion location that is aorto-ostial or within 5 mm of the origin of the LAD or LCX. 5. Target lesion with side branches >2.0 mm in diameter. 6. Target lesion involving a bifurcation (either stenosis of both main vessel and major branch or stenosis of just major branch). 7. Target lesion with severe calcification. 8. Target vessel exhibiting excessive tortuosity that may impede stent delivery and deployment at target lesion. 9. Target lesion that is located in a native vessel distal to an anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass.
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1 Introduction and Rationale

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in the western hemisphere. Since its introduction, coronary angioplasty has become a widely accepted treatment for CAD, providing high procedural success rates and symptom relief. However, coronary angioplasty alone is associated with a high rate of restenosis (30% to 50%), necessitating repeat revascularization procedures.[1] Treatment of CAD has been significantly advanced by interventional cardiology, particularly with the advent of coronary stents. In comparison with angioplasty alone, stents have reduced the incidence of angiographic and clinical restenosis, the recurrence of angina, the need for coronary arterial bypass graft (CABG) surgery, the need for repeat revascularization, and the occurrence of major adverse cardiac events (MACE).[2-4] This improvement in outcomes ushered in the bare metal stent (BMS) era, a variety of which were approved and used during the 1990s. Expanded indications for stenting of more complex lesion subsets (restenosed lesions, long lesions, small vessels, bifurcations, saphenous vein graft lesions, chronic total occlusions, acute myocardial infarctions, etc.) led to the exponential growth of the use of coronary stents. However, the long-term success of this therapy has been limited by the occurrence of in-stent restenosis.[3-6] Despite the effectiveness of intracoronary stents in maintaining a larger luminal diameter as compared to angioplasty alone, in-stent restenosis occurs within 6 to 9 months after stent placement in 15% to 35% of subjects.[3-6]

The Food and Drug Administration (FDA) approval of drug-eluting stents (DES), together with their positive results seen in subjects, caused BMS usage to drop precipitously in the years immediately following DES introduction. However, concern regarding the long-term safety of DES, specifically the possibility of an increased frequency of late stent thrombosis relative to BMS, tempered the use of DES in favor of BMS beginning in 2007. The incidence of stent thrombosis in randomized trials of DES (either paclitaxel-eluting stents or sirolimus-eluting stents) was found to be comparable to that of BMS, and ranged from 0.4% to 0.6% at 12 months.[7-10] Moreover, the observed rate of stent thrombosis in the 'real-world' clinical setting, where off-label use is common practice, is almost double the rate observed in clinical trials.[11] Further complicating matters is that stent thrombosis in subjects treated with DES can occur outside the 30-day period after stent placement typically seen in subjects treated with BMS. Several observational studies of subjects treated with DES in the 'real-world,' where off-label use approaches 60%,[12, 13] suggested an increased incidence of late stent thrombosis, [14] death and myocardial infarction (MI)[15-17] relative to subjects treated with BMS, although more recent data suggest otherwise.[18, 19] Based in part on the uncertainty of the relative risks of stent thrombosis with DES versus BMS, BMS continue to be used regularly in the treatment of coronary artery disease in routine clinical practice.[20]

The NIR® coronary stent has been on the European market since 1996 and on the US market since 1998. Its design is characterized by a "closed cell" geometry, which forms the basis for continuous support and smooth scaffolding. This design was improved upon with the NIRFLEX™ stent. The NIRFLEX coronary stent was designed to retain the characteristic "closed cell" design of the NIR stent while offering improved flexibility both before and after expansion. This flexibility led to a reduction in trauma after implantation, as demonstrated in independent trials in both the United States and Europe.

The Presillion™ and Presillion™ *plus* Stent Systems are a modification of the currently approved NIRFLEX Coronary Stent System (CE mark since March 2002). The Presillion and Presillion *plus* Stent Systems are approved devices in Europe and Israel (CE mark since March 2008 and May 2009, respectively; Israeli registration numbers 784-0001 and 784-0003, respectively). The Presillion plus Stent System is approved in the US (FDA PMA #P110004) and Canada (Health Canada approval #86087). The NIRxcell Stent System is an upgraded version of the Presillion *plus* Stent System, FDA approved (PMA# P110004/S001); CE mark since May 31, 2013; Israeli registration number 7840404 since March 11, 2014.

The NIRxcell Stent System is composed of the same L-605 CoCr Presillion stent (known as the PIONIR stent), but is mounted on a different, rapid exchange delivery system, with hydrophilic coating, and includes a semi-compliant balloon.

The raw materials that are used in the manufacture of the NIRxcell Stent System are the same as the raw materials used for the manufacture of the Presillion Stent System. Both systems are integrated under the same environmental conditions using the same processes, with small changes in parameter settings that have no influence on the systems' properties.

The safety and effectiveness of the Presillion and Presillion *plus* Stent Systems were evaluated in the PIONIR study, a non-randomized, multi-center, prospective, single-arm clinical study (clinicaltrials.gov reference # NCT00840775- unpublished data). The study enrolled 278 subjects at 16 sites in Europe (Germany, Sweden and Belgium) and Israel. The primary endpoint was the incidence of target vessel failure (TVF), defined as cardiac death, target vessel MI (Q wave or non–Q wave), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods, within 270 days of treatment with the Presillion/Presillion *plus* Stent System. This rate was compared with a performance goal that was derived from a meta-analysis of the literature reporting outcomes with approved BMS. The 270-day TVF rate was 8.7% and the upper bound of the exact one-sided 95% confidence interval was 12.7%. Since this upper bound was less than the established performance goal of 16.46%, the primary endpoint was considered to have been met.

The NIRTRAKS Post-Market Study is designed to supplement the post-market requirements for the long-term safety and effectiveness of the NIRxcell Stent System in the U Sby collecting additional information about the safety and effectiveness of the device in the treatment of stenotic lesions in de novo native coronary arteries in the US population. The primary efficacy endpoint will be evaluated by comparing the incidence of TVF within 3 years of treatment with NIRxcell Stent System with a performance goal derived from the development of a meta-analysis of 5 BMS trials.

2 Device Description and Intended Use

2.1 Device Description

2.1.1 General

NIRxcell CoCr Coronary Stent on RX System (NIRxcell Stent System, P110004/S001) is a single-use device designed and manufactured by Medinol Ltd. It comprises a balloon-expandable, intracoronary stent mounted on a rapid-exchange delivery catheter.

For the purposes of this clinical investigation, the NIRxcell Stent System is available in 32 device models to accommodate various reference vessel diameters and lesion lengths. For details refer to Table 1.

2.1.2 Detailed Information

NIRxcell Stent System

The NIRxcell stents are cut from panels of flat sheets of L-605 cobalt-chromium alloy, after which the stents are folded into cylinders and welded. The NIRxcell stent geometry is made up of alternating wide and narrow struts to enable the stent to be flexible in the unexpanded configuration and to support the vessel, while conforming to its curvature, in the expanded configuration. At the distal end of the catheter is a delivery balloon designed to expand to a controlled diameter and length when inflated. The balloon delivery catheter has 2 platinum iridium radiopaque marker bands defining the length and location of the mounted stent.

The usable length of the delivery system is 140 cm with a shaft profile of 2.1F (0.69 mm) / 2.6F (0.86 mm) (proximal/distal). It has a distal port (hole) approximately 30 cm 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 also has 2 markers on the proximal catheter shaft that indicate, approximately, the exit of the balloon catheter tip from the guiding catheter (brachial: 93 cm; femoral: 103 cm).

Table 1: NIRxcell Stent System: Device Matrix for NIRTRAKS Post-Market Study

MODEL	DESCRIPTION					
Catalogue Number	Nominal Stent System Size					
	Stent Labeled Diameter (mm)	Stent Labeled Length (mm)	Maximum Post Deployment Stent Diameter (mm)	Nominal Pressure (Atm)	Rated Burst Pressure (Atm) NLT	Minimum Guiding Catheter Compatibility (ID)
NXL25008US	2.5	8	3.0	12	18	5F
NXL25012US		12	3.0	12	18	5F
NXL25017US		17	3.0	12	18	5F
NXL25020US		20	3.0	12	18	5F
NXL27508US	2.75	8	3.5	12	18	5F
NXL27512US		12	3.5	12	18	5F
NXL27517US		17	3.5	12	18	5F
NXL27520US		20	3.5	12	18	5F
NXL27524US		24	3.5	12	18	5F
NXL27528US		28	3.5	12	18	5F
NXL27533US		33	3.5	12	18	5F
NXL30008US	3.0	8	3.75	12	18	5F
NXL30012US		12	3.75	12	18	5F
NXL30017US		17	3.75	12	18	5F
NXL30020US		20	3.75	12	18	5F
NXL30024US		24	3.75	12	18	5F
NXL30028US		28	3.75	12	18	5F
NXL30033US		33	3.75	12	18	5F
NXL35008US	3.5	8	4.25	12	18	5F
NXL35012US		12	4.25	12	18	5F
NXL35017US		17	4.25	12	18	5F
NXL35020US		20	4.25	12	18	5F
NXL35024US		24	4.25	12	18	5F
NXL35028US		28	4.25	12	18	5F
NXL35033US		33	4.25	12	18	5F
NXL40008US	4.0	8	4.75	12	18	5F
NXL40012US		12	4.75	12	18	5F
NXL40017US		17	4.75	12	18	5F
NXL40020US		20	4.75	12	18	5F
NXL40024US		24	4.75	12	18	5F
NXL40028US		28	4.75	12	18	5F
NXL40033US		33	4.75	12	18	5F

2.2 Intended Use of the Device

The NIRxcell Stent System is indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease associated with stenotic lesions in *de novo* native coronary arteries (length ≤30 mm) with a reference vessel diameter of 2.50 mm to 4.00 mm.

3 Purpose and Objectives

The purpose of this study is to collect and analyze additional information about the safety and effectiveness of the NIRxcell stents in the treatment of *de novo* stenotic lesions in native coronary arteries. Data will be collected at 30 days, 9 months and 1, 2 and 3 years post–index stenting procedure. The primary objective is to compare the incidence of TVF within 3 years after treatment with the NIRxcell Stent System with a performance goal derived from a meta-analysis of coronary stenting with BMS, per the results of the historical control group combined.

The long-term safety of the stenting procedure, including the occurrence of complications, will be evaluated through clinical data obtained before, during and after stent placement. Initial effectiveness of stent placement will be evaluated by determining acute success, including device success, lesion success and procedure success. The primary clinical outcome of TVF at 3 years post–index stenting procedure as well as a number of secondary outcomes will be used to determine the long-term clinical effectiveness of treating native coronary artery lesions with the investigational product. TVF was selected as the primary clinical outcome to allow for conclusive comparisons of the efficacy of the NIRxcell Stent System with other historical results.

The NIRTRAKS Post-Market Study will be performed according to the World Medical Association Declaration of Helsinki, and FDA regulation 21 CFR parts 803, 812, 50 & 54. The data collected will be used to support the post-market requirements for the NIRxcell Stent System.

4 Endpoints

The following study endpoints will be evaluated in all subjects enrolled in the NIRTRAKS Post-Market Study.

4.1 Primary Endpoint

The primary endpoint for this study is TVF, which is defined as a composite of cardiac death, target vessel MI, or clinically driven TVR by percutaneous or

4.2 Secondary Endpoints

4.2.1 **TVF** at 9 Months

4.2.2 **All Cause** Death at 30 Days, and 1, 2 and 3 Years

4.2.3 Cardiac Death at 30 Days, and 1, 2 and 3 Years

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

4.2.4 All Cause MI at 30 Days, and 1, 2 and 3 Years

4.2.5 MI is defined using the Academic Research Consortium (ARC) definitions (see Appendix 1-P).

4.2.6 Target Vessel MI at 30 Days, and 1, 2 and 3 Years

Target vessel MI is defined as any MI attributed to the target vessel.

4.2.7 Clinically Driven TLR at 30 Days, and 1, 2 and 3 Years

Clinically-driven target lesion revascularization (TLR) is defined as any revascularization at the target lesion associated with positive functional ischemia study or ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥50% by quantitative coronary angiography (QCA), or revascularization of a target lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

4.2.8 Clinically Driven TVR at 30 Days, and 1, 2 and 3 Years

Clinically-driven TVR is defined as any revascularization in the target vessel that is associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ≥50% by QCA, or revascularization of a target vessel with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

4.2.9 Acute Success Rates

Device success is defined as the attainment of <50% final residual stenosis of the target lesion using only the NIRxcell Stent System.

Lesion success is defined as the attainment of <50% final residual stenosis of the target lesion using any percutaneous method.

Procedure success is defined as attainment of <50% residual stenosis of the target lesion and no in-hospital death, MI or TLR.

4.2.10 Stent Thrombosis at Discharge, 30 Days, and 1, 2 and 3 Years

Acute stent thrombosis is defined as a thrombotic event occurring between 0 and 24 hours after stent implantation.

Subacute stent thrombosis is defined as a thrombotic event occurring between 1 and 30 days after stent implantation.

Late stent thrombosis is defined as a thrombotic event occurring between 30 days to 1 year after stent implantation.

Three separate categories of stent thrombosis using the ARC classification are recognized and defined in Appendix 1-P.

5 Study Design

This is a prospective, post-marketing, non-randomized, multi-center, single-arm clinical study to collect additional information about the safety and effectiveness of the NIRxcell Stent System in the treatment of *de novo* stenotic lesions in native coronary arteries in the US population. A total of 131 subjects will be enrolled in up to 15 sites in the US. The expected duration of subject enrollment is approximately 12 months. Clinical follow-up for all subjects will occur at 30 days, 9 months and 1, 2 and 3 years post–index stenting procedure. An unscheduled follow up may be conducted as clinically warranted.

5.1 Control of Systematic Error/Bias

By the nature of the type of the proposed study, blinding of the investigator and/or subject is not possible. However, several measures will be implemented for minimization of systematic error/bias:

- Basic screening will be completed by investigational sites of all potential candidates. Subjects who fail to meet the *clinical* inclusion and exclusion criteria will not be included in this study. Subjects who have met all the *clinical* inclusion and exclusion criteria will then be screened for angiographic eligibility criteria.
- All subjects who undergo angiographic screening will be entered onto the screening log. The screening log will include all subjects who have signed the informed consent.
- Measurements made by angiography will be standardized by use of an angiographic core laboratory. The core laboratory measurements will be used in all cases for purposes of data analysis.

  In determining subject eligibility for the study, the investigator's assessment of pre-procedure angiographic parameters will be used. However, the angiographic core laboratory will provide feedback to the sponsor concerning accuracy of assessments in relation to inclusion criteria such as lesion parameters and anatomic location.
- Electrocardiogram (ECG) tracings analysis will be standardized by use of an ECG core laboratory. The ECG core laboratory readings will be used in all cases for purposes of data analysis.
- Clinical monitors will verify subjects' data and ensure compliance with Good Clinical Practice (GCP), clinical protocol and other study requirements, according to the guidelines set forth in HCRI's monitoring standard operating procedures (SOP).
- An independent clinical events committee (CEC) will adjudicate all clinical endpoint events and investigator-reported adverse events that have the potential to be a clinical endpoint event. The CEC adjudication results will be used in all cases for purposes of data analysis.

5.2 Eligibility, Exclusions and Subject Discontinuations

All subjects presented to the angiographic suite for possible coronary artery revascularization are potential study candidates and will be screened for eligibility, and consented for possible inclusion. Every effort will be made to establish eligibility of the participants prior to enrollment. Prior to enrollment, subjects will have screening clinical laboratory, medical

history and physical exams to verify qualification into the study. If conducted within the appropriate time windows, and the subjects meet the pre-angiography inclusion and exclusion criteria, the screening results will also serve as baseline parameters. Angiographic eligibility will be based solely on angiography performed at the time of index procedure. Once a subject has signed the informed consent, angiographic eligibility has been confirmed, and the NIRxcell Stent System introduced into the subject's body, the subject is considered to be enrolled. Subjects who do not meet **all** inclusion (general and angiographic) criteria or meet **any** of the exclusion criteria should not be enrolled in the study. All subjects enrolled will be evaluated, regardless of sequence of treatment that ensues.

Once a subject has been enrolled in the study, he/she may withdraw his/her consent to participate in the study at any time without prejudice. Participation in this clinical investigation is entirely voluntary.

Possible reasons for subject discontinuation include but are not limited to the following:

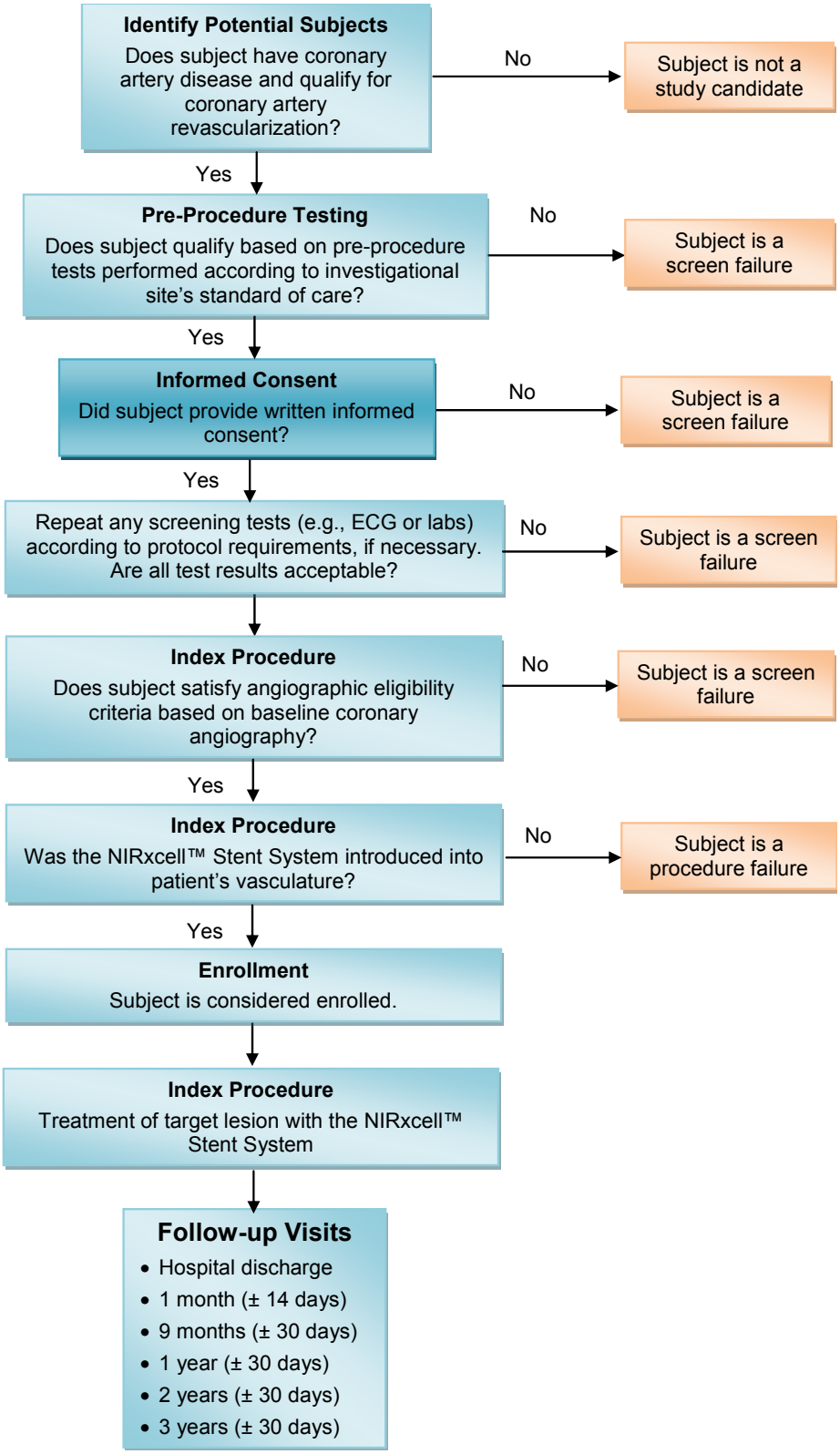
- Subject death
- Subject voluntary withdrawal
- Subject withdrawal by physician as clinically-indicated
- Subject lost-to follow-up as described below

Subjects withdrawn after treatment will not be required to undergo follow-up after withdrawal; however, they will still be considered part of the subject cohort.

All subjects enrolled in the study are considered eligible for follow-up and will be required to adhere to the follow-up schedule outlined in Section 9. If a subject cannot be contacted for a follow-up assessment and follow-up information cannot be obtained, he/she will be counted as "missed contact" for that specific schedule. Attempts shall be made to contact the subject in next follow-up schedule. A subject will be considered "lost to follow-up" only after the last scheduled follow-up assessment for that subject (3 years). If a subject is lost to follow-up, the methods used to attempt to contact the subject should be documented. At least 3 attempts should be made to contact the subject through all available routes, and a certified letter should be sent to the permanent address in file.

Figure 1 summarizes the above steps and follow-up period.

Figure 1: Study Flowchart



6 Criteria of Eligibility

6.1 Inclusion Criteria

Prior to enrollment in this study, candidates must meet **ALL** of the following criteria:

6.1.1 General Inclusion Criteria

1. Subject is ≥18 years old.
2. Subject is eligible for percutaneous coronary intervention (PCI).
3. Subject is eligible for dual anti-platelet therapy (DAPT) with aspirin plus either clopidogrel, prasugrel or ticagrelor for a minimum of 1 month.
4. Subject understands the nature of the procedure and provides written informed consent prior to the catheterization procedure.
5. Subject is willing to comply with specified follow-up evaluation and can be contacted by telephone.
6. Subject is an acceptable candidate for coronary artery bypass graft (CABG) surgery.
7. Subject has stable angina pectoris (Canadian Cardiovascular Society Classification [CCSC] 1, 2, 3 or 4) or unstable angina pectoris (Braunwald Class 1-3, B-C) or a positive functional ischemia study (e.g., exercise tolerance test [ETT], single-photon emission computerized tomography [SPECT], stress echocardiography or cardiac computerized tomography [CT]).
8. Female subjects of child bearing potential must have a negative pregnancy test within 7 days prior to enrollment in the study.

6.1.2 Angiographic Inclusion Criteria

1. Subject is indicated for elective stenting of a single stenotic lesion in a native coronary artery.
2. Reference vessel ≥2.5 mm and ≤4.0 mm in diameter by visual estimate.
3. Target lesion ≤30 mm in length by visual estimate (the intention should be to cover the whole lesion with 1 stent of adequate length).
4. Target lesion stenosis ≥50% and <100% by visual estimate.

6.2 Exclusion Criteria

Candidates must be excluded from this study if **ANY** of the following criteria is met:

6.2.1 General Exclusion Criteria

1. Subject is currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
2. Subject was enrolled in another stent trial within 2 years prior to the index procedure.
3. Any planned elective surgery or percutaneous intervention within nine (9) months post- procedure.

4. A previous coronary interventional procedure of any kind within 30 days prior to the procedure.
5. The subject requires staged procedure of either the target vessel or any non-target vessel within 9 months post-procedure.
6. The target lesion requires treatment with a device other than percutaneous transluminal coronary angioplasty (PTCA) prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
7. Previous drug-eluting stent (DES) deployment anywhere in the target vessel.
8. Any previous DES deployment within the past 12 months.
9. Any previous stent placement within 15 mm proximal or distal to the target lesion.
10. Co-morbid condition(s) that could limit the subject's ability to participate in the trial or to comply with follow-up requirements, or impact the scientific integrity of the trial.
11. Concurrent medical condition with a life expectancy of <3 years.
12. Documented left ventricular ejection fraction (LVEF) <25% at the most recent evaluation.
13. Evidence of an acute MI within 72 hours of the intended index procedure.
14. History of cerebrovascular accident or transient ischemic attack within 6 months prior to the index procedure.
15. Leukopenia (leukocytes $<3.5 \times 10^9$/liter).
16. Neutropenia (absolute neutrophil count $<1{,}000/mm^3$) ≤ within 7 days prior to enrollment.
17. Thrombocytopenia (platelets $<1{,}00{,}000/mm^3$) (within 7 days prior to enrollment).
18. Active peptic ulcer or active gastrointestinal (GI) bleeding.
19. Subjects who are ineligible for ≥1 month of DAPT because of bleeding diathesis or any other reason.
20. Known hypersensitivity or contraindication to aspirin, thienopyridine, both heparin and bivalirudin, cobalt, nickel, L-605 cobalt-chromium alloy or sensitivity to contrast media that cannot be adequately pre-medicated.
21. Serum creatinine level >2.5 mg/dL within 7 days prior to the index procedure.
22. Subject was previously enrolled in the PIONIR Study or the NIRTRAKS Post-Market Study.

6.2.2 Angiographic Exclusion Criteria

1. Unprotected left main coronary artery disease (obstruction >50% in the left main coronary artery that is not protected by ≥1 non-obstructed bypass graft to the left anterior descending (LAD) or left circumflex (LCX) artery or a branch thereof.

2. Target vessel exhibiting multiple lesions with >60% diameter stenosis outside of a range of 5 mm proximal and distal to the target lesion based on visual estimate or on-line quantitative coronary angiography (QCA).
3. Target lesion exhibiting an intraluminal thrombus (occupying >50% of the true lumen diameter) at any time prior to the start of the intervention.
4. Lesion location that is aorto-ostial or within 5 mm of the origin of the LAD or LCX.
5. Target lesion with side branches >2.0 mm in diameter.
6. Target lesion involving a bifurcation (either stenosis of both main vessel and major branch or stenosis of just major branch).
7. Target lesion with severe calcification.
8. Target vessel exhibiting excessive tortuosity that may impede stent delivery and deployment at target lesion.
9. Target lesion that is located in a native vessel distal to an anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass.

7 Treatment Methodology

Table 2: Summary of Study Procedures from Screening through End of Follow-Up

Study Requirement	Screening		Procedure	Post-Procedure						
	Within 7 Days Prior to Procedure	24 Hours Prior to Procedure		Hospital Discharge	30 Days (±2 Weeks)	9 Months (±1 Month)	1 Year (±1 Month)	2 Years (±1 Month)	3 Years (±1 Month)	Unscheduled Visit /Phone
Informed consent	X									
Medical history	X									
Clinical assessment and physical exam	X			X						X(7)
Telephone assessment					X	X	X	X	X	X
CBC w/differential (1)	X									
Serum creatinine	X									
INR, APTT	X									X(7)
Pregnancy test	X(2)									
CK/CK-MB/ troponin		X(3)		X(6)						X(7)
12-lead ECG		X(4)								X(7)
Record of relevant medications (5)		X		X	X	X	X	X	X	X
Coronary angiography			X							
Stenting			X							
Record of adverse events			X	X	X	X	X	X	X	X

APTT: activated partial thromboplastin time; CBC: complete blood count; CK: creatinine kinase; CK-MB: creatinine kinase myocardial band; ECG: electrocardiogram; INR: international normalized ratio

(1) Collection of CBC differentials during the index hospitalization should be done as per the respective institutions standard of care. However, if the white blood count (WBC) is abnormal, it is recommended to perform the CBC differential before and after the procedure.

(2) For females of childbearing potential.

(3) Pre-procedure cardiac enzymes: CK, CK-MB or troponin performed within 24 hours prior to the procedure may be used as the baseline cardiac enzymes provided there have been no signs or symptoms of myocardial ischemia between the time of cardiac enzymes test and the time of arterial access.

(4) Pre-procedure 12-lead ECG: an ECG performed within 7 days prior to the procedure may be used as the baseline ECG provided there have been no signs or symptoms of myocardial ischemia between the time of ECG and the time of arterial access.

(5) Relevant medications: statins, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), beta-blockers and anti-platelets.

(6) CK and CK-MB will be measured at 6- 8 hours post procedure, 12-16 hours post procedure and 20-24 hours post procedure (or upon discharge, whichever comes first). If any CK elevation (CK above ULN) is noted post procedure, CK and CK-MB measurements will continue to be performed every 8 hours for 24 hours starting from when the first elevation is noted and recorded on the appropriate eCRF. If total CK values are within normal ranges, CK-MB measurements may not be performed (per hospital standards). However, it is strongly encouraged that CK-MB measurements are obtained with every total CK drawn, even if CK values are within normal limits. It is also recommended that sites collect CK and CK-MB preferentially over troponin in the peri-procedural period subsequent to the index procedure. In the case where CK and CK-MB are not available, troponin can be used.

(7) These assessments and tests will be performed only if clinically warranted.

7.1 Subject Screening/Assessment

Signed written informed consent must be obtained for all subjects who are potential study candidates prior to enrollment. Additionally, the following evaluations must be completed for all subjects unless otherwise specified:

Within 7 Days of Enrollment:

- Medical history.
- Clinical assessment and physical examination.
- Complete blood count (CBC) with differential (if possible as per the respective institutions standard of care).
- Chemistry screen including serum creatinine.
- Coagulation including international normalized ratio (INR), activated partial thromboplastin time (APTT). Note: must be checked prior to heparin therapy.
- Pregnancy test (for females of childbearing potential).

Within 24 hours of Enrollment:

- CK, CK-MB or troponin levels.
- 12-lead ECG (an ECG performed within 7 days prior to the procedure may be used as the baseline ECG provided there have been no signs or symptoms of myocardial ischemia between the time of ECG and the time of arterial access). A copy of the ECG trace should be sent to the ECG core laboratory.
- Record of relevant medications.

7.2 Procedural Information

For information describing the procedural steps and materials necessary for appropriate use of the NIRxcell Stent System, refer to the US Instructions for Use.

Additionally, note the following:

- *Start of the Procedure and Enrollment*

  The start of the procedure is defined as the time of arterial cannulation. Actual enrollment in the study occurs at the time the study device is introduced into the body. If the angiogram performed at the index procedure indicates that the subject is not a candidate for the study, this subject is not considered enrolled.

- *Angiographic Protocol Requirement*
  - Following intracoronary injection of 50–200 μg nitroglycerin (NTG), obtain baseline angiograms using at least ≥2 near orthogonal views, best demonstrating the coronary artery stenosis, as specified in the angiographic protocol.
  - Before stent placement, obtain a single working view of the coronary artery stenosis, as specified in the angiographic protocol.
- *Pre-Dilatation*

  If the target lesion fulfills eligibility criteria, the target lesion must be pre-treated with standard percutaneous transluminal balloon angioplasty. This clinical protocol does not allow for direct stenting of the target vessel.

  Attention must be paid to the pre-dilatation technique to avoid balloon injury to any segment of the vessel that will not be entirely covered by the stent ('geographical miss').

  Pre-dilatation must be performed using a balloon with the following 3 characteristics:

  1. A diameter ≥0.5 mm smaller than the treatment stent.
  2. A length matching or shorter than the lesion length to be dilated (to avoid dilatation of the vessel wall adjacent to the stent).
  3. A length shorter than the stent to be implanted.

  The use of other therapy (e.g. cutting balloons, atherectomy, laser, thrombectomy, etc.) is not allowed.
- *Selection of Appropriately Sized Stent*

  Select an appropriately sized stent based on angiographic vessel measurements (approximately 2–4 mm longer than the measured shoulder-to-shoulder lesion length, with a stent to distal reference vessel ratio of 1:1 or 1.1:1.0). The intention should be to cover the whole lesion with 1 stent of adequate length.

  Note: Additional NIRxcell Stent Systems should be used, at the physician's discretion, for sub-optimal result, or in the event of bailout procedures, as defined below.
- *Bailout Procedures*

  The intention should be to cover the index lesion with 1 stent of adequate length. Bailout procedures and additional stenting for sub-optimal results should be avoided unless required for subject safety. If a subject enrolled in the study experiences a major dissection or an occlusive complication (as evidenced by decreased target vessel flow, chest pain, or ischemic ECG changes that do not respond to repeat balloon inflations, NTG, intracoronary verapamil, intracoronary diltiazem, or lytic agents), bailout procedures may be performed. For bailout procedures or in the event of a sub-optimal result, further stenting may be employed, at investigator's discretion, using the NIRxcell Stent Systems, as required.
- *End of the Procedure*

  The end of the procedure is defined as the time that the final guiding catheter is withdrawn from the subject. Closure of the arterial puncture site will be performed as per laboratory

standards. The hemostasis introducer sheath(s) may be removed when the subject's activated clotting time (ACT) is <150 seconds or per the physician's discretion. If a guide catheter is introduced once the procedure is considered over, as defined above, or the subject is returned to the procedure room and interventional therapy is performed, this should be considered a repeat intervention.

- *Adverse Events Recording*

  All adverse events (AEs) occurring following informed consent signature must be recorded.

  Note: Bailout procedures performed during the same catheterization as the index stenting procedure shall be considered part of the index procedure.

7.3 Post-Procedure Assessment (Hospital Discharge)

Clinical assessment of a subject's condition must be performed according to the details below. The research coordinator will review the follow-up requirements with the subject to help ensure compliance with the follow-up schedule. Telephone numbers must be obtained from the subject to ensure the ability to contact him/her. These phone numbers should include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

The following assessments will be performed at hospital discharge:

- Clinical assessment and physical examination.
- CK and CK-MB will be measured at 6- 8 hours post procedure, 12-16 hours post procedure and 20-24 hours post procedure (or upon discharge, whichever comes first). If any CK elevation (CK above ULN) is noted post procedure, CK and CK-MB measurements will continue to be performed every 8 hours for 24 hours starting from when the first elevation is noted and recorded on the appropriate eCRF. If total CK values are within normal ranges, CK-MB measurements may not be performed (per hospital standards). However, it is strongly encouraged that CK-MB measurements are obtained with every total CK drawn, even if CK values are within normal limits. It is also recommended that sites collect CK and CK-MB preferentially over troponin in the peri-procedural period subsequent to the index procedure. In the case where CK and CK-MB are not available, troponin can be used.Record of relevant medications (statins, angiotensin converting enzyme inhibitors [ACE-I], angiotensin receptor blockers [ARB], beta-blockers and anti-platelets).
- Record of all AEs that occurred since the end of the index procedure.

8 Concomitant Medications

Concomitant medications to be used before, during and after the stenting procedure are as follows:

Table 3: Summary of Concomitant Medications Regimen

	Pre-Procedure	Procedure	Post-Procedure
Aspirin	**A minimum of 150 mg (within 24 hours prior to procedure).**	**---**	**75–100 mg daily indefinitely.**
Clopidogrel or Prasugrel/ Ticagrelor	**Loading dose of 600 mg clopidogrel within 24 hours prior to index procedure or immediately post-procedure (within 30 minutes). Alternatively, loading dose of 60 mg prasugrel or 180 mg ticagrelor. No loading dose is required for subjects on chronic thienopyridine therapy.**	**---**	**Post-procedure treatment with the same thienopyridine agent for a minimum of 1 month as follows: Clopidogrel: 75 mg daily. Prasugrel: 10 mg daily; a lower dose of 5 mg daily is allowed for subjects <60 kg. Ticagrelor: 90 mg twice daily.**
Heparin or Bivalirudin	**---**	**Per routine hospital practice. For heparin, a bolus of 50–80 units/kg is recommended. If heparin is administered, it is recommended to maintain ACT of ≥250 seconds (or ≥200 seconds if a glycoprotein IIb/IIIa receptor blocker is administered) throughout the interventional portion of the procedure.**	**---**
Glycoprotein IIb/IIIa Inhibitor	**---**	**Per investigator's discretion.**	
Intracoronary Nitroglycerin or Intracoronary Isosorbide or Dinitrate	**---**	**To eliminate coronary artery spasm that would interfere with accurate measurement of lumen obstruction due to plaque alone, 100–200 µg nitroglycerin or 1–3 mg of isosorbide or dinitrate must be administered prior to baseline and post-intervention angiograms.**	**---**

9 Follow-Up Assessments

Follow-up will be conducted at 30 days, 9 months, and 1, 2, and 3 years post-procedure via telephone call. Refer to the text below for details.

Additional unscheduled follow up visits/phone calls may occur as clinically warranted.

The window for the 30-day follow-up contact will be ±2 weeks. For the 1-, 2- and 3-year contacts, the window will be ±1 month.

9.1 30-Day (±2 Weeks) Contact

- Record of relevant medications.
- Record of all AEs that occurred since last subject contact.

9.2 9-Month (±1 Month) Contact

- Record of relevant medications.
- Record of all AEs that occurred since last subject contact.

9.3 1-Year (±1 Month) Contact

- Record of relevant medications.
- Record of all AEs that occurred since last subject contact.

9.4 2-Year (±1 Month) Contact

- Record of relevant medications.
- Record of all AEs that occurred since last subject contact.

9.5 3-Years (±1 Month) Contact

- Record of relevant medications.
- Record of all AEs that occurred since last subject contact.

9.6 Unscheduled visit/Phone follow up

- Record of relevant medications.
- Record of all AEs that occurred since last subject contact.
- Additional assessments and tests may be performed if clinically warranted.

During each specified evaluation, the corresponding electronic case report form (eCRF) must be completed per the written instructions provided by the sponsor. Although not anticipated, should the appropriate authorized regulatory bodies request additional follow-up, the physicians and subjects will be requested to adhere accordingly.

Detailed Explanations

Adverse Events: Adverse events occurring (1) from time of index procedure to 30 days follow-up contact, (2) From 30 days follow up contact to 1 year follow-up contact, (3) From 1 year follow-up contact to 2 years follow-up contact, and (4) From 2 years follow-up contact to 3 years follow-up contact, will be recorded. In the event of an AE that is associated with repeat

angiography/revascularization, the event related coronary angiograms and catheterization report must be captured and submitted to the data center within 10 working days of knowledge of the event. Angiographic data collected during any repeat procedure on the target vessel must be made available to the CEC for an independent review and assessment. Likewise, the angiographic images should be submitted to the core laboratory for an independent review and assessment of the target lesion and study stent.

12-Lead ECG: According to each site's standard of care.

CBC With Differential: Hematology testing due to anti-platelet therapy should follow the routine standard of care.

CK, CK-MB and Troponin: CK, CK-MB or troponin will be obtained pre-procedure (within 24 hours of the index procedure). Post procedure, CK and CK-MB will be measured at 6- 8 hours, 12-16 hours and 20-24 hours post procedure (or upon discharge, whichever comes first). If any CK elevation (CK above ULN) is noted post procedure, CK and CK-MB measurements will continue to be performed every 8 hours for 24 hours starting from when the first elevation is noted and recorded on the appropriate eCRF. If total CK values are within normal ranges, CK-MB measurements may not be performed (per hospital standards). However, it is strongly encouraged that CK-MB measurements are obtained with every total CK drawn, even if CK values are within normal limits. It is also recommended that sites collect CK and CK-MB preferentially over troponin in the peri-procedural period subsequent to the index procedure. In the case where CK and CK-MB are not available, troponin can be used.

Relevant Medications: Statins, ACE-I, ARB, beta-blockers and anti-platelets.

10 Total Expected Duration of the Clinical Investigation

- The clinical investigation is estimated to commence in June 2015.
- The enrollment is estimated to commence in July 2015.
- Enrollment completion is estimated for October 2016.
- The last patient follow up at 3 years is estimated for October 2019.
- Total expected duration of the clinical investigation is approximately 4-5 years.

11 Adverse Events

In this study, subjects should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning (e.g. "How has your health been since the last contact?"). Any time during the study, the subject may volunteer information that resembles an AE. If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE eCRF.

11.1 Definition of Adverse Event and Serious Adverse Event

11.1.1 Adverse Event

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

NOTE 1: This definition includes events related to the study device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the study device.

In this study, AEs shall be assessed and documented at IC signing. All AEs are to be recorded through the end of the study on the appropriate subject case report forms and followed through to their resolution regardless of time window.

11.1.2 Adverse Device Effect

An adverse device effect (ADE) is defined as an AE related to the use of the study device.

NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the study device.

NOTE 2: This definition includes any event resulting from user error or from intentional misuse of the study device.

11.1.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that leads to:

1. Death
2. Serious injury that:
   a. Is a life-threatening illness or injury or
   b. Results in permanent impairment of a body function or permanent changes to a body structure or
   c. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body function.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the clinical study plan, and not meeting any of the serious criteria described above, is not considered to be an SAE. A planned hospitalization is one that is scheduled prior to the patient signing the informed consent for the study.

11.1.4 Serious Adverse Device Effect

A serious adverse device effect (SADE) is any anticipated ADE that has resulted in any of the consequences characteristic of an SAE.

11.1.5 Anticipated Adverse Event

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject, whether or not considered related to the study product(s) prescribed as part of the clinical protocol, predefined in the clinical protocol and/or Instructions for Use (IFU), product label that is identified or worsens during a clinical study.

11.1.6 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of a subject.

11.2 Device Deficiencies

All failures and NIRxcell deficiencies will be documented on the appropriate CRF.

Investigators are instructed to report all possible device deficiencies, malfunctions or user errors or inadequate labeling observed during the course of the trial. These incidents will be documented in the electronic case report form.

In case of a device deficiency, the device should be returned to Medinol, for analysis and be reported in the clinical results per the written instructions provided. 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, user errors, and inadequate labeling, as detailed below:

Device malfunction:

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigational Plan (CIP)

Malfunction per FDA CFR [§803.3(m)] means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Use error:

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user

- NOTE 1 - Use error includes slips, lapses, and mistakes.
- NOTE 2 - An unexpected physiological response of the subject does not in itself constitute a use error.

Inadequate labeling:

Label is not legible; label is torn; label is missing.

11.3 Documentation

AEs must be listed on the appropriate eCRF.

All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

All AEs (serious and non-serious) will be reported for the entire study period in accordance with national laws.

11.3.1 Intensity or Severity

The following categories of the intensity of an AE are to be used:

Mild: Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae;

Moderate: Interferes with the subject's usual activity, but the subject is still able to function;

Severe: Events that interrupt a subject's usual daily activity and generally require a systemic drug therapy or other treatment.

11.3.2 Relatedness

The Principal Investigator (PI) will evaluate if the AE or SAE is related to the investigational device or study procedure. Relatedness is defined in the following manner:

- UNRELATED: The event is clearly not related to the investigational trial device/procedures.
- UNLIKELY RELATED: The event is unlikely to be related to the trial device/ procedure.
- POSSIBLY RELATED: The event is possibly related to the trial device/procedure.
- RELATED: The event is clearly related to the trial device/procedure.

11.3.3 Outcome

The clinical outcome of the event at the time of last observation will be characterized as follows:

- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae

- Recovering/Resolving
- Fatal
- Unknown

11.4 Reporting of Adverse Events

11.4.1 Serious Adverse Events Reporting

All participating study sites should report SAEs to Medinol and HCRI within 24 hours of knowledge of the event preferably by completing an AE eCRF and in accordance with applicable national regulations. Report of a subject death must be submitted using the Study Exit eCRF along with a brief statement of the pertinent details, and the death records/certificate or autopsy report, if available/performed.

It is the responsibility of each Investigator to report all SAEs to the reviewing IRB, according to national regulations and IRB requirements. A copy of the IRB report should be forwarded to the sponsor or its authorized representative.

Reportable events to be reported by the sponsor to the FDA under 21 CFR 803 Medical Device Reporting (MDR)

"MDR reportable events" are events that the sponsor becomes aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3 and 803.50).

Any event which meets both basic reporting criteria A and B listed below is considered a reportable event and must be reported to the FDA. The criteria are as follows:

A. An event has occurred that led, or might have led, to one of the following outcomes:
    a) Death,
    b) Serious injury that:
        - Is a life-threatening illness or injury or
        - Results in permanent impairment of a body function or permanent changes to a body structure or
        - Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body function

B. The sponsor's device is suspected to be a contributory cause of the event.

This means that a death or serious injury was or may have been attributed to a medical device or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of [21 CFR 803.3]:

a) Failure
b) Malfunction
c) Improper or inadequate design

d) Manufacture

e) Labeling

f) User error

Additionally, it is the responsibility of the sponsor to submit the following reports to the FDA:

1. A "30-day initial report" must be submitted within 30 calendar days after the day the sponsor becomes aware of a reportable device-related death or serious injury, or a reportable malfunction.
2. A "5-day report" must be submitted to the FDA within 5 work days after the sponsor becomes aware of an MDR reportable event:
   - That necessitates remedial action to prevent an unreasonable risk of substantial harm to public health or
   - For which the FDA have made a written request for the submission of 5-day reports.
3. A "supplemental" or "follow-up report" must be submitted whenever the sponsor obtains information not known or available at the time of submission of the initial 30-day or 5-day report.

11.4.2 Unanticipated Adverse Device Effect Reporting under 21 CFR 803 & 812 Investigational Device Exemption

If a complication occurs that the Investigator believes may be a potential UADE, the site should immediately contact the sponsor or its authorized representative to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a patient, the site should immediately notify the sponsor.

The Investigator shall submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. All UADEs must be documented by the Investigator including the date of onset, a complete description of the event, possible reason(s) for the event, severity, duration, actions taken, and outcome. Copies of all supporting documents should be submitted concurrently with the UADE eCRF.

A report from the sponsor will be submitted to the FDA and to all reviewing IRBs and participating Investigators within 10 working days after the sponsor first receives notice of the effect. The sponsor will submit other reports as required by the FDA.

11.4.3 Device Deficiencies

All deficiencies and NIRxcell™ Stent System malfunctions will be documented on the appropriate eCRF and the malfunctioned device will be returned to Medinol, if applicable, per written instructions, for analysis and be reported in the clinical results. Device deficiencies should be reported to Medinol and HCRI within 24 hours, per the instructions of eCRF completion. The sponsor is responsible to report device deficiencies to the FDA per MDR regulations.

11.5 Reporting of Study Endpoint Adverse Events

Whenever a clinical event related to a study endpoint is suspected or identified, all supporting source documents (i.e. progress notes, discharge summaries, catheterization lab reports, ECGs, lab results, etc.) should be submitted according to CEC source documentation collection procedures as soon as they are available. The source documentation required for each reported event is listed in the CEC charter.

12 Statistical Methods

This is a prospective, multi-center, non-randomized, single-arm clinical study designed to collect additional information on the safety and efficacy of the NIRxcell Stent Systems in the treatment of *de novo* stenotic lesions in native coronary arteries in the US population. The primary endpoint to be evaluated in this study is TVF at 3 years, defined as a composite of cardiac death, target vessel MI, or clinically driven TVR by percutaneous or surgical methods within 3 years post-procedure. This rate will be formally compared against a performance goal, which is derived from a meta-analysis of coronary stenting with BMS as described below. The study will be conducted at a maximum of 15 centers in the United States, and will enroll 131 subjects.

12.1 Determination of Performance Metric

The NIRTRAKS Post-Market Study is designed as a single-arm registry, which will be compared against a performance goal derived from a meta-analysis of the primary endpoint, TVF at 3 years post-procedure, in BMS patients. To establish a TVF rate at 3 years following PCI with BMS, we performed a systematic search of the PubMed/MEDLINE literature database of articles published until November 25, 2011, with the following search criteria: "Stents"[Mesh] AND coronary AND ("long term"[title] OR "long-term"[title] OR "3 year"[title] OR "three year"[title]). We supplemented this search strategy with a manual search of secondary sources, including references cited in the primary articles. Subsequently, we limited the results to include only those studies with at least 3 years of follow-up and in which TVF was reported or could be calculated based on the outcomes reported.

The primary search criteria yielded 86 headings. After scanning the titles and abstracts of these headings, 8 full-text publications from 6 trials/programs were retrieved for additional analysis. One additional report was retrieved through manual search. Finally, the following 5 trials/programs were identified as relevant according to subject selection, type of intervention, and length of follow-up: TAXUS Clinical Program (I-IV),[22] ENDEAVOR II,[23] RAVEL,[24] SIRIUS,[25] and the SPIRIT FIRST trials.[26]

The studies identified employed diverse outcome criteria, and thus some adjustments for the reported data were made.

1. **Oculostenotic reflex**: The current post-market study will evaluate subjects based on follow-up assessments performed by telephone, and without mandatory angiographic assessment. Hence, any repeat interventions will be performed solely based on clinical symptoms. The observation that angiographic follow-up increases TLR and TVR rates when compared against clinical follow-up alone (the "oculostenotic reflex") has been made previously with both balloon angioplasty and BMS.[5,27, 28] Thus, our expected TVR rate (as a component of TVF) will be lower than those observed in studies that utilized mandatory angiographic assessment. To perform this adjustment, we analyzed 2 studies that reported differences in TVR rates between angiographically- and clinically-followed cohorts. The first study, TAXUS IV,[27] reported a TVR rate at 1 year of 18.9% in the angiographic cohort and 14.3% in the clinical cohort – a difference of 4.6%. The second study, ENDEAVOR II,[28] reported TVR rate at 8 months of 16.8% in the angiographic cohort and 8.2% in the clinical cohort – a difference of 8.6%. We averaged these 2 studies to assume the difference in TVR rate between angiographically and clinically followed cohorts to be 6.6%. We

used this estimate to correct the rate of 1 year TVR according to the percentage of subjects undergoing repeat angiography in the trials included. The number of non-clinical TVR was then reduced from the overall TVR at 3–5 years.

$$Clinically\ Driven\ (TVR_n) = TVR_n - \ 0.066 \cdot Y \cdot TVR_1$$

Where Y = percentage of subjects undergoing protocol driven angiography at 9–12 months.

2. **Target vessel MI**: Only 1 of the trials identified reported target-vessel MI rate (TAXUS). The 5-year ratio of target vessel MI to all MI in this trial was 0.75. We searched the medical literature for long-term results of clinical trials assessing BMS in similar subject populations, in which target-vessel MI was reported, but no additional data were found. We identified 1 trial in which target-vessel MI was adjudicated after DES implantations.[29] In this trial, the 2-year ratio of target vessel MI to all MI was 0.9. Thus, we assume that overall, the 3-year target-vessel MI is approximately 0.825 of the overall rate of MI reported in the trials identified.
3. **Target vessel non-fatal MI**: Only 1 of the trials identified reported the fatality rate of MI. In the RAVEL trial, the 3-year ratio of non-fatal MI to all MI was 0.75. We used this proportion for the other studies included in our analysis.
4. **TVF**: To match the TVF definition in the NIRTRAKS Post-Market Study, TVF was calculated as the sum of clinically driven TVR, target vessel non-fatal clinically relevant MI and cardiac death.
5. **TVF at 3 years**: In the ENDEAVOR II trial, 50% of the combined long-term outcome of death, MI and TVR occurred in the first 9 months post-procedure. For trials in which outcomes were reported for 4 or 5 years, we corrected the rates to 3 years by assuming that 50% of the events occurred during the first year, and the remainder were evenly distributed across the follow-up duration of years 2 to 5. Thus, the 3-year event rate was calculated according to the following formula:

$$TVF_3 = \ TVF_1 + \frac{TVF_n}{n-1}$$

Where $TVF_1 = 0.5 \cdot TVF_n$ and n = number of follow-up years reported in original publication.

We performed a random effects meta-analysis of the 3-year TVF rates from the BMS arms of included studies, following the approach in DerSimonian and Laird (1986).[31] Based upon our analysis, the endpoint rate of TVF derived from the meta-analysis is **23.2%** (95% CI 19.8%, 26.7%).

Table 4: Subject and Lesion Characteristics in BMS Trials

		Subject Characteristics			Lesion Characteristics		
Trial	**No. of BMS Subjects**	**Mean Age (y)**	**Women (%)**	**Diabetes Mellitus (%)**	**RVD (mm)**	**MLD (mm)**	**Length (mm)**
TAXUS I-IV	1397	62.2	28.3%	25.6%	2.73	0.91	14.6
RAVEL	118	59.7	32%	17.7%	2.64	Unknown	9.61
SPIRIT FIRST	25	61	24%	10%	2.71	Unknown	10.9
ENDEAVOR II	599	63	24.5%	22.2%	2.76	0.84	14.38
SIRIUS	525	62	30%	28%	2.81	0.97	14.4

Table 5: Target Vessel Failure Rates in BMS Trials

Trial	No. of BMS Subjects	Angio Follow-Up N (%)	TVR	Clinically Driven TVR	All MI	Target Vessel MI	Target Vessel Non-Fatal MI	All Death	Cardiac Death	TVF	TVF at 3 Years
	5-Year Data										
TAXUS I-IV	1397	1102 (78.9%)	--	21.8%*	**6.6%**	**5%**	3.75%	**9.1%**	**3.8%**	29.35%	22.01%
SIRIUS	525	353 (67.2%)	**30.5%**	29.5%**	**6.5%**	5.36%	4.02%	**8.4%**	**3.6%**	37.12%	27.84%
SPIRIT FIRST	25	25 (100%)	--	**36%**	**0%**	0%	0%	--	**0%**	36%	27%
	4-Year Data										
ENDEAVOR II	599	294 (49.1%)	--	17.2%†	**4.4% (non-fatal)**	3.63% (non-fatal)	3.63%	**5.2%**	2.24%‡	23.07%	19.23%
	3-Year Data										
RAVEL	118	118 (100%)	--	**17.7%§**	**7.1%**	5.86%	4.39%	**4.4%**	**2.7%**	24. 79%	24.79%

BMS: bare metal stent; MI: myocardial infarction; TVF: target vessel failure; TVR: target vessel revascularization.

* We assumed a 5-year clinically driven TLR rate of 16.8% based on a 5-year TLR rate of 16.8% in 295 subjects with no routine angiographic follow-up. In this trial the ratio of TVR to TLR at 5 years was 1.3. We therefore assumed the clinically driven TVR rate to be 1.3 times the clinically driven TLR rate.
** Based on a 1-year TVR rate of 22.9%.
† At 9 months, 26 events from the ENDEAVOR II cohort were reported as non-clinical (angio driven). These were deducted from the 129 events reported at 4 years.
‡ At 5 years, the proportion of cardiac deaths of all deaths was 0.42 in the TAXUS program and 0.43 in the SIRIUS trial. We used this proportion (0.43) to calculate the rate of cardiac deaths at 4 years in the ENDEAVOR II trial.
§ The sum of clinically driven TLR (15.0%) and all non-TLR TVR (2.7%).

12.2 Performance Goal

The goal of the primary analysis will be to assess the comparability of the observed primary endpoint rate for the study stent to the meta-analysis derived rate (23.2%). Based upon the meta-analysis, the expectation for the true primary endpoint rate for the study stent is equal to 23.2%. However, since strict equality cannot be assessed statistically, this non-randomized, single-arm study will assess if the study stent 3-year TVF rate falls significantly below 34.8%. Specifically, this study will assess the ability of the study stent to meet a performance goal of 34.8%, which is a 50% increase over the expected rate of 23.2% obtained from the meta-analysis.

12.3 Primary Endpoint and Sample Size Calculation

The null hypothesis for this study states that the NIRxcell will have a primary endpoint rate greater than or equal to 34.8%. The alternative hypothesis states that the NIRxcell will have a primary endpoint rate less than 34.8%.

Specifically:

$$H_o: \pi_{\text{NIRTRAKS}} \geq 34.8\%$$

$$H_A: \pi_{\text{NIRTRAKS}} < 34.8\%$$

where π_{NIRTRAKS} is the true primary endpoint rate for the study stent and the 34.8% is the meta-analytically derived performance goal (PG) for the primary endpoint rate. Rejection of the null hypothesis will signify that the performance goal has been met, and that the study stent's primary endpoint rate is less than 34.8%.

The primary hypothesis test will be carried out by comparing the upper bound of the exact 1-sided 95% confidence interval of the 3-year TVF rate to 34.8%, the PG. If this upper bound is less than 34.8%, then it will be considered that the study stent meets the performance goal. The necessary sample size for testing the primary hypothesis was estimated with PASS software using exact hypothesis testing based on the exact distribution with the following assumptions:

- Type I error (α) = 0.05 (1-sided).
- Statistical power ($1 - \beta$) = 83%.
- PG = 34.8%.
- π_{NIRTRAKS} = 23.2%.

An evaluable sample size of 105 provides 83% power to reject the above null hypothesis in favor of the alternative. Thus, 131 subjects will be enrolled to account for loss to follow-up, which is expected to be approximately 7.0% per year.

The loss to follow-up in previously published stent trials with long-term follow-up is low. In the SIRIUS[25] trial, complete data compliance for all 5-year follow-up end points was 93.6% and 94% in the intervention and control groups, respectively. At 9 months the clinical compliance was 100%[32] in both groups. In the ENDEAVOR II trial,[23] out of 1,197 enrolled subjects, 1,167 were followed for 4 years (97.4%). In the RAVEL trial[24], complete data sets were available for 94.2% of subjects randomly assigned to sirolimus-eluting stents and for

94.1% of subjects randomized to BMS. In the TAXUS IV trial,[22] out of 1,314 intention-to-treat (ITT) subjects, 5-year data were available for 1,294 (98.4%) subjects. In view of these data, we believe a yearly 7% loss-to-follow-up estimate is conservative and encompasses wide margins of safety.

12.4 Analysis Sets

12.4.1 Intention-to-Treat

The primary analysis set will be based on the principle of intention-to-treat. All statistical analyses in this study will be performed on the ITT population with each enrolled subject analyzed regardless of the actual treatment received.

12.4.2 Per-Protocol

Per-protocol (PP) analysis will also be conducted. Per-protocol is defined as all subjects who sufficiently comply with the study protocol. Compliance covers treatment received, availability of follow-up data (follow-up of at least 3 years, allowing for a visit window of 3 years ± 1 month), and absence of major protocol deviations.

12.5 Endpoint Analyses and Reporting of Results

Descriptive statistics will be used to present the data and to summarize the results. Categorical variables will be presented using counts and percentages. Proportions will be calculated using known non-missing values. Continuous variables will be summarized by presenting the number of observations (N), mean, 2-sided 95% confidence interval of the mean, standard deviation, median, minimum and maximum values. Unless otherwise indicated, all statistical tests and/or confidence intervals will be performed at $\alpha = 0.05$ (2-sided).

For adverse event reporting, which includes the primary and secondary safety endpoints, the primary analysis will be based on subject counts, not event counts. A subject with more than one event will be counted only once toward the event rate based on the total number of subjects with adverse events. Additionally, an event rate based on event counts will also be presented. Unless specified otherwise, statistical significance will be declared if the two-sided p-value is < 0.05.

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.1 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software. In general, data for all study subjects will be combined and presented. Individual data will be presented in subject listings.

12.6 Analysis of Baseline Demographics and Procedural Characteristics

Descriptive statistics will be generated for baseline demographics, procedural characteristics, and follow-up data collected. Categorical variables will be analyzed using frequency, incidence and event rate. For continuous variables collected in the study, analysis will include mean, median, standard deviation and range.

12.7 Analysis of Primary Endpoint

An assessment of the null and alternative hypotheses from Section 12.3,

$$H_o: \pi_{\text{ NIRTRAKS}} \geq 34.8\%$$

$$H_A: \pi_{\text{ NIRTRAKS}} < 34.8\%$$

will be carried out using the exact test of the binomial distribution at the 1-sided 0.05 level of significance on ITT subjects who experienced the primary endpoint or who had follow-up within 1 month (the allowable window for the 3-year contact) of 3-years post-procedure. If this upper interval is below 34.8%, the null hypothesis above will be rejected in favor of the alternative (the results of the exact confidence interval approach will yield the same conclusion as the 1-sided exact test of the null hypothesis). In addition, the assessment of the hypotheses will be carried out on all ITT subjects by (a) comparing the 1-sided upper 95% confidence interval of the Kaplan-Meier estimate of the primary endpoint rate to 34.8%; subjects not experiencing the endpoint will be censored at 3 years post-procedure or day of withdrawal, whichever is earlier; and (b) multiply imputing the primary endpoint incidence for subjects prematurely withdrawing prior to 3 years minus 1 month post-procedure and prior to experiencing the primary endpoint, followed by a test of hypothesis on the imputed data (see details in Section 12.8 below). The results of the various ITT analyses on the primary endpoint will be compared descriptively to assess the sensitivity of results to missing data.

Finally, the analysis will be carried out on the PP population (secondary analysis) using the exact test of the binomial distribution and an exact 1-sided upper 95% confidence interval.

12.8 Handling of Missing Data in the Analysis of the Primary Endpoint

The primary analysis set will be the ITT population, which includes all subjects enrolled into the study. Subjects who prematurely withdraw prior to the 3-year (minus the allowable 1-month window) contact and prior to experiencing the primary endpoint will have their missing primary endpoint result handled using the following 3 approaches; results will be compared across the 3 approaches for consistency:

1. Only subjects with appropriate follow up (at least 3 years minus 1 month) or who experienced the primary endpoint by 3 years will be included in the exact hypothesis testing, as discussed above. This is the primary analysis..
2. Multiple imputation: This will be used to impute primary endpoint status (yes/no) for subjects with missing primary endpoint data. The logistic regression approach to multiple imputation will be carried out using SAS PROC MI. The covariates to be used in the imputation model will be age, sex, prevalence of diabetes, target lesion length and reference vessel diameter. Five data sets will be imputed, and a 1-sided test of the above null hypothesis will be carried out on each data set using the normal approximation to the binomial distribution. SAS PROC MIANALYZE on the results of the 5 significance tests will then be used to obtain an overall assessment of the significance of the 1-sided test across the 5 data sets.
3. As a third analysis and as discussed above, the Kaplan-Meier estimate of the 3-year primary endpoint rate, and its 1-sided upper 95% confidence interval will be calculated. Subjects not experiencing the primary endpoint within 3 years will be

censored at 3 years or the date of withdrawal from the study, whichever is earlier. The upper confidence limit will be compared to 34.8%; if less than 34.8%, the primary endpoint rate will be considered to be significantly less than the performance goal in this analysis.

12.9 Analysis of Secondary Endpoints

All secondary endpoints (listed below) are dichotomous variables. Secondary endpoints will not be tested formally. Instead, secondary endpoints will be presented as the number and percentage of subjects experiencing the outcome, along with 2-sided exact 95% confidence intervals of the percentages. In addition, a Kaplan-Meier (K-M) estimate of the event-free survival rate and its corresponding standard error will be presented for death, MI, clinically driven TLR and TVR, with a corresponding K-M curve.

The secondary endpoints that will be reported are as follows:

1. **TVF** at 9 Months.
2. **All cause death** at 30 days, and 1, 2 and 3 years.
3. **Cardiac death** at 30 days, and 1, 2 and 3 years.
4. **All cause MI** at 30 days, and 1, 2 and 3 years.
5. **Target vessel MI** at 30 days, and 1, 2 and 3 years.
6. **Clinically driven TLR** at 30 days, and 1, 2 and 3 years.
7. **Clinically driven TVR** at 30 days, and 1, 2 and 3 years.
8. **Acute success rates**

   Device success: Attainment of <50% final residual stenosis of the target lesion using the NIRxcell Stent System only.

   Lesion success: Attainment of <50% final residual stenosis of the target lesion using any percutaneous method.

   Procedure success: Attainment of <50% residual stenosis of the target lesion and no in-hospital death, MI or TLR.
9. **Stent thrombosis** at hospital discharge, at 30 days, and 1, 2 and 3 years.

12.10 Pre-Planned Subgroup Analyses

A subgroup analysis will be performed according to the following characteristics: ethnicity, race, gender, age group (less than and over 65), obesity (less than and over body mass index [BMI] of 30), diabetes mellitus, and site of arterial access (trans-radial versus trans-femoral access). The TVF rate with 95% CIs will be provided for each subgroup. There will be no formal statistical analysis to compare TVR rates across these subgroups, as the study is not powered to detect such differences.

12.11 Analysis of Poolability of Data Across Study Sites

This is a multi-center clinical study, with standardization of subject enrollment, data entry and AE reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms. To present the data from this clinical study in a

summary form, a comparison across all sites on the primary endpoint will be completed via logistic regression to determine if the primary endpoint data can be pooled for the primary analysis. A 0.15 level of significance will be used to assess site poolability. A poolability *P* value < 0.15 will not necessarily preclude patients from being pooled across sites for the primary analysis. Rather, further analysis will be carried out to assess if it is appropriate to pool sites, such as (1) inspection of the primary endpoint rate in each site to assess if the primary endpoint rate is at least descriptively less than the performance goal at each site; (2) a comparison of the following variables across sites to assess if potential lack of site poolability on the primary endpoint may be due to differences in the following variables across sites: baseline demographics, procedural characteristics and protocol deviations.

The distributions of the above variables across the sites will be tabulated. To detect site differences, the Kruskal-Wallis test will be used for continuous variables and the Chi-Square test or the Fisher's exact test will be used for categorical variables, depending on sample size.

12.12 Clinical Events Committee

The clinical events committee (CEC) will be comprised of both interventional and non-interventional cardiologists who are not participants in the study and who have no conflict of interest with the study or the study 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 clinical study endpoint events. At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical endpoint event. The CEC will then meet regularly in approximately every 12 months following start of enrollment. The CEC will review and adjudicate study endpoint–related clinical events in which the required minimum data are available. The committee will also review and rule on all deaths that occur throughout the trial.

Once the specific criteria for clinical endpoints are established by the CEC, HCRI will be responsible for categorizing all clinical endpoint events when all necessary data are available.

13 Data Handling and Record Keeping

13.1 Source Documents

Source data is all information, original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' evaluation checklists, recording media such as DVD and video tapes, X-rays, subject files, and records kept at the laboratories and at other departments involved in the clinical trial.

Source documents will be used:

- For verification of the data documented in subjects' eCRF during monitoring visits.
- For adjudication of AEs. Standardized forms will be designed to ensure proper collection of all requested source documentation from the sites.

13.2 Electronic Case Report Form

A web-based clinical data collection and presentation system will be used in this study. The eCRF is the primary data collection instrument and will be provided to the sites as a secured, private facility over the internet. This system will include:

- Complete eCRF-based data collection, clarification and archival system.
- Online query creation and resolution.
- Electronic signatures compliant with 21 CFR Part 11.
- Complete audit trail history.

All data requested on the eCRF must be recorded. All missing data must be explained:

- If a space on the eCRF is left blank because the procedure was not done or the question was not asked, a comment must be created on the field to explain the blank field.
- If the item is not applicable to the individual case, a comment must be created on the field to explain the blank field.
- If any entry error has been made, to correct such an error, the data must be edited including a reason for the correction and the eCRF re-submitted.

Detailed description of the eCRF components as well as completion and handling instructions are provided in the eCRF Completion Guidelines.

The eCRF must be fully completed for each subject, electronically signed by the authorized personnel, and submitted to the data center. eCRFs documenting SAEs, UADEs, device failures and device malfunctions should be submitted via the Electronic Data Capture (EDC) system as soon as possible, preferably within 24 hours after the investigator becomes aware of the event.

All other eCRFs should be completed in a timely manner, preferably within 5 to 7 days of the subject's enrollment or follow-up visit.

All angiographic and ECG media should be prepared and sent to the corresponding core laboratory, preferably within 7 working days of data collection.

All collected study data will be made available (and sent in the appropriate format) to the sponsor, if requested, after the study has reached its primary endpoint at 3 years post-procedure.

13.3 Data Review

Primary data collection, based on source-documented hospital chart reviews, will be performed by the research coordinators at each investigational site. eCRFs will be completed prospectively in an expedited fashion. Sponsor-appointed monitors will provide clinical monitoring, including review of eCRF and parity checks with the source documentation.

eCRFs will be reviewed for completeness and clarity by the data center. Missing or unclear data will be requested as necessary throughout the study. The data center may request further documentation such as physician and/or catheter laboratory procedure notes when SAEs are reported.

Data entry and development of the primary database for the study will be managed by the data center. The data center will also be responsible for the quality control of the database and confirming the overall integrity of the data.

13.4 Records Retention

All study-related records and reports must be maintained in designated NIRTRAKS Post-Market Study administrative files at each investigational site. These files should be retained for a minimum of 5 years after: the date on which the study is terminated or completed, OR the date on which there is no pending/contemplated action in any International Conference on Harmonisation (ICH) region, OR the date that the records are no longer required for purposes of supporting a marketing approval in ICH regions, OR according to national regulatory requirements, whichever is later. The files may be discarded only upon notification from the sponsor. To avoid error, the principal investigator should contact the sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

The subject data for the study will be housed within the database at the data center. At the completion of the study, the site will be sent a CD with the final subject data for the particular site.

13.5 Study Device Accountability

The Primary Investigator will maintain adequate records of the receipt and disposition of the NIRxcell on the device inventory log or case report form (CRF), including stent size/dimensions; date implanted; subject identification number; and implanting Investigator.

14 Quality Control and Quality Assurance

14.1 Investigational Site Monitoring and Auditing

The study will be monitored according to applicable provisions of the sponsor's monitoring procedures, in conformance with World Medical Association Declaration of Helsinki, and local regulations for post-approval clinical studies. Additionally, applicable provisions of FDA regulation 21 CFR parts 812, 50 and 54 will be followed.

Monitoring visits to the investigational sites will be made periodically during the study to ensure that:

- The rights and well-being of study subjects are protected.
- The reported study data are accurate, complete and verifiable from source documents.
- The conduct of study is in compliance with approved protocol/amendment, with GCP, and with applicable regulatory requirements.

A monitoring plan will be prepared and shall include information such as:

- Parties (clinical research organization [CRO]/monitor and sponsor) and signatures.
- Purpose.
- Responsibilities.
- Processes, such as:
    - Types of visits and expected scope of activities in each.
    - Level of source document verification and the key data to be monitored.
    - Communication paths and data flow to be followed.
    - Frequency of visits.
    - Reporting and documentation of monitoring activities.

The principal investigator guarantees direct access to the study files, subject eCRFs and subject medical records, to staff of the sponsor and the sponsor's study contractor(s) personnel, as well as regulatory authorities that govern the conduct of clinical investigations.

The investigational sites may also be subject to a quality assurance audit by staff of the sponsor or the sponsor's study contractor(s) personnel, as well as inspection by regulatory authorities that govern the conduct of clinical investigations.

It is important that the investigators and the relevant site personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

14.2 Training

The training of clinical site personnel, as well as other personnel related to the study (i.e., CRO personnel) will be the responsibility of the sponsor. To insure uniform data collection and protocol compliance, training will cover topics such as investigational product, study protocol (with reference to applicable regulations), eCRF and completion instructions, and study processes and documentation (e.g., informed consent, safety handling and reporting, compliance handling and reporting). All users of the EDC system will be trained in accordance to 21 CFR

Part 11 guidelines. Training can take place via on-line EDC system training modules, webinars, or dedicated meetings, initiation visits, conference calls, specific letters to investigators, etc.

14.3 Protocol Deviations and Medical Emergencies

Protocol deviations are instances, in which the investigator or site personnel did not conduct the study according to the clinical protocol or the investigator agreement. In this study protocol deviations will be classified as follows:

Major deviation: any deviation from subject inclusion and exclusion criteria or subject informed consent procedures.

Minor deviation: deviation from a clinical protocol requirement such as incomplete/inadequate subject tests or examinations, non-compliance with medication regimens, missed follow-ups, follow-ups performed outside specified time windows, etc.

Investigators will not deviate from the protocol without the prior written approval of their IRB and the sponsor except when the change is necessary to eliminate apparent immediate hazards to the human subject or to protect the life or physical well-being of the subject or in unforeseen, isolated instances, where minor changes are made that will not increase the subject's risk or affect the validity of the study.

Study sites should report all protocol deviations on the applicable eCRF. Any deviation from the protocol made to protect the life or physical well-being of a subject in an emergency should be reported as soon as possible but no later than 5 working days after the emergency occurs. Investigators will also adhere to procedures for reporting protocol deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

14.4 Investigational Site Termination

The sponsor reserves the right to terminate an investigational site for any of the following reasons:

- Repeated failure to complete eCRFs.
- Failure to obtain informed consent.
- Failure to report SAE within 24 hours of knowledge
- Repeated protocol violations.
- Failure to enroll an adequate number of subjects.

15 Ethical and Regulatory Considerations

15.1 Compliance Statement

This trial will be conducted in accordance with this protocol, the Declaration of Helsinki and US Good Clinical Practice (21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 812), and the applicable regulatory requirements (such as 21 CFR Part 54, 21 CFR Part 11). The conduct of the trial will be approved by the appropriate Institutional Review Board (IRB) of the respective investigational site and the US Food and Drug Administration.

15.2 Institutional Review Board

This protocol and any amendments will be submitted to a properly constituted independent IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliations to the sponsor. If a membership list is not available, a waiver letter or minutes from the IRB meeting is required to indicate that none of the physicians involved in this study are members of the IRB or, if they are, that they are non-voting members or did not vote in the approval of this protocol. Investigators are responsible for obtaining and maintaining approval of the study by the IRB.

The sponsor may propose changes to the clinical protocol. Changes to the protocol must be approved in writing by the IRB; these changes will be considered as protocol amendments. A significant change is one that may increase risk or present new risk to the subject, or may adversely affect the validity of the study. Each investigator must receive approval for the amendment prior to implementing it at his/her investigational site.

15.3 Informed Consent Form

Signed written informed consent is mandatory and must be obtained from all subjects prior to their participation in the NIRTRAKS Post-Market Study. The investigator will explain to the subject in layman's terms all aspects of the consent. Informed consent must be obtained in accordance with ISO 14155:2011, FDA regulation (21 CFR Part 50) and the Declaration of Helsinki and shall inform the subject as to the objective and procedures of the study and possible risks involved. The subjects must be informed of their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care.

The NIRTRAKS Post-Market Study template informed consent form (ICF) that will be provided to the participating sites may be adjusted by site personnel but any such modification must be approved by the sponsor. The NIRTRAKS Post-Market Study ICF must be used in addition to the institution standard consent form. The IRB-approved study ICF must be sent to the sponsor for approval and a copy must be placed at the investigational site in the NIRTRAKS Post-Market Study binder. The ICF form must be signed and dated by the subject or the subject's legally authorized representative, and the investigator-designated research professional obtaining the consent. A signed copy of the ICF must be given to each subject enrolled in the study.

Modifications to the NIRTRAKS Post-Market Study ICF (e.g., additional safety or procedural information) and any written subject information throughout the study period, must be approved by the sponsor and, as necessary, the IRB and other regulatory authorities as required by country

law. If the modification of the ICF relates to any study methodology, then the subjects must be re-consented. The ICF may also be revised for minor non-procedural changes. For these changes, the site should check with its IRB to see if subject re-consent is required.

15.4 Confidentiality

At all times throughout the study, confidentiality shall be observed by all parties involved. All information and data sent to the data center, core laboratories and/or the sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The principal investigator consents to visits by the staff of the sponsor and the sponsor's study contractor(s) personnel, as well as regulatory authorities that govern the conduct of clinical investigations.

16 Reporting Requirements

16.1 Investigator Reporting Responsibilities

Investigators are required to prepare and submit the following data completely and accurately and within the time required:

Table 6: Investigator's Responsibilities for Preparing and Submitting Reports

Investigator reporting responsibilities		
Data Form	**Action Required**	**Requirements**
Subject enrollment eCRF page	Complete via EDC system	Within 7 days of enrollment.
Subject angiograms	Provide to angiographic core laboratory	Within 7 working days of exam
Subject ECG	Provide to ECG core laboratory	Within 7 working days of exam
SAE and UADE * Source documents should be sent to Monitoring CRO, upon request	Complete via EDC system	Within 24 hours of knowledge.
	Provide to IRB and FDA	As required.
AE	Complete via EDC system	If possibly or probably related to study device / procedure– complete eCRF within 24 hours of knowledge. Otherwise – complete within 10 working days of knowledge.
Subject death during the study	Complete via EDC system	Within 24 hours of knowledge.
	Provide to IRB and FDA	As required.
Subject withdrawal	Complete via EDC system	Within 7 working days of knowledge.
Device deficiencies	Complete via EDC system	Within 24 hours of knowledge.
Withdrawal of IRB approval	Provide to Medinol either verbally or via email	Within 5 working days of knowledge.
Deviations from the clinical protocol		
• Failure to obtain informed consent prior to procedure	Provide to Medinol (either verbally or via email) as well as to IRB and FDA. Also complete via EDC system	Within 5 working days of occurrence. The report will include a brief description of the circumstances justifying failure.

Investigator reporting responsibilities		
Data Form	**Action Required**	**Requirements**
• Other deviation	Complete via EDC system	Within 7 working days of knowledge.
	Provide to IRB and FDA	As required.
Progress reports / notifications of site activity (e.g.: end of enrollment, end of study, etc.)	Provide to IRB	Annually for the duration of the clinical study.
Final clinical summary report	Provide to IRB, once available	Report must be submitted within 3 months after termination or completion of the study.

16.1.1 Investigator's Final Report

Upon completion or termination of the study a final report will be prepared. This report will contain a critical evaluation of all data collected during the course of the study at each institution. The report must be signed by the principal investigator of the study and will be provided to the IRB as required. Any modifications to this final report must be reviewed and approved by the sponsor.

16.2 Sponsor Reporting Requirements

The sponsor and HCRI will prepare written progress reports and a final report. Medinol will submit the required reports as required by local law. This includes the following reports to the FDA according to 21 CFR 803:

Table 7: Sponsor's Responsibilities for Preparing and Submitting Reports

What to Report	Report Form	To Whom	When
30 day reports of deaths, serious injuries and malfunctions	Form FDA 3500A	FDA	Within 30 calendar days of becoming aware of an event
5-day reports for an event designated by FDA or an event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health	Form FDA 3500A	FDA	Within 5 work days of becoming aware of an event
18-month Progress Report*	PAS Progress Report	FDA	23 July 2015
24-month Progress Report*	PAS Progress Report	FDA	23 January 2016

What to Report	Report Form	To Whom	When
Progress Report*	PAS Progress Report	FDA	Annually on January 23
Final Report	Final Study Report	FDA	Anticipated - Dec 2019

*PAS progress reports provided to FDA after start of enrollment will be based on CEC adjudicated data.

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Appendix 1-P: Study Definitions

ABRUPT CLOSURE

Abrupt Closure: Defined as the occurrence of new (during the index procedure) severely reduced flow (Thrombolysis in Myocardial Infarction [TIMI] grade 0–1) within the target vessel that persists and requires rescue by stenting or other treatment, or results 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 patent but has reduced flow. Abrupt closure also does not connote transient closure with reduced flow in which the index treatment application does reverse the closure.

Subabrupt Closure: Defined as abrupt closure that occurs after the index procedure is completed (and the subject has left the catheterization laboratory) and before the 30-day follow-up evaluation.

Threatened Abrupt Closure: Defined as a grade B dissection and ≥50% diameter stenosis or any dissection of grade C or higher.

ACUTE SUCCESS[1]

Device Success: Attainment of <50% residual stenosis of the target using only the NIRxcell Stent System.

Lesion Success: Attainment of <50% residual stenosis of the target lesion using any percutaneous method.

Procedure Success: Attainment of <50% residual stenosis of the target lesion and no in-hospital death, MI or TLR.

ADVERSE DEVICE EFFECT (ADE)

An ADE is defined as an AE related to the use of the study device.

> **NOTE 1:** This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the study device.
>
> **NOTE 2:** This definition includes any event resulting from user error or from intentional misuse of the study device.

ADVERSE EVENT (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study device.

> **NOTE 1:** This definition includes events related to the study device or the comparator.

[1] All analyses to determine acute success measures will be conducted utilizing *in-stent* residual stenosis values. When in-stent % residual stenosis is not available, in-lesion % residual stenosis will be used to complete the analysis.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the study device.

ANTICIPATED ADVERSE EVENT

Any undesirable experience (sign, symptom, illness, abnormal laboratory value or other medical event) occurring to a subject, whether or not considered related to the study product(s) prescribed as part of the clinical protocol, predefined in the clinical protocol and/or Instructions for Use (IFU), product label that is identified or worsens during a clinical study.

BRAUNWALD CLASSIFICATION OF UNSTABLE ANGINA

Severity

Class 1: New onset of severe or accelerated angina. 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.

Class 2: Angina at rest, subacute. Subjects with 1 or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Class 3: Angina at rest, acute. Subjects with 1 or more episodes of angina at rest within the preceding 48 hours.

Clinical Circumstances in Which Unstable Angina Occurs

Class A: Secondary unstable angina. Subjects in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia. Such conditions reduce myocardial oxygen supply or increase myocardial oxygen demand and include anemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrhythmia, unusual emotional stress, thyrotoxicosis, and hypoxemia secondary to respiratory failure.

Class B: Primary unstable angina. Subjects who develop unstable angina pectoris in the absence of an extracardiac condition that have intensified ischemia, as in class A.

Class C: Postinfarction unstable angina. Subjects who develop unstable angina within the first 2 weeks after a documented acute myocardial infarction.

CANADIAN CARDIOVASCULAR SOCIETY CLASSIFICATION (CCSC) OF ANGINA

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

Class II: Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first hours after awakening. Angina if walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III: Marked limitations of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.

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

CLINICALLY DRIVEN TARGET LESION REVASCULARIZATION (TLR)

Revascularization at the target site associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ≥50% by QCA, or revascularization of a target site with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

CLINICALLY-DRIVEN TARGET VESSEL REVASCULARIZATION (TVR)

Revascularization in the target vessel associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ≥50% by QCA, or revascularization of a target vessel with diameter stenosis ≥70% by QCA without either angina or a positive functional study.

CEREBROVASCULAR ACCIDENT (CVA; see *Stroke*)

The occurrence of cerebral infarction (ischemic stroke) and intracerebral hemorrhage and subarachnoid hemorrhage (hemorrhagic stroke).

***DE NOVO* LESION**

Defined as a native coronary artery lesion not previously treated.

DEATH

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

Vascular Death: Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other vascular diseases.

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.

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

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) CLASSIFICATION

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

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

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

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

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

Grade F: Filling defect accompanied by total coronary occlusion.

EMERGENT BYPASS SURGERY

Defined as coronary bypass surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

IN-SEGMENT MEASUREMENT

Defined as the measurements either within the stented segment or within 5 mm proximal and distal to the stent edges.

IN-STENT MEASUREMENT

Defined as the measurements within the boundaries of the stent.

LESION CLASS (American College of Cardiology/American Heart Association Class)

Type A Lesions: Minimally complex, discrete (length <10 mm), concentric, readily accessible, non angulated segment (<45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, and an absence of thrombus.

Type B Lesions: Moderately complex, tubular (length 10–20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (>45°, <90°), irregular contour, moderate or heavy calcification, total occlusions <3 months old, ostial in location, bifurcation lesions requiring double guide wires, and some thrombus present.

Type C Lesions: Severely complex, diffuse (length >20 mm), excessive tortuosity of proximal segment, extremely angulated segments >90°, total occlusions >3 months old and/or bridging collaterals, inability to protect major side branches, and degenerated vein grafts with friable lesions.

MINIMAL LUMINAL DIAMETER (MLD)

The average of 2 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 ARC Definition[2]

Classification	Biomarker Criteria*	Additional Criteria
Peri-procedural PCI	Troponin >3 times URL or CKMB >3 times URL	Baseline value <URL
Peri-Procedural CABG	Troponin >5 times URL or CKMB >5 times URL	Baseline value <URL AND any of the following: new pathologic Q waves‡ or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium
Spontaneous (>48 h following PCI, >72 h following CABG)	Troponin >URL or CKMB >URL.	Baseline value <URL and any of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB), development of pathological Q waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Silent	No biomarker data available.	New pathologic‡ Q waves or LBBB.
Sudden Death	Death before biomarkers obtained or before expected to be elevated.	Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus by angiography or autopsy.
Reinfarction, spontaneous and periprocedural (base definition; infarction extension)	Stable or decreasing values on 2 samples >6 h apart and 20% increase 3–6 h after second sample.	If biomarkers not stable (increasing or peak not reached), then insufficient data to diagnose recurrent myocardial infarction.

Adapted from Global Task Force Universal Definition of Myocardial Infarction, Thygesen *et al*.
PCI: percutaneous coronary intervention; h: hour; URL: upper range limit (99th percentile of normal reference range); CKMB: creatinine kinase myocardial band isoenzyme; CABG: coronary artery bypass graft; LBBB: left bundle branch block; ECG: electrocardiogram.
*Baseline biomarker value required before study procedure and presumes a typical rise and fall.
‡Pathologic Q waves may be defined according to the Global Task Force, Minnesota code or Novacode.

NO REFLOW

Defined as a sustained or transient reduction in antegrade flow that is not associated with an obstructive lesion at the treatment site.

PERCENT DIAMETER STENOSIS

The value calculated as 100 x (RVD – MLD)/RVD using the mean values from 2 orthogonal views (when possible) by QCA.

2 Cutlip DE, Windecker S, Mehran R *et al*. for the Academic Research Consortium. Clinical endpoints in coronary stent trials: A case for standardized definition. *Circulation* 2007;115:2344–2351.

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.

PERCUTANEOUS CORONARY INTERVENTION (PCI)

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

RESTENOTIC LESION

Defined as a lesion in a vessel segment that has undergone prior percutaneous treatment with or without a stent placement.

REFERENCE VESSEL DIAMETER (RVD)

Defined as the average of normal segments within 10 mm proximal and distal to the target lesion from 2 orthogonal views using QCA.

SERIOUS ADVERSE EVENT (SAE)

A Serious Adverse event (SAE) is any AE event that leads to:

1. Death,
2. Serious injury that :
    a. Is life-threatening illness or injury
    b. Results in permanent impairment of a body function or permanent changes to a body structure or
    c. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body function.

    NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the clinical study plan, and not meeting any of the serious criteria described above , is not considered to be an SAE. A planned hospitalization is one that is scheduled prior to the patient signing the informed consent for the study.

STENT THROMBOSIS - ARC DEFINITION

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 subject has left the catheterization lab.

Timing

Acute stent thrombosis*	0 to 24 hours post–stent implantation
Subacute stent thrombosis*	>24 hours to 30 days post–stent implantation

Late stent thrombosis†	30 days to 1 year post–stent implantation
Very late stent thrombosis†	>1 year post–stent implantation

*Acute/subacute can also be replaced by early stent thrombosis. Early stent thrombosis (0–30 days) is a definition currently used in the community. †Including primary as well as secondary late stent thrombosis. Secondary late stent thrombosis is a stent thrombosis after a target segment revascularization.

Categories (Definite, Probable, and Possible)

Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

*Angiographic Confirmation of Stent Thrombosis**

Presence of an intracoronary thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent, and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest.
- New ischemic ECG changes that suggest acute ischemia.
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI).

Non-occlusive: intracoronary thrombus is defined as a spheric, ovoid, or irregular non-calcified 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.

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

*The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

Probable Stent Thrombosis

Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within first 30 days.†
- Regardless of time after index procedure, any MI 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. †For studies with ST-elevation MI population, exclusion of unexplained death within 30 days may be considered evidence of probable stent thrombosis.

Possible Stent Thrombosis

Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

STROKE

Defined as 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.

PROTOCOL DEVIATION

An incident in which the investigator or site personnel did not conduct the study according to the clinical protocol or the investigator agreement.

Major deviation: any deviation from subject inclusion and exclusion criteria or subject informed consent procedures.

Minor deviation: deviation from a clinical protocol requirement such as incomplete/inadequate subject tests or examinations, non-compliance with medication regimens, missed follow-ups, follow-ups performed outside specified time windows, etc.

TARGET LESION

The lesion intended to be treated with the treatment device.

TARGET LESION REVASCULARIZATION (TLR)

TLR is defined as any percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. All TLRs should be classified prospectively as clinically indicated 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 in which 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 FAILURE (TVF)

Defined as a composite of cardiac death, target vessel myocardial infarction (MI), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods.

TARGET VESSEL REVASCULARIZATION (TVR)

TVR is defined as any 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.

THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) CLASSIFICATION

TIMI 0: No perfusion.

TIMI 1: Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.

TIMI 2: Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.

TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

TRANSIENT ISCHEMIC ATTACK (TIA)

Defined as 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.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

A UADE is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of a subject.

ACRONYMS AND/OR ABBREVIATIONS

Acronym/ Abbreviation	Term
ACE-I	Angiotensin converting enzyme inhibitor
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
APTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ARC	Academic Research Consortium
atm	Atmospheric pressure
AVF	Arteriovenous fistula
BMI	Body mass index
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBC	Complete blood count
CCSC	Canadian Cardiovascular Society Classification
CE	Conformité Européenne
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
cm	Centimeter
CoCr	Cobalt-chromium
CRO	Contract research organization
CT	Computed tomography
CVA	Cerebrovascular accident
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ETT	Exercise tolerance test

Acronym/ Abbreviation	Term
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
HCRI	Harvard Clinical Research Institute
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFU	Instructions for Use
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
K-M	Kaplan-Meier
LAD	Left anterior descending coronary artery
LBBB	Left bundle branch block
LCX	Left circumflex coronary artery
LIMA	Left internal mammary artery
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MDR	Medical device reporting
mg	Milligram
MI	Myocardial infarction
MLD	Minimum luminal/lumen diameter
mm	Millimeter
NHLBI	National Heart, Lung, and Blood Institute [Dissection Grade Classification]
NQWMI	Non–Q-wave myocardial infarction
NTG	Nitroglycerin
PCI	Percutaneous coronary intervention
PG	Performance goal
PMA	Premarket approval
PP	Per-protocol
PTCA	Percutaneous transluminal coronary angioplasty
QCA	Quantitative coronary angiography
QWMI	Q-wave myocardial infarction

Acronym/ Abbreviation	Term
RIMA	Right internal mammary artery
RVD	Reference vessel diameter
SAE	Serious adverse event
SAS	Statistical analysis system
SOP	Standard operating procedure
SPECT	Single-photon emission computed tomography
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target lesion revascularization
TVF	Target vessel failure
TVR	Target vessel revascularization
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
URL	Upper reference limit
US	United States
USA	United States of America
WBC	White blood cell