Study Name:

Onyx ONE Clear Study: A Single Arm Study with Resolute Onyx in ONE-Month DAPT for High-Bleeding Risk Patients who are considered One-Month Clear

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Medtronic

Clinical Investigation Plan

Study Title	**Onyx ONE Clear Study: A Single Arm Study with Resolute Onyx in ONE-Month DAPT for High-Bleeding Risk Patients who are considered One-Month Clear**	
Study Product Name	Medtronic Resolute Onyx Zotarolimus-Eluting Coronary Stent System	
Sponsor/Local Sponsor	**Medtronic Vascular** 3576 Unocal Place Santa Rosa, CA 95403, USA	**Medtronic Japan Co., Ltd.** 1-2-70 Konan, Minato-ku, Tokyo Japan 108-0075
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Contents

1. Glossary

Acronyms / Terms	Definition
ACC	American College of Cardiology
Acute closure	**Acute closure:** The occurrence of new (during the procedure) severely reduced flow (TIMI grade 0-1) within the target vessel that persisted and required rescue by stenting or other treatment or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not mean "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not mean transient closure with reduced flow in which the index treatment application does reverse the closure. **Subacute closure:** Abrupt closure that occurs after the procedure is completed (and the patient left the catheterization laboratory) and before the 30-day follow-up evaluation. **Threatened acute closure:** A grade B dissection and ⩾50% diameter stenosis or any dissection of grade C or higher.
Acute coronary syndrome (ACS)	An umbrella term where blood supply to the heart muscle is suddenly blocked. Includes unstable angina, non ST-elevation myocardial infarction and ST-elevation myocardial infarction
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE: This definition includes events related to the investigational medical device or the comparator. NOTE: This definition includes events related to the procedures involved. NOTE: For users or other persons, this definition is restricted to events related to investigational medical devices.
AHA	American Heart Association
Antiplatelet Therapy	Prescription or intake of aspirin or a P2Y12 inhibitor (e.g. clopidogrel, ticlopidine, prasugrel, ticagrelor). Patients may or may not be on oral anticoagulant medication.
ARC	Academic Research Consortium
Bleeding Academic Research Consortium (BARC)[1]	**Type 0**: no bleeding **Type 1**: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional **Type 2**: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation **Type 3a:** Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) Any transfusion with overt bleeding **Type 3b:** Overt bleeding plus hemoglobin drop ⩾5 g/dL* (provided hemoglobin drop is related to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

[1] Mehran R, Rao S, Bhatt D, et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-2747

Acronyms / Terms	Definition
	Bleeding requiring intravenous vasoactive agents **Type 3c:** Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision **Type 4**: CABG-related bleeding+ Perioperative intracranial bleeding within 48 h Reoperation after closure of sternotomy for the purpose of controlling bleeding Transfusion of ⩾5 U whole blood or packed red blood cells within a 48-h period† Chest tube output ⩾2L within a 24-h period **Type 5**: fatal bleeding **Type 5a:** Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious **Type 5b:** Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation +CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event. *Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin) †Cell saver products are not counted
CABG	Coronary artery bypass graft
Calcification	Readily apparent radiopacities within the vascular wall at the site of the stenosis and is classified as none/mild, moderate (radiopacities noted only during the cardiac cycle before contrast injection), and severe (radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen).
CEC	Clinical Events Committee
C.I.	Confidence Interval
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
Clinically-driven target lesion revascularization (CD-TLR)	Revascularization at the target lesion associated with positive functional ischemia study or ischemic symptoms AND an angiographic minimal lumen diameter stenosis ⩾50% by QCA, or revascularization of a target lesion with diameter stenosis ⩾70% by QCA without either angina or a positive functional study.
Clinically-driven target vessel revascularization (CD-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.
cTn	Cardiac troponin
CV	Curriculum Vitae

Acronyms / Terms	Definition
Death	**Cardiac death:** Any death due to immediate cardiac cause (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause /will be classified as cardiac death. This includes all procedure-related deaths including those related to concomitant treatment. **Vascular death:** Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause. **Non-cardiovascular death:** Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.
DES	Drug-eluting stent
Device Success	Attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only.
Dissection, NHLBI (National Heart, Lung, and Blood Institute) Classification[2]	**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.
DSMB	Data and Safety Monitoring Board (may also be referred to as Data Monitoring Committee, or DMC)
DTL	Delegated Task List
Dual antiplatelet therapy (DAPT)	Prescription/intake of two anti-platelet medications, with one being aspirin or an aspirin-containing drug and the other a P2Y12 inhibitor (e.g. clopidogrel, prasugrel, ticlopidine, ticagrelor).
eCRF	Electronic Case Report Form
ESC	European Society of Cardiology
ECG/EKG	Electrocardiogram
GP	Glycoprotein
High-Bleeding Risk (HBR)	Patients satisfying one or more of the following criteria: • Adjunctive chronic oral anticoagulation treatment planned to continue after PCI • Age ≥ 75 years • Baseline Hgb <11 g/dl (or anemia requiring transfusion during the 4 weeks prior to procedure) • Any prior documented intracerebral bleed • Any documented stroke in the last 12 months • Hospital admission for major bleeding during the prior 12 months • Active non-skin cancer currently undergoing treatment or surveillance (in lieu of treatment). • Planned daily NSAID (other than aspirin) or steroids for ≥30 days after PCI • Planned surgery that would require interruption of DAPT (within the next 12 months) • Renal failure defined as Creatinine clearance <40 ml/min • Thrombocytopenia (PLT <100,000/mm^3)

[2] Detre, K., R. Holubkov, S. Kelsey, M. Bourassa, D. Williams, D. Holmes, Jr., G. Dorros, D. Faxon, R. Myler, K. Kent, et al. 1989. One-year follow-up results of the 1985-1986 National Heart, Lung, and Blood Institute's Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 80 (3): 421-8.

Acronyms / Terms	Definition
	• Severe chronic liver disease defined as subjects who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-treat: All subjects who signed the informed consent with an attempted implant procedure. Time zero begins at the date of the index procedure.
IVUS	Intravascular ultrasound
Lesion Class (American College of Cardiology/American Heart Association Class)[3]	**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 to 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 guidewires, and some thrombus present. *Type B1:* One adverse characteristic. *Type B2:* Two or more adverse characteristics. **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**.**
Lesion success	The attainment of <30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method
LTFU	Lost-To-Follow-Up
Major bleeding	Hospitalization for bleeding that required transfusion or other related evaluation/treatment
Major adverse cardiac event (MACE)	Death, myocardial infarction, or clinically driven repeat target lesion revascularization by percutaneous or surgical methods
mg	Milligram
Third Universal Definition of Myocardial Infarction (3rd UDMI)[4]	All composite endpoint data will be reported per 3rd UDMI definitions. **Criteria for acute myocardial infarction** The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI: • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: o Symptoms of ischemia. o New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). o Development of pathological Q waves in the ECG. o Imaging evidence of new loss of viable myocardium or new regional wall motion

[3] Smith, S. C., Jr., J. T. Dove, A. K. Jacobs, J. W. Kennedy, D. Kereiakes, M. J. Kern, R. E. Kuntz, J. J. Popma, H. V. Schaff, D. O. Williams, et al. 2001. ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 37 (8): 2215-39.

[4] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal Definition of Myocardial Infarction. *Circulation* 2012.

Acronyms / Terms	Definition
	abnormality. ○ Identification of an intracoronary thrombus by angiography or autopsy. • Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. **Criteria for prior myocardial infarction** Any one of the following criteria meets the diagnosis for prior MI: • Pathological Q waves with or without symptoms in the absence of non-ischemic causes. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause. • Pathological findings of a prior MI.
MLD	Minimum luminal/lumen diameter
mm	Millimeter
µg	Microgram
NQWMI	Non-Q wave myocardial infarction
One-month clear	Subjects who are event-free of any the following within one month after stenting: myocardial infarction (MI), repeat coronary revascularization, stroke, stent thrombosis (ARC definite/probable), and death. Subject must be adherent to DAPT for the total 1-month period, where adherence means without interruption of aspirin and/or P2Y12 inhibitor for >3 days. Subjects discontinue either aspirin or P2Y12 inhibitor after one month and continue on single antiplatelet therapy (SAPT).* *Please refer to sections in this protocol on planned staging procedures and anti-coagulant use for extended definitions concerning 1-month DAPT use.
Oral anticoagulant (OAC)	Type of oral medication used to prevent or reduce coagulation of blood. Includes vitamin K antagonists (e.g. warfarin) and novel anticoagulants (NOACs)/ directly acting oral anticoagulants (DOACs) (e.g. apixaban, rivaroxaban, dabigatran, edoxaban)
Percent diameter stenosis (%DS)	The value calculated as 100 x (RVD – MLD)/RVD using the mean values from two orthogonal views (when possible). Percent diameter stenosis is visually estimated during angiography by the Investigator.

Acronyms / Terms	Definition
Percutaneous coronary intervention (PCI)	All interventional cardiology methods for treatment of coronary artery disease.
Perforation	Perforations will be classified as follows: **Angiographic perforation**: perforation detected by the clinical site or the core laboratory at any point during the procedure. **Clinical perforation**: perforation requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, acute closure, myocardial infarction, or death. **Pericardial hemorrhage/tamponade**: perforation resulting in cardiac tamponade.
POBA	Plain old balloon angioplasty
Procedure success	Attainment of <30% residual stenosis by QCA (or <20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.
PTCA	Percutaneous transluminal coronary angioplasty
QCA	Quantitative coronary angiography
QWMI	Q wave myocardial infarction
RDC	Oracle Clinical Remote Data Capture
Restenotic lesion	A lesion in a vessel segment that has undergone prior percutaneous treatment with or without a stent placement.
Reference vessel diameter (RVD)	The average of normal segments within 10 mm proximal and distal to the target lesion from two orthogonal views. RVD is visually estimated during angiography by the Investigator.
Rx	Rapid-Exchange
SADE	Serious Adverse Device Effects: Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event
SAE	Serious Adverse Event: An adverse event that a) led to death b) led to serious deterioration in the health of the subject, that either resulted in 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Single Antiplatelet Therapy (SAPT)	Prescription/intake of only one anti-platelet drug (aspirin or P2Y12 inhibitor). Patients may or may not be on oral anticoagulant medication.
SOP	Standard Operating Procedure
Stent thrombosis	All stent thrombosis data will be reported per the Academic Research Consortium (ARC) definition[5]: Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the catheterization lab.

[5] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.

<table>
<tr><th>Acronyms / Terms</th><th>Definition</th></tr>
<tr><td></td><td colspan="3">Timing
Acute stent thrombosis* 0 - 24 hours post stent implantation
Subacute stent thrombosis* >24 hours – 30 days post stent implantation
Late stent thrombosis >30 days – one year post stent implantation
Very late stent thrombosis >one year post stent implantation
* Acute or subacute stent thrombosis can be replaced by the term early stent thrombosis

Categories of evidence
Definite (either by angiographic or pathologic confirmation):
• Angiographic confirmation of stent thrombosis is considered to have occurred if:
• Thrombolysis in Myocardial Infarction (TIMI) flow is:
• TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus
• TIMI flow grade 1, 2, or 3, originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus
• AND at least one of the following criteria has been fulfilled within a 48-hour time window:
• New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)
• New ischemic ECG changes suggestive of acute ischemia
• Typical rise and fall in cardiac biomarkers (refer to definition non-procedural related MI)
Note: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)
• Pathologic confirmation of stent thrombosis: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy
Probable: Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
• Any unexplained death within the first 30 days
• Irrespective of the time after the index procedure any myocardial infarction (MI), which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
Possible: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of study follow-up</td></tr>
<tr><td>Stroke or Cerebrovascular Accident (CVA)</td><td>An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.[6] Categorical description of stroke</td><td>Ischemic</td><td>An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Note: Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.</td></tr>
<tr><td></td><td></td><td>Hemorrhagic</td><td>Hemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.</td></tr>
</table>

[6] Adapted from Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–89 (19).

Acronyms / Terms	Definition
	type, classified into 1 of 3 mutually exclusive categories (ischemic, hemorrhagic, undetermined) — [ ] — **Note**: Subdural hematomas are intracranial hemorrhagic events and not strokes. Undetermined — Undetermined: An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.
Target lesion (TL)	Any lesion treated or attempted to be treated during the study procedure with the assigned stent. The target lesion is the treated segment starting 5 mm proximal to the stent and ending 5 mm distal to the stent.
Target lesion failure (TLF)	Cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically driven target lesion revascularization (TLR) by percutaneous or surgical methods.
Target lesion revascularization (TLR)	Repeat PCI or CABG to the target lesion. See also clinically driven target lesion revascularization.
Target vessel (TV)	The arterial segment and any branches and/or parent vessel that possess the target lesion. *Note:* Side branches less than 2.0 mm in diameter will not be considered 'significant' and therefore the disease in these vessels will not be considered significant. *Note:* Grafts to the parent vessel will be treated as side branches to that vessel for Inclusion/Exclusion Criteria evaluation, and for event evaluation and reporting, such as TVMI and TVR assessments
Target vessel failure (TVF)	Cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization. Target vessel failure will be reported when ANY of the following events occur: • Recurrent MI occurs in territory not clearly attributed to a vessel other than the target vessel • Cardiac death not clearly due to a non-target vessel endpoint • Target vessel revascularization is determined
Target vessel myocardial infarction (TVMI)	An MI that occurs in a territory that cannot be clearly attributed to a vessel other than the target vessel.
Target vessel revascularization (TVR)	Repeat PCI or CABG to the target vessel. See also clinically driven target vessel revascularization.
Thrombolysis in Myocardial Infarction (TIMI) Classification[7]	**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.
Thrombus	**Non-occlusive thrombus:** Intracoronary thrombus is defined as a (spheric, ovoid or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three 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.

[7] The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. 1985. *N Engl J Med* 312 (14): 932-6.

Acronyms / Terms	Definition
	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 originating from the side branch).
Total occlusion	A lesion with no flow (TIMI 0). Total occlusions are usually classified as persisting less than or more than 3 months (chronic total occlusion).
Transient ischemic attack (TIA)	A focal neurological abnormality of sudden onset and brief duration (lasting less than 24 hours) that reflect dysfunction in the distribution of the effected artery. TIAs include transient monocular blindness (e.g., amaurosis fugax defined as a transient episode of monocular blindness, or partial blindness, lasting ten minutes or less) and transient hemispheric attacks.
Triple therapy (TT)	Prescription/intake of dual antiplatelet therapy plus an oral anticoagulant medication
Unstable angina	Per the ACC/AHA 2002 Guideline Update for the Management of Patients with Unstable Angina and Non ST-Segment Elevation Myocardial Infarction there are three (3) principal presentations of unstable angina (UA)[8]: • **Rest Angina**. Angina occurring at rest and prolonged, usually >20 minutes. • **New-onset Angina**. New-onset angina of at least CCS Class III Severity. • **Increasing Angina**. Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by greater than or equal to 1 CCS class to at least CCS Class III severity).
URL	Upper Reference Limit, defined as 99th percentile of normal
USADE	Unanticipated Serious Adverse Device Effect
Vascular Complication	Vascular complications include the following: • Hematoma at access site > 5 cm • False aneurysm • AV fistula • Retroperitoneal bleed • Peripheral ischemia/nerve injury • Any transfusion required will be reported as a vascular complication unless a clinical indication clearly other than catheterization complication is present • Vascular surgical repair

[8] Braunwald, E., E. M. Antman, J. W. Beasley, R. M. Califf, M. D. Cheitlin, J. S. Hochman, R. H. Jones, D. Kereiakes, J. Kupersmith, T. N. Levin, et al. 2002. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 40 (7): 1366-74.

2. Synopsis

Title	**Onyx ONE Clear Study: A Single Arm Study with Resolute Onyx in ONE-Month DAPT for High-Bleeding Risk Patients who are considered One-Month Clear**	
Clinical Study Type	Prospective, Multi-center, Pre-market Single Arm Study	
Product Name	Medtronic Resolute Onyx Zotarolimus-Eluting Coronary Stent System (Resolute Onyx stent)	
Sponsor	Medtronic Vascular 3576 Unocal Place Santa Rosa, CA 95403, USA	Medtronic Japan Co., Ltd. 1-2-70 Konan, Minato-ku, Tokyo Japan 108-0075
Treatment	Resolute Onyx stent with short duration of dual antiplatelet therapy (DAPT) in high-bleeding risk patients	
Purpose	The purpose of this study is to evaluate the clinical safety and effectiveness of the Resolute Onyx stent in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment receiving reduced duration (one month) of DAPT following stent implantation	
Product Status	The Resolute Onyx stent is approved for commercial use in the geographies identified to execute this study	
Primary Objective	To evaluate the clinical safety of the Resolute Onyx stent with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment	
Secondary Objective	To evaluate the clinical effectiveness of the Resolute Onyx stent with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment	
Study Design	Prospective, multi-center, single arm study enrolling eligible subjects in the United States and Japan. The enrollment period is anticipated to be approximately 10 months. Subjects will remain in the study with follow-up clinical assessments through 2 years, study exit, or death, whichever comes first.	
Blinding	There is no blinding in this study	
Sample Size	A total of 700 subjects are required in the US and 100 subjects may additionally be enrolled in Japan. Subjects will be enrolled in up to 70 centers	
Trial Sites	A separate listing will be made available for trial sites	
Inclusion/Exclusion Criteria	**Key Inclusion Criteria**: All subjects who are acceptable candidates for treatment with a drug-eluting stent in accordance with applicable guidelines for percutaneous coronary interventions, who additionally meet pre-defined criteria for being high-bleeding risk and are candidates for one-month DAPT. **Key Exclusion Criteria:** • Subjects requiring a planned PCI procedure after one month of index procedure • Subject with planned surgery or procedure necessitating discontinuation of DAPT within one month following index procedure • Subject not expected to comply with long-term single antiplatelet therapy • Subjects with life expectancy of less than two years	

Study Procedures and Assessments	Screening and implant (index) procedure; Clinic visit health status assessment (every effort should be made for the subject to return to the investigative site): • one month Subject contact health status assessments (by telephone, e-mail, or office visit): • 2 months • 6 months • 1 year • 2 years Angiography should be performed for cardiovascular-related post-procedure clinical events (e.g., MI) to determine if the event is attributable to the target vessel or a non-target vessel. The reason for any repeat angiography (either clinically driven or non-clinically driven) must be documented on the electronic case report form (eCRF).
Safety Assessments	All Serious Adverse Events (SAEs) and endpoint-related events will be evaluated by Medtronic safety department. Quarterly progress reports on study enrollment status and rates of cardiac death, MI, cardiac death/MI and stent thrombosis will be provided to FDA. The Clinical Events Committee (CEC) will adjudicate pre-defined clinical endpoint events. The Data and Safety Monitoring Board (DSMB) will evaluate safety data on an ongoing basis and will advise Medtronic on the continuing safety of the study, to ensure the well-being of the current participants and those yet to be enrolled, as well as the continuing validity and scientific merit of the study.
Primary Endpoint	Composite of cardiac death and myocardial infarction at one year for a one-month clear population [time frame: one month to one year]

3. Introduction

3.1. Background

The practice of percutaneous coronary intervention has made considerable technical advancements in the last three decades, greatly impacting therapy options for the treatment of coronary artery disease. Extending beyond the initial option of balloon angioplasty, the advent of bare metal stents in the 1990s improved the safety and the effectiveness of percutaneous coronary intervention compared to balloon angioplasty alone.[9,10,11,12] However, there were limitations with bare metal stents. With restenosis still occurring with such rates as 20-40% of coronary lesions after implantation of a standard bare metal stent[13], frequent repeat revascularization procedures were required which, in turn, negatively impacted patients' quality of life as well as society's health care expenditures.

The introduction of first-generation drug-eluting stents (DES), as marked by the launch of the Cypher stent in 2003, provided stents with localized and controlled release of anti-restenotic agents that have resulted in significantly reduced restenosis and need for repeat revascularization.[14,15] However, as with many early generation devices, early drug-eluting stents were also not without their limitations. Due to concerns that these early generation DES may be at risk of increased rates of late (30 days to one year) and very late (beyond one year) stent thrombosis, and due to the fact that there was limited clinical evidence to demonstrate safety otherwise, guidelines initially recommended at least a full year of dual antiplatelet therapy (DAPT) regimen after DES implantation[1617]. This drug regimen was meant to reduce the risk for thrombotic complications after stent implantation, and typically consisted of aspirin and a thienopyridine. It was only after the technological advancement in design and manufacture of newer generation drug-eluting stents, combined with the now available abundance of supportive long-term safety data, that clinical practice guidelines have very recently been updated.[18,19] Current guidelines have shortened the minimum dual-antiplatelet therapy for much of the DES-treated population from one year to six months, with provisions for even shorter dual antiplatelet therapy for patients at high risk for bleeding. These "high-bleeding risk" patients are estimated to be approximately 15% of those treated, although up to 53%[20] of those treated for percutaneous coronary

[9] Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. Mar 19 1987;316(12):701-706.
[10] Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331(8):496-501.
[11] Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, et al. for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331(8):489-495.
[12] Kimura T, Yokoi H, Nakagawa Y, Tamura T, Kaburagi S, Sawada Y, Sato Y, Hamasaki N, Nosaka H, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med. 1996;334(9):561-566.
[13] Kastrati A, Mehilli J, Dirschinger J, Pache J, Ulm K, Schuhlen H, Seyfarth M, Schmitt C, Blasini R, Neumann FJ, Schomig A. Restenosis after coronary placement of various stent types. Am J Cardiol. 2001;87(1):34-39.
[14] Lemos PA, Serruys PW, Sousa JE. Drug-eluting stents: cost versus clinical benefit. Circulation. Jun 24 2003;107(24):3003-3007.
[15] O'Neill WW, Leon MB. Drug-eluting stents: costs versus clinical benefit. Circulation. Jun 24 2003;107(24):3008-3011.
[16] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary InterventionA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Journal of the American College of Cardiology 2011;58:e44-e122.
[17] Wijns W, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European heart journal 2010;31:2501-55.
[18] Levine GN, Bates ER, Bittl JA, Brindis RG, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease. J Thorac Cardiovasc Surg. 2016; 152 (5):1243-1274.
[19] Valgimigli M, Bueno H, Byrne R, et al. 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2017; 39(3):213-260.
[20] de Boer SP, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma . Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non- participants.Eur Heart J. 2011;32(17):2161-7

intervention may be excluded from all-comer studies. These include patients previously excluded from DES procedures due to age, underlying comorbidities, (i.e., low ejection fraction, chronic renal insufficiency) and other reasons, who are not able to be subjected to longer term dual antiplatelet therapy use.

In the face of increasingly challenging coronary lesion and vessel anatomies, and with newer generation drug-eluting stents that have established long term safety and effectiveness and are considered to be the current choice of treatment, Medtronic developed the Resolute Onyx Zotarolimus-Eluting Coronary Stent system (Resolute Onyx stent) to answer the demand for more flexible, and highly deliverable devices with enhanced radiopacity while maintaining the structural integrity needed to safely and efficaciously treat complex disease.

The Resolute Onyx stent represents Medtronic's fourth generation drug-eluting stent which incorporates thinner stent struts, reduced strut lengths, increased strut width to thickness ratio, change to the number of crowns for certain designs, and increased radiopacity over predicate stents, while retaining the proven characteristics of the Resolute stent. The thinner stent struts are expected to improve acute deliverability performance by way of crossing profile and flexibility. The increased radiopacity improves the acute performance by ensuring accurate and complete lesion coverage. The zotarolimus drug and drug concentration of approximately 1.6 $\mu g/mm^2$ of stent surface area remain the same as the predicate Resolute products. The BioLinx polymer, polymer thickness and drug coating formulation also remain the same. Additional non-clinical data may be found in the Resolute Onyx IFU and Investigator's Brochure, if applicable.

The RESOLUTE Clinical Program provides clinical evidence on the Resolute Onyx stent and includes the following: the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study and the RESOLUTE Onyx 2.0 mm Clinical Study designed to assess the safety and efficacy of the Resolute Onyx stent for the treatment of lesions, amenable to treatment with a Resolute Onyx 2.0 mm stent (RESOLUTE ONYX 2.0 mm Clinical Study) and Resolute Onyx 2.25 mm – 4.0 mm stents (RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study).

The RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study outcomes validated the established safety and effectiveness of the predicate Resolute stents. The study met the primary endpoint of in-stent late lumen loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA), demonstrating non-inferiority ($p < 0.001$) when compared to the historical control in-stent late loss value from the RESOLUTE US Angio/IVUS Sub-study.

The RESOLUTE ONYX 2.0 mm Clinical Study assesses the safety and efficacy of the Resolute Onyx stent for the treatment of *de novo* lesions in native coronary arteries with RVD allowing the use of a 2.0 mm diameter stent. The primary endpoint of target lesion failure at 12 months was 5.0%, fulfilling the pre-specified performance criteria.

The RESOLUTE ONYX Post Approval Study (PAS) will augment the body of evidence supporting the safety and effectiveness of the Resolute Onyx stent and extend this evidence in a wider global patient population with the full-size matrix of Resolute Onyx (2.0 mm - 5.0 mm diameter sizes). The study is currently enrolling subjects in the United States and Europe.

Assurance of long term safety and effectiveness data on the Resolute stents is demonstrated in a *post hoc* pooled analysis of patient-level data from the RESOLUTE Clinical Trial Program, designed to collect robust clinical evidence on the Resolute stent in both simple and complex clinical presentations. The pooled analysis of 7618 patients, demonstrated a low rate of

cardiac events as well as stent thrombosis, particularly after the first year, that remained stable at 5 years.[21] These data demonstrate consistent clinical evidence supporting the safe and effective use of the next generation of Resolute Onyx.

While developing safe and effective DES is vital, expanding the clinical evidence with contemporary DES and use of post-procedural dual antiplatelet therapy (DAPT) is equally important, especially when considering the optimal duration of DAPT. Prior ESC recommendations which were supported by earlier generation DES data and very limited DAPT duration data, had suggested that DAPT duration for most patients be 6-12 months depending on patient subgroup. Notably, observational data have suggested that a significant proportion of patients either interrupt or are unable to tolerate DAPT for such duration.[22] Most recently, the ESC guidelines were updated to incorporate very short DAPT data including data from the LEADERS FREE study, a one month randomized, controlled DAPT study comparing BioFreedom DCS against a bare metal stent[23]. Also applicable are the 2016 ACC/AHA guidelines which indicate that in patients at higher risk of bleeding, DAPT discontinuation may be reasonable after 3 months in stable patients or after 6 months in ACS patients, based on currently available information. Importantly, the guidelines highlight the fact that decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference.[24]

The generation of clinical evidence supporting recommendations on DAPT duration in diverse populations is important to both the physician and to the patient. DAPT related data provide critical information needed for physicians for circumstances under which treatment duration decisions post-DES implantation may be complicated by concerns such as for patients' safety (i.e., clinical status, bleeding) or unplanned surgical interventions. For the patient, in addition to a priority of safety and well-being, concerns may stem from individualized preference as well as affordability.[25]

While older literature may have focused on the terms under which longer-term DAPT may benefit the patient, there is a limited selection of clinical research on short DAPT in the contemporary DES. Contemporary evidence from published studies that identified patients with high-bleeding risk from the LEADERS FREE study, ZEUS study, SENIOR study, and the RUDI-Free Registry. These studies included a high-bleeding risk patient population that was reflective of real world use and included complex patients such as STEMI. For the Resolute Onyx stent, Medtronic has also conducted detailed analysis of the RESOLUTE Clinical Trial Program data to better understand the safety outcomes of the Resolute Onyx stent with one-month DAPT.

[21] Yeh RW, Silber S, Chen L, et al. 5-year safety and efficacy of Resolute Zotarolimus-eluting stent: the RESOLUTE Global Clinical Trial Program. JACC Cardiovasc Interv. 2017;10(1):247-254.
[22] Silber S, Kirtane AJ, Belardi JA, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute Zotarolimus-eluting stent implantation. *Eur Heart J.* 2014;35(29):1949-1956
[23] Valgimigli M, Bueno H, Byrne R, et al. 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2017;39(3):213-260.
[24] Levine GN, Bates ER, Bittl JA, Brindis RG, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease. J Thorac Cardiovasc Surg. 2016; 152 (5):1243-1274.
[25] Kandzari D, Silber S, Windecker S, Brar S, Lee LC, Kirtane A. Pharmacodynamic considerations and clinical impact of dual antiplatelet therapy interruption after Resolute Zotarolimus-eluting stent implantation. Presentation. ACC 2014.

The LEADERS FREE Study compared the Biosensors BioFreedom BA9 DES with the Biosensors Gazelle Bare Metal Coronary Stent in a 1:1 randomized controlled study.[26] The BioFreedom stent consists of a 316L steel bare metal stent platform coated with Biolimus A9 drug that is crimped on to a rapid exchange delivery catheter system. This prospective, blinded trial randomized 2466 high-bleeding risk (HBR) PCI patients and mandated DAPT for one month only, followed by long-term single anti-platelet therapy. LEADERS FREE demonstrated that BioFreedom was superior to a bare-metal stent with respect to the primary safety endpoint of cardiac death, MI, definite/probable stent thrombosis and the primary effectiveness endpoint of clinically-driven (CD) target lesion revascularization (TLR) at one year.

At one year, with respect to the primary safety endpoint of cardiac death, MI, and definite/probable ST, the BioFreedom stent had a reported rate of 9.4% vs. the bare metal stent (BMS) rate of 12.9% (p=0.005 for superiority). Individual components of safety include the cardiac death rate of 4.2% vs. 5.3%, MI rate of 6.1% vs. 8.9% (p=0.01), and definite/probable ST rate of 2.0% vs. 2.2% (p=0.70) for the BioFreedom stent and BMS stent respectively. The primary efficacy endpoint of CD-TLR was reported at 5.1% for the BioFreedom stent and 9.8% for the BMS comparator arm (p<0.001 for superiority). Additional secondary efficacy endpoints included urgent TLR rate, 3.3% vs. 5.8% (p=0.004), CD-TLR rate, 5.7% vs. 10.5% (p<0.001), any TVR rate 5.8% vs. 10.9% (p<0.001) and any revascularization rate 9.4% vs. 12.9% (p<0.005) for the BioFreedom stent vs. the BMS arm respectively.[27]

The ZEUS study compared BMS to the Endeavor zotarolimus eluting stent (ZES). One of the study's findings showed that in patients at high-bleeding risk, a treatment strategy of the Endeavor stent followed by a personalized course of DAPT, including a 1-month DAPT therapy, resulted in a lower risk of MACE compared with BMS.[28,29] CD/MI rates from the ZEUS study reflected rates expected from a high-bleeding risk population that included stable as well as acute coronary syndrome subjects.

The SENIOR trial is a randomized single-blind trial that compared outcomes between BMS and DES in elderly patients with a short duration of DAPT.[30] Results showed that for the primary endpoint of major adverse cardiac and cerebrovascular events at 1 year, events occurred in 68 (12%) patients in the DES group and 98 (16%) in the BMS. Bleeding complications occurred in 26 (5%) in the DES group and 29 (5%) in the BMS group, and stent thrombosis occurred in 3 (1%) in the DES group and 8 (1%) in the BMS group. The authors concluded that among elderly patients who have PCI, a DES and a short duration of DAPT is better than BMS and a similar duration of DAPT with respect to the occurrent of all-cause mortality, myocardial infarction, stroke, and ischemia-driven target lesion revascularization.

[26] Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *NEJM* Oct 14, 2015.
[27] Urban P, Abizaid A, et al. LEADERS FREE Biolimus-coated vs. Bare-metal Coronary Stents in High Bleeding Risk Patients. TCT2015.
[28] Ariotti S, Adamo M, Costa F, et al. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. JACC Cardiovasc Interv 2016;9:426-36.
[29] Valgimigli M, et al. *J Am Coll Cardiol*. 2015;65:805–15
[30] Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. The Lancet 2017.

Recently, outcomes from the RUDI-FREE Registry (an observational, single-arm registry of 1103 subjects at 16 Italian centers) were presented at the EuroPCR conference in 2017. RUDI-FREE aimed to assess the safety and efficacy of polymer-free biolimus-eluting BioFreedom stent in a real-world, all-comer population, evaluating subjects different from LEADERS FREE, ie, not only focusing on high-bleeding risk patients, and assessing DAPT use. The primary safety endpoint, a composite of cardiac death, MI, and definite/probable stent thrombosis at 12 months was 4.1%. Additionally, at 12 months the TLR rate was 1.4%, TVR rate was 1.8%, TVMI rate was 1.0%, def/prob ST rate was 1.1% and a definite ST rate was reported at 0.4%. Patient-oriented outcomes included a BARC ≥3 bleed rate of 1.2% and all-cause death of 3.9%. Although this study was not a head-to-head comparison, high-bleeding risk subjects from the RUDI-Free Registry evaluated against the LEADERS FREE population for the primary endpoint showed no difference in the risk of the composite of cardiac death, MI, and stent thrombosis (p=0.28). [31]

To investigate whether early interruption and/or discontinuation of DAPT after implantation of current-generation DES is associated with a higher risk of stent thrombosis, Silber et al., performed a *post hoc* pooled analysis of 4896 patients who received the predicate Resolute DES to evaluate DAPT interruption. The investigators found that while interruptions of DAPT within one month were associated with high risk of adverse outcomes, interruptions occurring between 1 and 12 months were associated with low rates of stent thrombosis and adverse cardiac outcomes.[32]

In light of these data, Onyx ONE Study, a large, multicenter randomized trial enrolling 2000 subjects, has been initiated to study the safety and efficacy of the Resolute Onyx stent as compared to the BioFreedom stent in patients at high risk for bleeding. Both study arms will have one month of DAPT therapy and study a population that includes stable and acute coronary syndrome subjects, including subjects with STEMI, multivessel disease, left main, bifurcations. The trial has enrolled over 900 patients as of June 2018 and is expected to complete enrollment by Fall 2018.

3.2. Purpose

The purpose of this study is to evaluate the clinical safety and effectiveness of the Resolute Onyx stent in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment receiving reduced duration (one month) of DAPT following stent implantation.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective

To evaluate the clinical safety of the Resolute Onyx stent with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment with respect to a composite endpoint rate of cardiac death and myocardial infarction

[31] Sardella G, Patients at High Bleeding Risk (HBR): Lessons from LEADERS FREE. Polymer-free biolimus-eluting stents in all-comers patients: analysis of DAPT Cessation and Clinical Outcome after BioFreedom Stent Implantation. RUDI-Free Registry. euroPCR 2017.

[32] Silber S, Kirtane AJ, Belardi JA, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute Zotarolimus-eluting stent implantation. *Eur Heart J.* 2014;35(29):1949-1956

4.1.2. Secondary Objective

To evaluate the clinical effectiveness of the Resolute Onyx stent with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment

4.2. Endpoints

4.2.1. Primary Endpoint

Composite of cardiac death and myocardial infarction at one year for a one-month clear population [time frame: one month to one year]

4.2.2. Secondary Endpoints

The following will be assessed at all follow-up time points (1, 2, 6 months, 1 and 2 years), except acute success:

- Acute success (device, lesion, procedure)
- All deaths, including cardiac death
- Major adverse cardiac event (MACE)
    - Defined as death, myocardial infarction, or clinically driven repeat target lesion revascularization by percutaneous or surgical methods
- Composite of cardiac death and myocardial infarction
- Target vessel failure (TVF)
    - Defined as cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization
        - Target vessel failure will be reported when ANY of the following events occur:
            - Recurrent MI occurs in territory not clearly attributed to a vessel other than the target vessel
            - Cardiac death not clearly due to a non-target vessel endpoint
            - Target vessel revascularization is determined
- Target lesion failure (TLF)
    - Defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically driven target lesion revascularization (TLR) by percutaneous or surgical methods.
- All revascularizations (TLR, TVR and non-TVR)
- Stent thrombosis (def/prob)
- Stroke
- Bleeding per BARC criteria
    - BARC 3 to 5
    - BARC 2 to 5
    - All BARC

5. Study Design

The Onyx ONE Clear Study is a prospective, multi-center, single arm study enrolling eligible subjects at qualified study centers. Subjects will remain in the study with follow-up clinical assessments through 2 years, study exit, or death, whichever comes first. The study population will consist of subjects with coronary artery disease undergoing stent implantation with

the Resolute Onyx stent receiving DAPT through one month, before transitioning to single antiplatelet therapy (SAPT) thereafter.

A total of 700 subjects will be enrolled in the United States, and 100 subjects may additionally be enrolled in Japan. Subjects will be enrolled in up to 70 centers over an approximate 10-month period or until study enrollment is completed. Subjects may receive treatment of one or more lesions. Planned staged procedures within 30 days of procedure are allowed. Subjects who are enrolled will be considered part of the Intent-to-Treat (ITT) population and followed through for two years if they receive Resolute Onyx stent only or exit after one year if they receive other non-study device (e.g. non-Resolute Onyx stent, POBA and drug-coated balloon).

As this study examines the use of the study devices with one-month DAPT, the medication regimen described in this protocol should be strictly adhered to. Longer or shorter duration of DAPT use outside the protocol mandated duration has potential impact on the outcomes of the study and will be marked as a study deviation. To prevent or mitigate slow enrollment, selection of actively participating study centers and adjusting to an adequate number of study centers will be considered. Additionally, enrollment parameters are included in the study to avoid introduction of bias to the study results.

Key measures taken to minimize potential sources of bias:

- Enrollment of subjects is limited by inclusion and exclusion criteria
- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and safety-endpoint related adverse events. Endpoint results will be based on CEC adjudications
- An external, independent Data and Safety Monitoring Board (DSMB) will evaluate safety data and advise the Sponsor regarding continued safety of the study to ensure the well-being of the subjects
- An independent Angiographic Core Lab will evaluate baseline and all event angiograms
- Statistical analyses will be independently validated
- Study centers are to follow their institutional procedures for maintenance of angiography and laboratory equipment used for assessing the study variables
- Study monitors will verify subject data and ensure compliance with this Clinical Investigation Plan and other study requirements, (e.g., informed consenting processes, event reporting, etc.)

5.1. Duration

Screening and implant (index) procedures are estimated to take 10 months to enroll 700 subjects. Clinic visit health status assessments will be documented at the 1-month time point. Subject contact health status assessments will be documented at 2 months, 6 months, 1 year, and 2 years. The study will be conducted to allow data collection and analysis for 2 years from treatment of the final subject or until the study has been formally terminated. The total study duration is estimated to be 34 months from first enrolled subject through final follow-up.

5.2. Rationale

DAPT has long been standard of care following DES implantation; however, the duration of DAPT remains widely debated. Whereas patients treated with bare metal stents (BMS) were given one month of DAPT, following safety concerns with first generation DES over increased risk of very late stent thrombosis, the recommended duration was lengthened. However, with the technical advancement of newer generation DES, some of the original concerns, specifically around polymer biocompatibility which formed the basis of these longer DAPT recommendations, are no longer relevant.

After stent implantation, DAPT not only reduces the risk of stent thrombosis and recurrent ischemic events, but it also increases the risk for bleeding events. Various studies comparing different shorter and longer DAPT durations have shown conflicting results, making decisions on DAPT duration very challenging for physicians. The very latest European guidelines incorporates the recent DAPT clinical data to recommend 6 months of DAPT after DES implantation, while shorter DAPT duration (one-month DAPT with a Class IIB, Level C recommendation; 3 month DAPT with a Class IIA, Level B recommendation) may be considered in stable patients at high-bleeding risk (HBR).[33] Similarly, American guidelines also state that in stable ischemic heart disease patients, DAPT should be given for at least 6 months, but current data suggests that DAPT discontinuation after 3 months may be reasonable in patients who are at high risk of bleeding (e.g. patients on oral anticoagulant therapy) or who are at high risk of severe bleeding complication or who develop significant overt bleeding (class IIb).[34]

Historically, most DES trials have excluded HBR patients a population that is estimated at around 15% of PCI patients. Studies that enrolled HBR patients specifically have been limited to the ZEUS trial and more recently, the LEADERS-FREE Trial. The ZEUS study compared BMS to the Endeavor zotarolimus eluting stent (DES). One of the study's findings showed that in patients at high-bleeding risk, a treatment strategy of the Endeavor stent followed by a personalized course of DAPT, including a 1-month DAPT therapy, resulted in a lower risk of MACE compared with BMS.[35] The most recent study that focused on HBR patients is the LEADERS-FREE trial, which compared the BioFreedom drug-coated stent (DCS) to a bare metal stent platform.[36] The trial showed superior outcomes with the BioFreedom stent compared to BMS treatment in HBR patients on a 1-month DAPT course.

The Resolute Onyx Zotarolimus-Eluting Coronary Stent System (Resolute Onyx stent) is the latest iteration of the Resolute DES platform. The safety and effectiveness of the Resolute DES product family has been demonstrated in over 17,000 patients that were studied in the RESOLUTE Global Clinical Program, including over 10 clinical studies and non-randomized registries. Specifically, in an analysis of 7,618 patients, the Resolute stent demonstrated a low rate of cardiac events and a 1.2% stent thrombosis rate through five years follow-up.[37]

A post-hoc analysis of 4,896 patients from the RESOLUTE Global Clinical Program published by Silber et al,[38] concluded that while randomized clinical trials were needed, DAPT interruptions between 1 to 12 months after Resolute stent implantation were associated with low rates of ST and adverse cardiac outcomes. Based on this analysis, the instructions for use has the following language approved by Conformité Européenne (CE mark) authorities:

> *One-year data from the RESOLUTE Clinical Program indicates low stent thrombosis rates for those that interrupted or discontinued DAPT any time after one month. While physicians should adhere to current ESC or*

[33] Valgimigli M, Bueno H, Byrne R, et al. 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2017;39(3):213-260.
[34] Levine GN, Bates ER, Bittl JA, Brindis RG, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease. J Thorac Cardiovasc Surg. 2016; 152 (5):1243-1274.
[35] Valgimigli M, et al. *J Am Coll Cardiol*. 2015;65:805–15
[36] Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *NEJM* Oct 14, 2015.
[37] Yeh RW, et al. *J Am Coll Cardiol Intv*. 2017;10:247–54.
[38] Silber S, Kirtane AJ, Belardi JA, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute Zotarolimus-eluting stent implantation. *Eur Heart J.* 2014;35(29):1949-1956

ACC/AHA/SCAI Guidelines for PCI, patients who interrupt or discontinue DAPT medication one month or more after stent implantation are considered at low risk and showed no increased risk for stent thrombosis.

Optical Coherence Tomography (OCT) imaging is an accepted high-resolution method to evaluate stent strut coverage and malapposition once a stent has been implanted. Since incomplete endothelization and positive remodeling has been correlated to the incidence of stent thrombosis,[39] demonstration of early healing is desirable when considering DAPT discontinuation. Data on OCT after Resolute stent implantation from the ORION study showed improved early rapid healing with Resolute Integrity DES at 2 months (92.2% strut coverage with Resolute compared to 86.5% with BioMatrix, *P*=0.06), and at 3 months (95.4% vs 86.6%; *P*=0.004).[40] In the Onyx 1-Month OCT Study, patients implanted with the Resolute Onyx DES demonstrated an excellent early healing profile with an average of 88% of struts covered by neointimal formation (new cell growth over stent struts) and 92.3% of the total stented area showing complete strut coverage at one month[41].

Both ESC and ACC guidelines acknowledge that there is limited clinical evidence of dedicated DAPT studies in HBR patients, especially with existing stents. Therefore, there is a strong need for additional trials that evaluate the optimal DAPT duration in HBR patients undergoing implantation of current generation DES.

The Onyx ONE Clear Study is a single-arm study that compares the Resolute Onyx stent with a performance goal. The purpose of this study is to demonstrate that DAPT can be discontinued at one month in HBR patients treated with the Resolute Onyx stent. As certain events occurring within the first month after procedure would prevent the subject from having the option to be treated with one-month DAPT, and since we have seen historically that most events occur within the first month[42], to help assess for events relevant to the objectives of this study, the primary analysis focuses on a "one-month clear" population. To be deemed one-month clear, subjects need to be event-free of any the following within one month after stenting: MI, repeat coronary revascularization, stroke, stent thrombosis (ARC definite/probable), and death. Subject must be adherent to DAPT for the total 1-month period, where adherence means without interruption of aspirin and/or P2Y12 inhibitor for >3 days during the first month after the index PCI or last staged PCI procedure. Subjects discontinue either aspirin or P2Y12 inhibitor after one month and continue on single antiplatelet therapy.

6. Product Description

6.1. Resolute Onyx Stent and Delivery System

The Medtronic device in this clinical study is the Resolute Onyx Zotarolimus Eluting Coronary Stent System (Resolute Onyx stent). The size matrix is shown in the table below. Resolute Onyx is a drug-eluting stent (DES) and is comprised of four main components:

1. Onyx Bare Metal Stent platform: a pre-mounted cobalt alloy and platinum-iridium alloy based stent

[39] Guagliumi G, et al. *J Am Coll Cardiol Intv*. 2010;3:531–9
[40] Lee SW, et al. Late-Breaking Trials and Trial Updates in Coronary Interventions. Presented at: EuroPCR; May 16-19, 2016; Paris.
[41] Roleder T., Kedhi E., et al. Favourable vessel healing after ONYX stent implantation at 30-day follow-up. Presentation. EuroPCR; May 21-25, 2018; Paris.
[42] Silber S, Kirtane AJ, Belardi JA, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute Zotarolimus-eluting stent implantation. *Eur Heart J.* 2014;35(29):1949-1956

2. Delivery system: Resolute Onyx Rapid Exchange Delivery system; or Resolute Onyx Over-the-Wire Delivery System (only available in the US)
3. Polymer system: BioLinx Polymer System
4. Zotarolimus: Anti-proliferative drug component/active pharmaceutical ingredient

Table 1. Size Matrix for Resolute Onyx

Stent Length (mm)	Stent Diameter (mm)								
	2.00	2.25	2.50	2.75	3.00	3.50	4.00	4.50	5.00
8	RONYX20008X*	RONYX22508X	RONYX25008X	RONYX27508X	RONYX30008X	RONYX35008X	RONYX40008X	---	---
12	RONYX20012X*	RONYX22512X	RONYX25012X	RONYX27512X	RONYX30012X	RONYX35012X	RONYX40012X	RONYX45012X*	RONYX50012X*
15	RONYX20015X*	RONYX22515X	RONYX25015X	RONYX27515X	RONYX30015X	RONYX35015X	RONYX40015X	RONYX45015X*	RONYX50015X*
18	RONYX20018X*	RONYX22518X	RONYX25018X	RONYX27518X	RONYX30018X	RONYX35018X	RONYX40018X	RONYX45018X*	RONYX50018X*
22	RONYX20022X*	RONYX22522X	RONYX25022X	RONYX27522X	RONYX30022X	RONYX35022X	RONYX40022X	RONYX45022X*	RONYX50022X*
26	RONYX20026X*	RONYX22526X	RONYX25026X	RONYX27526X	RONYX30026X	RONYX35026X	RONYX40026X	RONYX45026X*	RONYX50026X*
30	RONYX20030X*	RONYX22530X	RONYX25030X	RONYX27530X	RONYX30030X	RONYX35030X	RONYX40030X	RONYX45030X*	RONYX50030X*
34	---	RONYX22534X*	RONYX25034X	RONYX27534X	RONYX30034X	RONYX35034X	RONYX40034X	---	---
38	---	RONYX22538X*	RONYX25038X	RONYX27538X	RONYX30038X	RONYX35038X	RONYX40038X	---	---
	---, sizes not available. *: size may not be commercially available in Japan.								

Resolute Onyx Stent

The Onyx stent is similar in design to the Integrity stent and utilizes the same continuous sinusoid manufacturing technology. The stent design has been modified to introduce reduced strut dimensions relative to the Integrity stent. The thinner struts result in a lower crossing profile which may facilitate easier tracking and crossing to the lesion site, increasing the deliverability of the device over the predicate stents. The Onyx stent also has an increased strut width to thickness ratio relative to both Integrity and the Driver/MicroDriver stent platform utilized by the Endeavor Resolute product. The Onyx stent has a strut to width ratio that allows it to better maintain radial strength. The stent is manufactured from a composite wire which has an outer shell of the identical cobalt alloy as used for the Integrity stent and an inner core of a platinum/iridium alloy an alternate, more radiopaque material.

Resolute Onyx Delivery System

The Resolute Onyx stent is mounted on a Rapid Exchange or Over-the-Wire delivery system which incorporates design and process improvements to provide enhanced deliverability. Additionally, the Resolute Onyx delivery system offers an increase (from the predicate) in nominal burst pressure from 9atm to 12atm and an increase in rated burst pressure, from 16atm to 18atm for the 2.0 mm – 4.0 mm sizes. The 4.5 mm and 5.0 mm sizes have a 16 atm rated burst pressure.

Graphic representations of the Resolute Onyx Rapid Exchange and Over-the-Wire delivery systems are presented in Figure 1 and Figure 2, respectively.

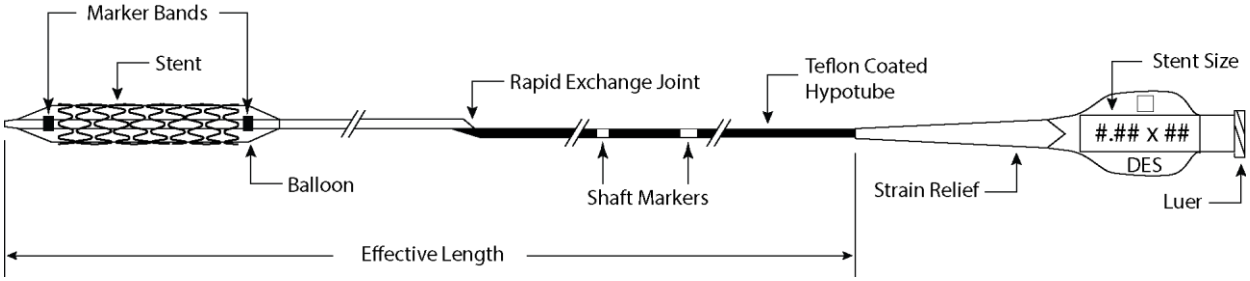

Figure 1. Resolute Onyx Rapid Exchange Delivery System (with Stent)

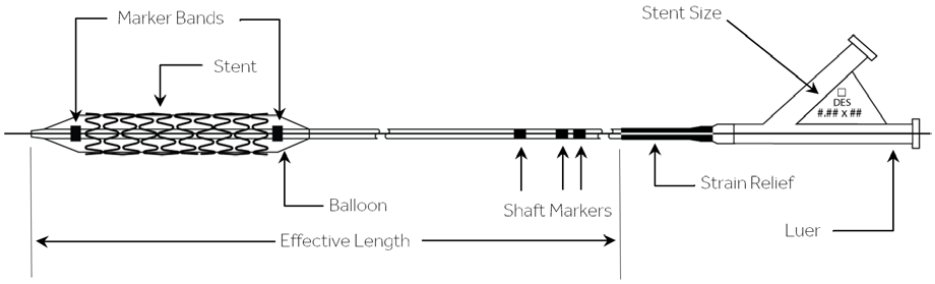

Figure 2: Resolute Onyx Over-the-Wire Delivery System (with Stent)

BioLinx Polymer System

The Resolute Onyx stent polymer coating is identical to its predicates, Resolute Integrity and Endeavor Resolute, and consists of an inactive Parylene C primer coating and drug-polymer layer containing BioLinx. BioLinx is a blend of the proprietary components C10 and C19, and PVP (polyvinyl pyrrolidone). Collectively, these polymer components do the following:

- The Parylene C aids in adhesion of the subsequent drug-polymer layer onto the stent surface
- The BioLinx controls the elution of zotarolimus from the device.

Zotarolimus Drug Substance

The therapeutic agent utilized in the Resolute Onyx stent is zotarolimus, a proprietary chemical entity identical to the therapeutic agent utilized on the predicate Endeavor Resolute and Resolute Integrity products. It is a tetrazole-containing macrocyclic immunosuppressant, and potent antiproliferative agent. The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin) and thus inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. Similar to Resolute Integrity and Endeavor Resolute, the function of zotarolimus on the Resolute Onyx stent is intended to reduce the incidence of restenosis in coronary interventions. The Resolute Onyx stent has a nominal drug dose of approximately 1.6 µg zotarolimus per mm^2 of the stent surface, identical to Resolute Integrity and Endeavor Resolute, which have been proven to reduce the incidence of restenosis in coronary interventions.

Resolute Onyx Materials

All materials (inclusive of non-blood and blood contacting materials) used in the Resolute Onyx product are consistent with its previously approved predicates or have established precedence through use in other commercially marketed products. Therefore, the Resolute Onyx product and the predicate Resolute products share the same the biological characteristics. Additionally, all materials in the Resolute Onyx product have successfully completed a full suite of biocompatibility testing per ISO 10993.

6.2. Resolute Onyx DES Manufacturing Facility

Medtronic Ireland,
Parkmore Business Park West,
Galway, Ireland
FDA Establishment Registration Number - 9612164

6.3. Packaging

The Onyx ONE Clear Study will be conducted in geographies where the product is commercially available. The packaging and labeling are in accordance with local regulations. For detailed information on intended use of the device, indications and contraindications, as well as a complete list of warnings, precautions and potential adverse effects, please refer to the respective Instructions for Use.

Resolute Onyx stent packaging details:

- Package contains one coronary stent pre-mounted on a custom stent delivery system, sterilized by EtO gas diffusion
- Use by the "Use-By" date noted on the package
- This device is for single use. This device is intended to contact body tissues. Do not reuse, reprocess or resterilize

6.4. Intended Population

The population intended for enrollment are subjects with an indication for percutaneous coronary intervention deemed at high risk for bleeding and/or candidates for 1-month DAPT and are acceptable candidates to receive treatment with the Resolute Onyx stent.

The Resolute Onyx stent is intended for use in patients eligible for percutaneous transluminal coronary angioplasty. The Resolute Onyx stent is intended to improve coronary luminal diameters of either single or multiple vessels as an adjunct to coronary interventions and to reduce restenosis. The stent is intended as a permanently implanted device. All labeling for devices will be done in compliance with local regulatory requirements.

6.5. Equipment

Study sites should follow their institutional procedures for maintenance of angiography, diagnostic, and laboratory equipment used for assessing the study variables. Maintenance and calibration report will be monitored periodically.

6.6. Product Use

Please refer to the Resolute Onyx stent Instructions for Use for commercially approved product use. The Resolute Onyx stent will be used in line with commercially approved intended use.

6.7. Product Training Requirements

The study investigator(s) will be selected to ensure that he/she is qualified by training, education, and experience to perform stenting procedures in coronary arteries.

The stenting procedure should be performed according to this protocol and to the respective Instructions for Use for the Resolute Onyx stents. A representative of Medtronic will provide and document initial training on the Onyx ONE Clear Clinical Investigation Plan requirements prior to study center activation. Medtronic and/or its designees are responsible for training of designated clinical site personnel.

6.8. Product Storage

All information regarding the storage and handling of the devices as indicated in their respective IFUs (and IB, if applicable to the region) must be taken into account.

6.9. Product Accountability

The Resolute Onyx stent is a commercialized product. This study will use commercially available product and labeling with appropriate documentation of specific device identifiers, e.g. the lot and reference/serial numbers of the used stent(s). Commercially available Resolute Onyx stents will be obtained and returned, if applicable, by the centers per routine hospital procedures for commercial products. Existing approved procedures for commercial product regarding distribution, shipment, storage, handling, of these devices will be followed. For Japan, steps will be taken to ensure product accountability as appropriate for the region.

6.10. Product Return

Any non-functioning devices should be returned to Medtronic following local regulations for return of commercial product.

7. Selection of Subjects

7.1. Study Population

Candidates with evidence of coronary artery disease with lesions suitable for stent implantation who are at high risk for bleeding or unsuitable for more than one-month DAPT will be considered for further screening and consent to be enrolled and take part in this study. The study population will consist of subjects with coronary artery disease who have been implanted or are intended to undergo stent implantation with the Resolute Onyx stent receiving DAPT through one month. The study is designed to have a similar population to that studied in the randomized controlled global study, Onyx ONE.

7.2. Subject Enrollment

A total of 700 subjects in the U.S. are required for this study. Additionally, 100 subjects may be enrolled in Japan. Subjects will be enrolled in up to 70 centers over a 10-month period or until study enrollment is completed. Enrollment parameters are included in the study to avoid introduction of bias to the study results due to disproportionate enrollment.

A maximum of 140 subjects (approximately 20% of the primary analysis population) may be enrolled at one study center. While all sites are expected to contribute to enrollment, there is no set minimum requirement for the number of subjects enrolled at each study center; however, it is expected that a minimum of five (5) subjects will be enrolled per study center.

All subjects who meet eligibility requirements will be asked to participate. Subjects will be considered enrolled into the trial after the following criteria have been met:

1. The signed and dated informed consent has been obtained
2. The patient and target vessel(s)/lesion(s) have met all of the inclusion and none of the exclusion criteria
3. The study stent is introduced into the guide catheter

Subjects who undergo consenting and have confirmation of coronary angiography anatomy eligibility and the Resolute Onyx stent was attempted but was not implanted will be considered part of the intent-to-treat (ITT) population. These subjects will be followed through the one-year endpoint. After the one-year follow-up, the subject will exit the study.

Subjects will complete their participation in the study when all study assessment windows for the duration of the study have passed, subjects have completed all study follow-up assessments, or subject exits the study for other reasons (e.g., investigator withdrawal or subject death). For all subjects, a study exit form will be completed.

7.3. Inclusion Criteria

All subjects who are acceptable candidates for treatment with a DES in accordance with applicable guidelines for percutaneous coronary interventions, per manufacturer's Instructions for Use, who additionally meet pre-defined criteria for being high-bleeding risk and/or are candidates for 1-month DAPT and in the opinion of the investigator, the potential benefit of 1-month DAPT to the subject outweighs the potential risk, can be considered. Subjects must be at least 18 years of age.

To qualify as high-bleeding risk and/or a candidate for 1-month DAPT, subject must meet at least one of the following criteria:

- Adjunctive chronic oral anticoagulation treatment planned to continue after PCI
- Age ≥ 75 years old
- Baseline Hgb <11 g/dl (or anemia requiring transfusion during the 4 weeks prior to procedure)
- Any prior documented intracerebral bleed
- Any documented stroke in the last 12 months
- Hospital admission for major bleeding during the prior 12 months
- Active non-skin cancer currently undergoing treatment or surveillance (in lieu of treatment)
- Planned daily NSAID (other than aspirin) or steroids for ≥30 days after PCI
- Planned surgery that would require interruption of DAPT (within the next 12 months)
- Renal failure defined as Creatinine clearance <40 ml/min
- Thrombocytopenia (PLT <100,000/mm^3)
- Severe chronic liver disease defined as subjects who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
- Expected non-compliance for at least 6 months DAPT for other medical reasons

7.4. Exclusion Criteria

- Pregnant and breastfeeding women
- Subjects requiring a planned PCI procedure after one month of index procedure

- Procedure planned to require non-study stents, stand-alone POBA, or stand-alone atherectomy
- Active bleeding at the time of inclusion
- Cardiogenic shock
- Subject with planned surgery or procedure necessitating discontinuation of DAPT within one month following index procedure
- Subject not expected to comply with long-term single antiplatelet therapy
- A known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, P2Y12 inhibitors, mTOR inhibiting drugs such as zotarolimus, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g., BioLinx™), stainless steel (or other metal ions found in 316L stainless steel), zinc, or a sensitivity to contrast media, which cannot be adequately pre-medicated.
- PCI during the previous 6 months for a lesion other than the target lesion of the index procedure
- Participation in another clinical study within 12 months after index procedure
- Subjects with life expectancy of less than 2 years

8. Study Procedures

8.1. Schedule of Events

Subjects will undergo initial screening and complete the informed consent process prior to any study-related assessments if applicable, i.e., study procedure(s) is not institution's standard of care.

Table 2. Schedule of Treatments and Assessments

	Baseline	Procedure[1]	Post-procedure	Discharge	One Month Clinic Visit[2]	Follow-up[3]
Eligibility criteria	●					
Informed consent	●					
Medical and cardiac history	●					
Angina status	●				●	●
Pregnancy test[4]	●					
Angiogram		●[5]				
Adverse event data[6]	●	●	●	●	●	●
Device deficiency data	●	●	●	●	●	●
Cardiac biomarkers[7]	●[8]		●[9]	●[9]		
Other lab values (creatinine, haemoglobin, WBC, platelet)	●[10]					
12 lead ECG[11]	●			●		
Anti-platelet medication	●	●	●	●	●	●
Protocol deviation reporting	●	●	●	●	●	●

1. End of procedure is defined as removal of the guide catheter.
2. Clinical visit is planned at one month. See **Staged Procedures** section for additional details regarding timing of follow-up.
3. Additional follow-up, as assessed by telephone, email, or office visit, is planned at 2, 6 months and 1, 2 years. See **Staged Procedures** section for additional details regarding follow-up.
4. For women of childbearing potential only
5. Submit all angiograms to core lab. Baseline angiograms should be collected if the subject consents pre-procedure or if collected per standard of care. All cardiovascular event angiograms should be collected.
6. Any adverse event related to endpoint (includes all bleeding), SAEs, adverse device effects, or device deficiencies should be collected from start of procedure until the completion of study or study exit.
7. CK/CK-MB and/or Troponin values must be collected post-procedure and when possible (due to consenting), pre-procedure.
8. Cardiac biomarkers will be collected pre-procedure within 72 hours (for both index and staged procedures) if subject consented prior to procedure or per standard of care.
9. Cardiac biomarkers will be measured post-procedure between 18 and 24 hours for index and staged procedures, or prior to discharge, whichever comes first.
10. Other lab values will be done within 7 days pre-procedure.
11. A 12-lead ECG will be performed within 72 hours pre-procedure (baseline) and 24 hours post-procedure or prior to discharge if <24 hours. Relevant copies of ECGs, which include copies of the baseline ECG at screening and discharge, event ECGs (most abnormal ECG and last ECG recorded), angiogram films and medical records (admission, discharge notes, reports, documentation for transfusions and cardiac biomarker values) will be collected for death or any (suspected) MI or (suspected) ST that occurs after the index procedure for adjudication purposes by a CEC.

8.1.1. Clinical Laboratory Procedures and Tests

It is expected that all sites participating in this study conduct basic standard of care that is required for proper assessment of a PCI patients, including 12-lead ECG, cardiac biomarkers, and collection of lab values (creatinine, hemoglobin, WBC, and platelet values). Relevant copies of ECGs, which include copies of the baseline ECG at screening and discharge, event ECGs (most abnormal ECG and last ECG recorded), angiogram films and medical records (admission, discharge notes, reports, documentation for transfusions and cardiac biomarker values) will be collected for death or any (suspected) myocardial

infarction or (suspected) stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Events Committee (CEC).

Cardiac enzyme values must be collected within the specified times to help determine presence or absence of myocardial infarction after procedure. Troponin is preferred, but CK or CK-MB is acceptable if it is collected per institutional standard. If the total CK value are utilized and are within normal ranges, CK-MB measurements may not be performed if this is per hospital standards. However, CK/CK-MB or troponin must be measured at least once post-procedurally, within an 18-24 hour window or before discharge. It is encouraged that CK-MB measurements are obtained with every total CK drawn, even if CK values are within normal limits. In the case of multiple measurements prior to discharge, first enzyme measurement and the peak value should be documented on the case report forms. If the subject is noted to have troponin or CK elevation post-procedure, per the Third Universal Definition, troponin or CK/CK-MB treatments should be continued to be performed every 6 hours for 24 hours, starting from when the first elevation is noted. Myocardial infarctions will be adjudicated to the Third Universal definition[43].

Patients who are consented prior to procedure should collect cardiac biomarkers, baseline angiograms, and other laboratory tests. Cardiac biomarkers (CK/CK-MB and/or troponin) should be collected within 72 hours pre-procedure (for both index and if applicable, staged procedures). Baseline angiograms should be submitted to the Angiographic Core Lab. Other lab values (creatinine, hemoglobin, WBC, and platelet values) should be collected within 7 days of procedure and 12-lab ECGs should be performed within 72 hours pre-procedure.

For patients who are consented within 24 hours after procedure, baseline cardiac biomarkers and baseline angiograms should be collected if following standard of care for the institution. Baseline angiograms (pre-procedure or at procedure) should be submitted to the Angiographic Core Lab. Other lab values (creatinine, hemoglobin, WBC, and platelet values) should be collected within 7 days of procedure and 12-lab ECGs should be performed within 72 hours pre-procedure.

After procedure, any post-procedure or event angiograms should be submitted to the Angiographic Core Lab. Cardiac biomarkers (CK/CK-MB and/or troponin) should be collected between 18 and 24 hours for index and if applicable, staged procedures, or prior to discharge, whichever comes first. A 12-lead ECGs should be collected 24 hours post-procedure or prior to discharge if less than 24 hours of procedure.

Table 3. Follow-up Interval Windows

Follow-up Interval	Window
30 days	± 5 days
2 months	± 10 days
6 months	± 14 days
1 year	± 30 days
2 years	± 30 days

[43] Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J, E-pub. August 24, 2012

8.2. Subject Screening

All subjects evaluated for potential PCI should be assessed for study eligibility. A qualified member of the study center's research team will review the subject's medical history and screen for study eligibility. Study centers may be asked to maintain a record of each subject screened by the study center along with the reason(s) for study exclusion.

8.3. Subject Consent

All subjects must complete an Informed Consent Form prior to undergoing any study-related assessments, other than procedures conducted per standard treatment at the institution. While consenting should be completed prior to the stent placement procedure when possible, subjects may complete informed consent up to 24 hours after receiving a Resolute Onyx stent if the subject is receiving standard treatment at the institution, if local regulatory requirements allow this. Study centers must comply with local regulatory requirements and Institutional Review Board (IRB) policies for obtaining informed consent.

In advance of the consent discussion, the patient should receive the IRB and Medtronic-approved Informed Consent Form. During the consent discussion, the investigator or his/her designee (only in geographies where allowed) must fully inform the patient of all pertinent aspects and risks of the study. All items discussed in the Informed Consent Form must be explained by study center staff designated on the Delegation Task List. The language used shall be as non-technical as possible and must be understandable, read aloud to the prospective subject and the impartial witness, where applicable. Informed Consent Forms should be made available in patient's native language.

Where allowed by the institution, in the event that the patient is unable to provide written informed consent, verbal consent from the patient or written assent from a legally acceptable representative will be accepted to facilitate enrollment. The legal representative may provide written consent on behalf of the patient only after having been fully informed about the registry. Where a patient is providing verbal consent, an impartial witness must be present during the entire informed consent discussion. Once consent has been given, the witness must sign and personally date the consent form, to confirm that the information contained within the informed consent and any further information provided by the investigator was explained to and apparently understood by the patient and that consent was freely given. Where a patient has initially verbally consented or a patient's legally acceptable representative has assented on behalf of the patient, written consent should be sought from the patient as soon as, in the investigator's opinion, the patient is capable of understanding the process and capable of signing the consent form.

Neither the investigator nor the study center staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights. The patient will be provided ample time to read and understand the Informed Consent Form and to consider participation in the study. All questions about the study should be answered to the satisfaction of the subject.

When the patient decides to participate in the clinical study, the site's current IRB and Medtronic-approved Informed Consent Form must be signed and personally dated by the subject and investigator designee. If the patient is consented within the allowed time frame after Resolute Onyx DES implantation, the time should be documented along with the date. If applicable, a witness shall also sign and personally date the consent form to attest that the information in the Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all required parties have signed and dated the Informed Consent Form, the investigator/or designee must provide the subject with a copy of the signed and dated Informed Consent Form. The consent process must be documented in the subject's medical record.

8.4. Revisions in Subject Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the study. The investigator or designee should inform the subject in a timely manner.

Medtronic will revise the written Informed Consent Form whenever new information becomes available that may be relevant to the subject's continued participation in the study. The revised information will be sent to the investigator for approval by the IRB and regulatory authority, if required. After approval by the IRB, a copy of this information must be provided to the participating subjects, and the information process as described above, in the section on Subject Consent, needs to be repeated.

8.5. Antiplatelet Medications

Antiplatelet medication dosing should be administered per hospital routine and in line with applicable guidelines on percutaneous coronary interventions and the IFU of the device. During the index procedure, heparin or bivalirudin will be administered as per hospital standard of care. Use of GPIIb/IIIa blockers during the index procedure is left to the discretion of the investigator. All antiplatelet and anticoagulant medications will be recorded on the eCRF throughout the study. The following are the recommendations for antiplatelet treatment:

Pre-procedure:

A loading dose of aspirin of 250-500 mg orally or via IV in aspirin-naïve patients. P2Y12 inhibitor pre-treatment and loading doses should be performed according to institutional standard practice. Decisions regarding other antiplatelet and anticoagulant therapies are left to the discretion of the treating physician.

Post-procedure to ≤30 days:

- Aspirin: daily dose 75-100 mg recommended per DAPT guidelines
- P2Y12 inhibitor: standard daily dose recommended by DAPT guidelines, with clopidogrel, 75mg once daily, being the preferred agent

>30 days post-procedure to (indefinite):

- Aspirin 75-100 mg daily or clopidogrel 75 mg daily recommended per DAPT guidelines

Note 1: For staged procedures, DAPT schedule will be calculated from the date of the staged procedure.
Note 2: Subjects who suffer a stent thrombosis during the first 30 days may be maintained on DAPT beyond 30 days at the investigator's discretion.
Note 3: The clinical profile of subjects included in the study make it unlikely that more potent antiplatelet agents than clopidogrel will be used. Should this be considered justified by the investigator, however, then the dose regimens of

other antiplatelets (e.g. prasugrel or ticagrelor) should follow the regimen recommended by the appropriate DAPT guidelines whenever possible.
Note 4: Subjects being treated with oral anticoagulants may receive single antiplatelet therapy (e.g., clopidogrel) plus an oral anticoagulant from the date of the index procedure onwards.

8.6. Medication Adherence

Patient adherence to the one-month DAPT regimen is highly important for this study. The investigator and team should take extra steps to ensure this is communicated with the patient. To be deemed one-month clear for DAPT discontinuation at 1-month, subjects must not interrupt aspirin and/or P2Y12 inhibitor for longer than 3 days during the first month after the index PCI or last staged PCI procedure. Subjects must also continue on single antiplatelet therapy (SAPT) after one month of DAPT through the end of the study. Subjects will be provided a medication reminder card and also instructed to inform the investigator and team on any changes in medication including medication stop date, reason for stopping medication, medication restart date, and medication dosage. Dual antiplatelet therapy compliance will be assessed in the clinic at the 1-month visit as well as in follow-up contacts and will be recorded in the eCRF.

8.7. Procedure

Treatment of the target lesion(s) should be performed according to the IFU that is provided with each Resolute Onyx stent. The beginning of the procedure is defined as the time the guide catheter is inserted into the subject.

There is no limitation to the number of treated vessels and lesions. Full lesion coverage will be ensured by implantation of one or multiple stents. Operators are instructed to insert only the Resolute Onyx stent. In the case that multiple stents are required, a staged procedure is planned, or revascularization occurs, the Resolute Onyx stent should be used. No mixture of DES is permitted in a given subject unless the study stent cannot be placed, in which case the recommendation would be for the operator to use another device at Investigator's discretion.

Optimal technique in placement and in expansion of the assigned DES should be practiced. While recommended, the decision to perform predilatation and post dilatation is left to Investigator's discretion. In the case it is used, post-dilatation should be performed with an appropriately sized (length and diameter) non-compliant balloon to assure that the stent is in full contact with the vessel wall. Do not use the stent delivery system for post-dilatation.

If the procedure involves treating a bifurcation lesion, a single-stent strategy (the provisional stenting technique) is recommended. This provisional technique recommends stent placement in the main branch, finalized with proximal optimization technique, followed by placement of a second stent if inadequate results are found in the side branch (such as threatened closure of the side branch, dissection type B or worse, cases of TIMI flow <3, or residual stenosis more than 80%). Provisional stenting is currently sanctioned by both ACC/AHA and ESC revascularization guidelines.[44] [45] All standard ancillary devices (e.g., guidewires, sheaths/guiding catheters, pre-dilatation balloons) used during the preparation and procedure should be used in accordance with the manufacturer's instructions.

[44] Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). European Journal of Cardio-Thoracic Surgery 2014; 46(4): 517-92
[45] ACC; Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011; 58(24): e44-122

Patients receiving non-study stents, or who undergo any non-study procedure for the treatment of coronary artery disease (i.e. any procedure other than PCI with Resolute Onyx stent), are considered major protocol deviations and will be followed for ITT analysis through one year only. The end of the procedure is defined as the time the guide catheter is removed from the subject.

At discharge, clinical status will be assessed. Per informed consent, a letter will be sent to the subject's referring physician providing information on the subject's participation in the study, including a schedule for follow up time points and instructions to transition from DAPT to single antiplatelet therapy after 30 days according to the informed participation by the patient.

After the end of the study, subjects will return to routine care as provided by their physician per standard practice.

8.8. Staged Procedures

Treatment of all target lesions with the Resolute Onyx stent within a single PCI is encouraged, if reasonable and safe. However, when staging is required for clinical reasons, the staged procedures should be performed within 30 days from index procedures and similar to index procedure, with a Resolute Onyx stent. A staged procedure is considered a subsequent treatment of a lesion in a vessel not treated at index that is present at the time of the index procedure. Staging should be pre-specified at the time of the index procedure ~~and follow-up should be calculated from the date of index procedure~~. Cardiac enzymes should be obtained before and after the staged procedure, with the same steps as that taken for the index procedure. Lesions and vessels treated with Resolute Onyx stent at the staged procedure are considered target lesions and vessels.

In addition, staged procedures should meet the following requirements:

- Staged procedures must be pre-specified at index procedure AND completed within 30 days of index procedure to qualify as a planned staged procedure. Any additional procedure to the index procedure that does not meet these requirements may be considered as a revascularization and follow-up will be based on the timing of index procedure.
- Resolute Onyx stents should be used at both index and at staged procedures.
- Staged procedures in the target vessel(s) treated at index are NOT allowed.
- Staging should not involve a segment directly adjacent to a segment treated during the index PCI.
- Every urgent coronary reintervention before the planned staged procedure is considered an event.
- Duration of DAPT is one month following the staged procedure.
- For one-month clear analysis, the "clear" definition should be extended to one month beyond the planned staged procedure.
- Follow-up for the one month and two month time points will be calculated from the date of staged procedure; remaining follow ups will be calculated from the index procedure.

8.9. Bailout

For subjects who consent prior to procedure, bailout procedures should be avoided unless required for subject safety. If bailout procedures are performed, justification should be documented on the eCRF.

If a subject in this study experiences a major dissection or an occlusive complication (as evidenced by decreased target vessel flow, chest pain, or ischemic ECG changes which do not respond to standard rescue techniques), bailout procedures may be performed. For these events occurring during the study procedure, additional stenting with the Resolute Onyx DES may be employed as a bailout treatment. In the event a Resolute Onyx DES cannot be implanted, the operator may deploy another device at Investigator's discretion to complete the procedure successfully. Subjects with bailout non-study stent(s) will be followed for ITT analysis through one year and DAPT is per physician discretion.

Target lesion(s) is/are to be selected with the intent to cover each lesion with a single stent. If incomplete coverage occurs during the procedure, additional stenting with assigned study stents may be employed to provide complete coverage.

Refer to IFU for procedural guidelines.

8.10. Treatment Failure

Study stent(s) that enter the guide catheter and fail to be implanted at the intended location are considered treatment failures and should be recorded in the eCRF. Treatment failures should be followed-up for safety purposes through one year and these subjects and lesions will be included in the ITT population but not the primary analysis. Subjects experiencing total treatment failure (i.e., no Resolute Onyx stent treatment) will not be replaced. After the one-year time frame, total treatment failures should be exited from the study.

8.11. Assessment of Effectiveness

Assessments of effectiveness will include acute device, lesion, and procedural successes as well as adjudication of any revascularizations reported through each subject's follow-up.

8.12. Assessment of Safety

Reports of all adverse events related to endpoint (including bleeding), SAEs, adverse device effects and device deficiencies, with the return of the device when possible, will be evaluated by Medtronic. The Clinical Events Committee (CEC) will review and adjudicate clinical events possibly related to study endpoints that need adjudication throughout the duration of the study.

8.13. Recording Data

Data collected on each subject will be recorded on a web-based eCRF. This study will utilize an Oracle Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Each enrolled subject is assigned a unique study ID number. Records of the subject/subject ID relationship will be maintained by the study site. Individual subject medical information obtained as a result of this study will be considered confidential.

Authorized site personnel as indicated on the Delegation Task List (DTL) will record the required data on eCRFs. Study personnel delegated for eCRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter be provided with a user name and password to access the system. Passwords are individual and cannot be shared.

The eCRFs must be completed and updated to reflect the latest observations on the subjects participating in the study. The investigator (or delegated personnel by investigator) will electronically sign the appropriate pages of each eCRF. In the U.S. the delegated personnel will be an approved sub-investigator, and in Japan this may be study staff that has been delegated to enter information into the electronic data system as a copy from medical records or other materials. The Oracle Clinical RDC

system maintains an audit trail of entries, changes, and corrections in eCRFs. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the investigator shall re-approve this eCRF.

The hospital files (electronic or paper) will constitute source data. For the purpose of adjudication of events by the CEC, relevant event-related source documents (e.g. angiograms, procedural details, worksheets, etc) will be redacted and collected for events that need to be adjudicated by the CEC. In Japan, availability of source documentation may be limited due to hospital policies. If a specific source document is not available, necessary information may be transcribed on to the relevant CRF page.

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g., angiogram variables, procedural details) may vary from center to center.

The principal investigator is responsible for ensuring that all sections of each CRF are complete and correct and that those entries can be verified against source data.

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this study. The study database will employ validation programs (e.g., range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation.

8.14. Investigator records

At a minimum, the following records must be kept by the investigator:

- All approved versions of the Clinical Investigation Plan
- Medtronic- and IRB- approved Informed Consent Form
- Fully signed Clinical Trial Agreement and confidentiality agreement (if not included in the Clinical Trial Agreement) (for US sites)
- Financial disclosures: if the financial interests change during the course of the study or within one year of completion of the study, the investigator is obliged to inform the sponsor of such financial change
- Insurance certificates, if applicable
- Completed Delegated Task List and Curriculum Vitae of all investigational site personnel
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log and subject identification log
- Signed, dated, and fully executed Informed Consent Forms
- The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.
- Lab certificates / Lab normal ranges
- Fully executed eCRFs and corrections (in the EDC or as copy on site)
- Reports of Adverse Events and Device Deficiencies
- IRB approval letter, voting list and correspondence
- Clinical Study Report (including statistical analysis), if applicable

8.15. Investigator reporting responsibilities

The investigator is responsible to ensure that all work and services related to this trial described herein, or incidental to those described herein, are conducted in accordance with the highest standards of medical and clinical research practice, the requirements of the IRB, the investigational plan, the terms of the Investigator Agreement, and all applicable local laws and regulations, including (except in Japan):

- 21 CFR 812: Investigational Device Exemptions
- 21 CFR 50 (Subpart B): Informed Consent of Human Subjects (21 CFR 50.20 General Requirements for Informed Consent)
- 21 CFR 54 (Part 54): Financial Disclosure by Clinical Investigators

Table 4 describes the Investigator reporting responsibilities.

Table 4. Investigator Reporting and Data Submission Responsibilities

Report / Data Submission	Submit to	Description/Constraints
CRFs (screening failure, inclusion/exclusion, baseline, follow-up, non-compliance, event, study exit)	Sponsor	Submit via EDC (guidelines: within 7 days)
Angiographic media	Angiographic Core Laboratory	Submit to Core Laboratory (guidelines: within 7 days)
Adverse Events	Sponsor & IRB	Refer to Section 10 for reporting requirements
Progress Report	Sponsor & IRB	Provide if required by local law or IRB
Withdrawal of IRB approval	Sponsor	Investigator must report a withdrawal of the reviewing IRB within 5 working days of the investigator's part of the investigation.
Final Report	IRB	This report must be submitted within 3 months after termination or completion of the investigation or the investigator's part of the investigation, or per local IRB requirements.
Deviations from Investigation Plan		
Deviation from Investigation Plan (Other – Non-Emergent)	Sponsor &IRB	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects (and is not an emergency), then the deviation must be approved by Medtronic and the reviewing authority prior to its implementation. If the deviation does not affect these issues (study soundness, rights, safety, etc.) then only Medtronic must approve it

Deviation from Investigation Plan (Emergency)	Sponsor & IRB	Notification must be made as soon as possible if the deviation was made to protect the life or physical well-being of a subject in an emergency
Failure to Obtain Informed Consent (not required for Japan sites)	Sponsor & IRB	The Investigator must notify Medtronic and the reviewing authority within 5 working days after device use. The report must include a brief description of the circumstances justifying the failure to obtain informed consent.

8.16. Sponsor record maintenance responsibilities

At a minimum, the sponsor will keep the following records:

- All essential correspondence related to the clinical study
- Signed Investigator Agreement
- Current curriculum vitae for each Principal Investigator at all sites
- Current curriculum vitae for all other investigators and site team members (for US sites)
- Delegated Task List (DTL)
- SAE, AEs related to endpoint (including bleeding), adverse device effects, and device deficiency information
- All data forms, prepared and signed by the Investigators, and received source documentation and core lab reports
- Clinical investigation protocol and subsequent amendments
- Site monitoring reports
- Financial disclosure information
- Study training records for site participants and internal trial staff members
- Contact lists of all participating investigators/investigative sites, IRB information, study monitors and Sponsor staff members including the medical expert; Sponsor will maintain these lists and provide updates to the necessary parties.
- Sample of device labeling
- Insurance certificates, if applicable
- IRB approval documentation and voting list and correspondence
- Lab certificates (except in Japan) / Lab normal ranges
- Statistical analyses
- Clinical Investigation Report

8.17. Sponsor reporting responsibilities

Sponsor reporting requirements are summarized in Table 5.

Table 5. Sponsor Reporting Requirements

Report	Submitted to

Serious Adverse Event (SAE) Adverse Device Effect (ADE) or Device Related Adverse Event Device Deficiency that might have led to a SADE	Regulatory authorities: Reporting timeframe as per local requirement. IRB: Reporting timeframe as per local IRB requirement.
Serious Adverse Device Effects (SADE) Unanticipated Adverse Device Effect (UADE) Unanticipated Serious Adverse Device Effect (USADE)	Regulatory authorities: Submit as soon as possible, but not later than within 10 working days after the Sponsor first receives notice of the event, as per local reporting requirement. IRB: Reporting timeframe as per local IRB requirement.
Study enrollment status and rates of cardiac death, MI, cardiac death/MI and stent thrombosis	Progress reports will be provided to FDA on a quarterly basis

Medtronic will conduct an evaluation of the UADE in accordance with CFR 812.46(b) and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after Medtronic first receives notice of the effect. Thereafter, Medtronic shall submit such additional reports concerning the effect as FDA requests. Events reported for this study from all geographies will be reviewed and assessed for UADE reporting to the FDA. Events deemed to be UADEs will be submitted per local reporting requirements.

A list of potential adverse events related to the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System can be found in the Instructions for Use.

8.18. Deviation Handling

A study deviation is defined as an event where the investigator or site personnel did not conduct the study according to the Clinical Investigation Plan, applicable laws or regulations, IRB, or the investigator agreement.

Regulations require that investigators maintain accurate, complete and current records, including documentation of any deviations from the investigation plan including the date of and reason for the deviation. The deviations must be reported to the sponsor on the eCRF.

Investigators are required to obtain prior approval from the Medtronic Clinical Research Department before initiating changes in or deviations from the investigation plan, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study files.

Deviations shall be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Deviations to protect the life or physical wellbeing of the subject in an emergency must be reported to Medtronic and the IRB within five working days.

Subject-specific deviations will be reported on the non-compliance eCRF. Deviations that are not subject specific (e.g., unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement) will be reported

to Medtronic in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their IRB requirements.

The study center's compliance with the clinical investigation plan will be assessed on an ongoing basis. Corrective and preventive action plans will be developed and implemented to secure compliance. In cases of serious non-compliance, the sponsor may decide to stop subject enrollment and site participation at an investigational site based on its assessment of repeated occurrences of significant non-compliance.

Examples of deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the Informed Consent used
- Failure to obtain IRB approval before the start of the study
- Treated subject did not meet inclusion/exclusion criteria
- Follow-up visit not done
- Reportable adverse events not reported in the required time frame as required by regulation or as specified in protocol
- Source data permanently lost
- Enrollment of patients during lapse of IRB approval

8.19. Subject Withdrawal or Discontinuation

A study subject has the right to discontinue participation in the study at any time without penalty or loss of benefits to which the subject is otherwise entitled. A withdrawn subject will be treated according to standard of medical care and will not be replaced. Subjects will be included in the analyses up to the time that consent was withdrawn.

If an investigator decides to withdraw a subject or if the subject decides to withdraw from the study, the investigator will document the reason for withdrawal, if known, and indicate any rationale for the withdrawal from the study in the subject's file. If a subject is withdrawn from the study due to problems related to the investigational device, continued follow-up may be requested by the sponsor to assess subject safety. In all other cases, no additional data will be captured after the subject withdraws or is removed from the study, unless the information is publicly available. Subjects have the right to withdraw from the study at any time without explaining why and without any consequences.

Subject Lost-To-Follow-Up (LTFU) should be avoided as much as possible and investigators are urged to do their utmost best to maintain subject follow-up compliance. Continuous attempts (e.g., phone, email, certified letter) throughout the final follow-up period should be made to contact the subject, the subject's family or referring physician before documenting a subject LTFU (at least three documented attempts must be made). It is recommended that death study databases (e.g. SSDI) should be checked before subjects are considered LTFU. A subject is not considered LTFU until the subject's final follow-up window has closed. Once a subject has completed their final follow-up visit, a study exit form must be completed.

9. Risks and Benefits

9.1. Potential Risks

This study assesses the use of a shorter duration of DAPT use for a specific patient population treated with DES. Stent drug, stent materials, and technique related standard percutaneous coronary diagnostic and treatment procedures will not be changed. Therefore, the risks associated with this study are related to a reduced duration of DAPT in subjects. As recent evidence have suggested that major bleeding is correlated with adverse events[46], this study balances the potential risks of shorter DAPT such as a higher risk for thrombotic complications after stent implantation, with the potential benefit of reducing the bleeding risk in a population that is at high risk for bleeding complications. These "high-bleeding risk" patients are estimated to be approximately 15% of those treated for PCI and include patients excluded due to age, underlying comorbidities, (i.e. low ejection fraction, chronic renal insufficiency) and other reasons, who are not able to be subjected to longer term dual antiplatelet therapy use. In many drug-eluting stent studies, these high-bleeding risk patients have been excluded from the study population.

While there is early clinical evidence suggesting that the clinical risks around usage of a shorter DAPT treatment after DES implantation may be low[47], there is limited conclusive evidence in a wider population suggesting short DAPT duration may be safe and effective for all patients. However, the high-bleeding risk population has been identified in published guidelines as a subgroup that may be suitable for shorter DAPT compared to other patients treated with DES, with evidence supporting DAPT duration as short as one month.[48] [49] In addition, the LEADERS FREE study was conducted with a population of high-bleeding risk patients with the understanding that these included patients with potential to be at higher clinical risk and still demonstrated safety and effectiveness with 1-month DAPT when compared to a bare-metal stent. This high-bleeding risk population in the LEADERS FREE study included subjects who had clinical or anatomic features that posed a higher ischemic risk, including subjects who had multivessel disease (1493/2399 (62.2%)), ACS (659/2432 (27.1%)), diabetes (805/2427 (33.2%)), hypertension (1913/2427 (78.8%)), bifurcation (15.5%), in-stent restenosis (2.5%) and chronic total occlusion (4.7%). While rates of adverse clinical outcomes were higher in these subgroups as compared to treatment of simple lesions, the investigators did not find patients to be at higher risk in these subgroups that would trigger concern. These data were pre-specified and also published by the LEADERS FREE investigators.[50] [51] Given that the Onyx ONE Clear Study inclusion/exclusion criteria are similar to that of LEADERS FREE, it is expected that similar proportions will be enrolled and have clinical or anatomic features that pose a higher ischemic risk.

In addition, the study design will minimize the risks through observance of strict study center and investigator selection criteria, careful subject selection and management, rigorous adherence to a standardized schedule of evaluations and adverse event monitoring. Risks may be further limited by continued monitoring of subjects following the index procedure. The investigators are also expected to perform continuous monitoring, assessment and documentation of any risks. The device used in this study is commercially available and has a proven safety record.

[46] Morice, LEADERS FREE 1 year Presentation. TCT 2017.
[47] Silber S, Kirtane AJ, Belardi JA, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute Zotarolimus-eluting stent implantation. *Eur Heart J.* 2014;35(29):1949-1956
[48] Levine GN, Bates ER, Bittl JA, Brindis RG, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease. J Thorac Cardiovasc Surg. 2016; 152 (5):1243-1274.
[49] Valgimigli M, Bueno H, Byrne R, et al. 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2017;39(3):213-260.
[50] Naber CK, Urban P, Ong PJ, et al. Biolimus-A9 polymer-free coated stent in high bleeding risk patients with acute coronary syndrome: a LEADERS FREE ACS sub—study. EHJ. 2017:38, 961-969.
[51] Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *NEJM* Oct 14, 2015.

Standard risks associated with the medical device used in this study and risks associated with percutaneous treatment procedures are provided in the device IFU. Additional risks, which are not known at this time, may also exist.

In addition, all efforts will be made to minimize these risks by selecting investigators who are experienced and skilled in interventional procedures including stenting, by clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled, and by ensuring that treatment and follow-up of the subject are consistent with current medical practices.

9.2. Risks Related to Devices

The risks associated with using the study device are related to the drug, the stent materials, and risks associated with standard percutaneous coronary diagnostic and treatment procedures.

As outlined in the commercially available IFU for the study device, physicians should make decisions about duration of DAPT on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and subject preference. While there are no new risks identified specific for this study, risks from product commercial IFU include the following:

Percutaneous Coronary Diagnostic and Treatment Procedures

Risks associated with using these products are those associated with percutaneous treatment procedures for a stenotic coronary artery. The complications relating to standard PTCA and stenting include, but are not limited to the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction to anti-coagulation and/or anti-thrombotic therapy, contrast material, or stent and/or delivery system materials, drug, and polymer coating
- Aneurysm, pseudoaneurysm, or arteriovenous fistula
- Arrhythmias (including ventricular fibrillation)
- Balloon rupture
- Bleeding
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue device or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Incomplete stent apposition
- Increased risk of restenosis of stented segments
- Infection or fever
- Myocardial infarction
- Pericarditis

- Peripheral ischemia / peripheral nerve injury
- Renal failure
- Shock / pulmonary edema
- Stable or unstable angina
- Stent deformation, collapse, or fracture
- Stent migration or embolization
- Stent misplacement
- Stroke or transient ischemic attack
- Thrombosis (acute, sub-acute, or late)

Additional Potential Risks Related to Resolute Onyx stent

Additional potential adverse events that have been associated with zotarolimus include but are not limited to:

- Anemia
- Diarrhea
- Dry Skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia)
- Rash

The types of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings. These additional risks may include, but are not limited to, the following:

- Allergic reaction
- Focal inflammation at the site of stent implantation
- Restenosis of the stented artery

9.3. Potential Benefits

Clinical practice guidelines have been updated recently to reduce the duration of DAPT after technological advancements in design and manufacture of newer generation DES, while leveraging the now available abundance of supportive long-term safety data of currently marketed DES. This study identifies a specific population which may benefit from shorter DAPT treatment due to a high risk for bleeding. Risk of major bleeding may prevent these patients from receiving a DES and limit treatment to a POBA or a bare-metal stent which may not be the preferred treatment. Reducing the duration of DAPT to one month may allow high bleeding patients to be treated with a DES as it may reduce the bleeding risks for this patient population. Recent evidence such as presented on the LEADERS FREE trial relating to the occurrence of major bleeding to higher mortality rates suggests also that shorter DAPT may have a positive impact on the risk of the patient to have adverse events.[52] In addition, study participation contributes to expanding the knowledge base with respect to the use of the Resolute Onyx stent systems with a specific time frame for DAPT. As highlighted by recent changes in both the ESC/EACTS and ACC/AHA guidelines on DAPT, the generation of clinical evidence supporting recommendations on DAPT duration in

[52] Morice. LEADERS FREE at 1 year Presentation. TCT 2017

diverse populations is important to both the physician and to the patient. DAPT related data provide critical information needed for physicians for circumstances under which treatment duration decisions post-DES implantation may be complicated by concerns such as patient safety (e.g., clinical status, bleeding) or unplanned surgical interventions. For the patient, in addition to a priority of safety and well-being, concerns may stem from individualized preference as well as affordability.

Importantly, as highlighted by current guidelines, decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgement, assessment of the benefit/risk ratio, and patient preference. However, there are strong potential benefits for the subject, especially one that is at higher risk for bleeding or who would otherwise not be able to receive treatment with a DES.

9.4. Risk Benefit Rationale

Appropriate risk management activities have been performed on the Resolute Onyx stent, resulting in a positive risk-to-benefit rationale as confirmed by previous regulatory approvals in different global regions.

Ultimately, it is the balance between the need for DAPT use after DES implantation and the risk for bleeding that provides the basis for this study. Based on our current knowledge, while the included patient population is at higher risk for bleeding, participation in this study does not impose significant additional risks to the subject when compared to the existing DAPT treatment regime based on current guidelines and clinical evidence that has been obtained in recent studies, including LEADERS FREE. Subjects at high-bleeding risks may benefit from a shorter duration of DAPT due to the reduced risk of bleeding events and potential sequelae that exist with prolonged DAPT. As recent studies have shown that the occurrence of major bleeding events can be linked to higher rates of mortality, the opportunity to reduce the risk of such bleeding events is important to patient safety. Furthermore, the use of DES compared to bare-metal stents has been compared in many studies and have led to general consensus that DES is preferred to bare-metal stents. Under these premises, the availability of clinical evidence on short DAPT use in a high-bleeding risk population provides opportunities for patients for potentially safer treatment. In this carefully selected population of patients with high risk for bleeding, it is anticipated that the potential benefits of the study outweigh the potential risks.

10. Adverse Events and Device Deficiencies

10.1. Definitions/Classifications

For the purpose of this clinical investigation, Medtronic defines adverse events as shown below. In case country specific definitions and safety reporting regulations are stricter than mandated, reporting will be done in compliance with the country specific safety regulations. For Japan, please also refer to the investigator's brochure for additional reference to possible AEs and device deficiencies.

While ISO14155:2011 has been carefully considered for this study, due to the nature and regulatory strategy of this study, including the post-approval status of the Resolute Onyx product, the scope of adverse event reporting has been limited to reporting of all endpoint-related AEs (including all minor bleeding), SAEs, adverse device effects, and device deficiencies.

Medical occurrences that are inherent to a surgical procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include, but are not limited to, those listed in Table 6. These medical occurrences should not be reported as adverse events during this study.

Table 6. Expected, non-reportable events related to a surgical procedure

Event Description	Timeframe (hours) from the procedure
Anesthesia related nausea / vomiting (with or without treatment)	24
Low-grade fever (<37.8°C)	48
Pain at access site (with or without standard treatment and patient not returning to clinic to have additional treatment)	72
Sleep problems (insomnia) (with or without treatment)	72
Back pain related to laying on table (with or without treatment)	72

For the purposes of the clinical report, Medtronic will classify the following adverse events according to ISO 14155:2011. Where the definition indicates "device," it refers to any component of the Resolute Onyx stent used in the study.

Table 7. Adverse Event Definitions

Adverse Event (AE): (ISO14155:2011 3.2) Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical 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 investigational medical devices.
Adverse Device Effect (ADE): (ISO14155:2011 3.1) Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE): (ISO 14155:2011 3.37) An adverse event that a) led to death b) led to serious deterioration in the health of the subject, that either resulted in 1. a life-threatening illness or injury, or 2. a permanent impairment of a body structure or a body function, or 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36) Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event
Unanticipated Serious Adverse Device Effect (USADE): (ISO 14155:2011 3.42)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report
Device deficiency: (ISO 14155:2011 3.15) Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling

10.2. Reporting of Adverse Events

Investigators are required to report adverse events and device deficiencies as described in the table below, from the start of procedure until subject's exit from the study. Reportable adverse events will be reported to the sponsor and documented on the Adverse Event eCRF and in the subject's medical records. All assessments prior to subject enrollment are considered standard of care.

Reportable events will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained). The investigator will report events that may occur to the Sponsor, and will assess seriousness, relationship (relatedness to the device, procedure and therapy where applicable), subsequent intervention required, resolution status and whether or not the adverse event resulted in the subject's discontinuation from the study. The following table outlines the five different levels of causality for every adverse event to be classified against.

Table 8. Causality Assessment[53]

Not related	Relationship to the device or procedures can be excluded when: - the event is not a known[54] side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);

[53] Guidelines on Medical Devices. Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC/and 93/42/EEC; MEDDEV 2.7/3 revision 3; May 2015

[54] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.

	- the event does not depend on a false result given by the investigational device used for diagnosis[55], when applicable; - harms to the subject are not clearly due to use error; - in order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedure; - the event involves a body-site or organ that • the investigational device or procedures are applied to; • the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis[56], when applicable; - in order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The investigator will provide further information regarding reportable adverse events as requested by the Sponsor. Previously reported Adverse Events information should be updated when the status of the event changes, including change in actions taken, change in outcome, or change in relatedness. Adverse events that occur during and are recorded in this study are required to be reported to Medtronic via the AE or device deficiency eCRF, as per the timeframes listed in Table 9.

[55] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

[56] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

Table 9. Investigator AE Reporting Requirements to Medtronic and IRB

Event Type	Investigator Timeframe for Reporting to Medtronic
Serious Adverse Event (SAE) and any adverse-event related to endpoint (including all bleeding)	Immediately, but no later than 7 calendar days of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) (Device or procedure Related Adverse Event)	Submit in a timely manner (15 calendar days) of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 7 calendar days of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but no later than 2 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to an SADE	Immediately, but no later than 7 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency	Submit in a timely manner (15 calendar days) of the investigator's / site's first knowledge of the event

In addition, investigators are obliged to report appropriate adverse events to their IRB in accordance with the requirements and local regulations.

All events and complaint reporting will be reviewed by Medtronic. This process is part of postmarket vigilance. Medtronic will review and report all reportable events (including device deficiencies) according to national regulations in acceptably timely conditions. For events, this review will include the determination whether the SAE meets regulatory reporting requirements. The Sponsor will ensure timely SAE reporting to meet global regulatory requirements. The Medtronic employee who first becomes aware of an SAE/Device Deficiency related to a Medtronic device will immediately report this device-related SAE/Device Deficiency to the Medtronic Product Experience Management (PXM) Galway, Ireland. The Medtronic PXM Galway, Ireland will ensure prompt review, and appropriate reporting.

10.3. Recording and Reporting of Device Deficiencies

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

Malfunction is defined as 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. Product labels, Instructions for Use, User Manuals, and if appropriate an IB, for this study are provided separately.

Device deficiency information will be collected throughout the study and reported to Medtronic. Device deficiencies that did not lead to an AE should be reported on the Device Deficiency eCRF. Device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an adverse event only. Device deficiencies that did not lead to an AE but could have led to a serious adverse device effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting. All reportable device deficiencies and malfunctions will be documented on the appropriate eCRF, one form for each deficiency, and further reported to the IRB (if required) within the IRB required timeframe and local and national regulations.

10.4. Emergency Contact for Reporting Events and Device Deficiencies

Investigators should contact their responsible Medtronic study contact if they have any questions regarding reportable AEs or device deficiencies. Sponsor contact information (including name, title, address, and telephone number(s) is subject to change and will be maintained in a document separate from the clinical investigation plan and provided to sites.

For reportable AEs or device deficiencies that require immediate reporting (see Table 7), initial reporting shall be done by completing the appropriate eCRF. If the eCRF is not available during the required reporting period, the reportable AE or device deficiency should be reported to Medtronic by alternate means, such as the responsible site manager. In due time, the reportable AE or device deficiency needs to be entered in the eCRF as well.

11. Data Review Committees

11.1. Clinical Event Committee

The Clinical Event Committee (CEC) is composed of independent cardiologists who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study. Criteria will be established for selected complications and clinical events. At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The CEC will meet regularly to review and adjudicate pre-defined clinical endpoint events. If needed, the adjudication committee will require collection of additional source documentation from the clinical centers. The procedures by which the CEC will operate will be documented in a separate CEC charter.

11.2. Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) will evaluate safety data on an ongoing basis and advise Medtronic about the continuing safety of the study, to ensure the well-being of the current participants and those yet to be enrolled as well as the continuing validity and scientific merit of the study. The primary responsibility of the DSMB is to monitor the health, safety, and welfare of subjects. The DSMB will be composed of physicians from the fields of cardiology and interventional cardiology and at least one biostatistician with experience in analysis of clinical studies. The members of the DSMB will not be investigators in the study and will be independent of Medtronic.

Prior to the first DSMB review, guidelines for the identification and evaluation of significant safety findings and/or increased frequency of events that may impact the rights, safety or welfare of subjects will be established. All materials, discussions, and proceedings of the DSMB are completely confidential. The proceedings of each DMSB meeting will be recorded in

minutes. The DSMB Chairperson will be responsible for providing a written recommendation regarding study conduct (e.g., continue as planned, specify a modification, or termination) to Medtronic and the Study Principal Investigators. All final decisions, regarding study modifications rest with the Executive Committee and Sponsor. Details around the procedures of the DSMB are documented in a separate DSMB charter.

11.3. Executive Committee

The Executive Committee is composed of the study governance members including the study leadership and committee members. Their role is to provide overall supervision of the study, advise in study design, provide feedback on current practice and to assist in communications with clinical investigational sites. This committee will meet periodically by teleconference or in person to monitor the progress of the study, including subject enrollment, clinical site progress, and protocol compliance. The Executive committee will also be responsible for reviewing the final results and determining the methods of presentation and publication.

12. Statistical Design and Methods

The Onyx ONE Clear Study is a prospective, multi-center, single arm study for a commercially approved product. A total of 700 US subjects deemed at high risk for bleeding and/or medically unsuitable for more than one month DAPT treatment will be treated with the Resolute Onyx stent and studied for a one month DAPT treatment. Additionally, 100 subjects may be enrolled in Japan.

The primary objective is to evaluate the clinical safety of the Resolute Onyx stent as compared to the Performance Goal (PG) with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment.

12.1. Primary Endpoint

The primary endpoint in this trial is the composite of cardiac death and myocardial infarction at one year for a one-month clear population [timeframe: one month to one year].

12.1.1. Primary Hypothesis

The primary endpoint of the study will be compared to a PG of 9.7%. The study hypotheses are:

H_0: $\pi \geq 9.7\%$

H_A: $\pi < 9.7\%$

Where π denotes the binary rate of cardiac death and myocardial infarction at one year in a one-month clear population [timeframe: one month to one year]. This one-sided test will be carried out at the 0.025 significance level using the binomial exact test.

12.1.2. Hypothesis

Based on historical short DAPT studies with high-bleeding risk patient populations (LEADERS FREE, ZEUS, and SENIOR), the weighted average of cardiac death and myocardial infarction at one year was 9.6%. As disproportionally higher rates of STEMI, unstable angina, and multi-vessel disease were identified in the ZEUS study population which could have led to a higher rate of cardiac death, the ZEUS rate was revised. Similarly, the SENIOR rate contribution was derived from the published rates based on subjects with planned one-month DAPT use.

Approximately 3% of CD/MI events occurred in LEADERS FREE study at 30 days. To account for a "one-month clear" population, the weighted CD/MI rate at 12 months will be discounted by 3%, resulting in an average rate of 6.6%. In addition, to account for the 3% population that will also be removed from the denominator of the rates, the expected CD/MI rate between 30 days and one year is more accurately represented as 6.8%.

The performance goal (9.7%) incorporated a clinically acceptable margin of 2.9% to the expected rate.

In defining a "one-month clear" population, an attrition rate of 20% will be applied to account subjects who interrupted or discontinued DAPT (greater than 3 cumulative days) within the first one month of procedure, who were excluded due to events that would prohibit them from discontinuing DAPT beyond one month, who failed to transition from DAPT to SAPT one month after procedure, and who were lost to follow-up. Peri-procedural MIs will not exclude the patient from being considered as "one month clear". For the secondary endpoints like TLF, all available biomarkers (including peri-procedural) will be forwarded to the CEC to be used towards the adjudication of events.

12.1.3. Sample Size Calculation and Methods

Assuming a one-sided alpha level of 0.025 and a true event rate of 6.8%, an effective sample size of 1360 subjects will yield a greater than 97% power to reject the null hypothesis. Assuming a 20% attrition rate, a total sample size of 1700 subjects will be needed.

The outcomes from 700 US subjects enrolled in this study will be combined with those of 1000 subjects from the Resolute Onyx arm of the Onyx ONE Study to form the total sample size of 1700. In addition, subjects enrolled in Japan who have completed their one-year follow-up at the time when the 700 US subjects have completed their one year follow up will also be included in the primary analysis.

12.2. Analysis Populations

Intent-to-Treat (ITT): All subjects who signed the informed consent with an attempted implant procedure. Time zero begins at the date of the index procedure.

Primary Analysis: ITT subjects who are one-month clear and received the Resolute Onyx stent only. Time zero begins at the date of the index procedure.

12.3. General Analysis Overview

Descriptive statistics of continuous outcomes will be presented with sample size, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized with frequencies and percentages. All statistical analyses will be performed using SAS for Windows (version 9.1 or higher) or other widely accepted statistical or graphical software. Patient data listings and tabular and graphical presentations of results will be provided. Statistical analyses will be independently validated. Additional details on the analysis will be provided in the Statistical Analysis Plan (SAP) for this study.

12.4. Analysis of the Primary Endpoint

Cardiac death and myocardial infarction will be adjudicated by the CEC. The CD/MI rate at one year in a one-month clear population [timeframe: one month to one year] will be compared with the performance goal of 9.7%, with a one-sided binomial exact test at the 0.025 significance level. The analysis for the primary endpoint will be performed in ITT subjects who are one-month clear and received the Resolute Onyx stent only.

12.5. Analysis of Secondary Endpoints

For secondary endpoints, event/success rates, and 95% two-sided confidence interval will be provided. The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot. Further details on the secondary endpoints will be included in the Statistical Analysis Plan.

12.6. Analysis of Baseline Characteristics

All clinically relevant baseline variables will be tabulated and reported. Categorical variables will be reported using counts and percentages, and continuous variables will be reported by giving the number of known values, the mean, standard deviation, minimum and maximum values.

12.7. Analysis of Subgroups

Subgroup analyses of the primary endpoint include but are not limited to the following patient characteristics. Further details on subgroup analysis are included in the Statistical Analysis Plan.

- Acute Coronary Syndrome
- Diabetes
- Sex
- Age
- Stent / Lesion Characteristics (multiple vessels, multiple lesions, overlapping stents)

12.8. Interim Analysis

Interim analyses are not planned in this trial.

12.9. Additional Analysis

There may be additionally 100 subjects enrolled in Japan. Once all enrolled subjects (US and Japan) have had the chance to complete 1-year follow up, an additional report (including subjects from Onyx ONE Clear as well as the Onyx-arm of Onyx ONE Global Study) may be prepared as requested by PMDA.

12.10. Missing Data

Deviations from original statistical plan will be avoided, and every effort will be undertaken to minimize missing data. In time-to-event outcomes, dropouts will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. Unless otherwise specified, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data. Further details are provided in the Statistical Analysis Plan.

13. Economic Analysis

Economic analysis of Resolute Onyx stent in specific study centers may be assessed to determine the relative cost effectiveness after treatment including procedural cost estimated from the viewpoint of the hospital including quality of life instruments. Analysis may include medical costs, procedural aspects of the study such as the use of pre- and post- dilatation, the number of DES attempted to be used, length of stay and any other ancillary devices utilized. Additional details will be listed in the statistical analyses plan.

Access to health economic source documents at each center, if needed, should be made available to the Sponsor in order to enable collection of relevant clinical and cost data.

14. Ethics

14.1. Statements of Compliance

- In the United States, this study will be conducted in compliance with the protocol, good clinical practice (GCP) and 21CFR812. This study is designed to reflect the GCP principles outlined in ISO 14155:2011. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. ISO14155 will not be followed for full device accountability and Adverse Event reporting except in regions where noted.
- The study will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki (2013) are implemented in this study by means of the Informed Consent (IC) process, IRB approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.
- In Japan, the trial will be conducted in accordance with the ethical principles of the Japan GCP Ordinance, the Pharmaceutical and Medical Device Act as well as ISO 14155:2011.
- Regulatory agency approval to conduct the study will be obtained in participating geographies (where applicable). Study centers will not be activated nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency has been obtained (as appropriate). Additionally, any requirements imposed by a local regulatory agency or IRB shall be followed, as appropriate.
- Each study center must provide Medtronic with a copy of the study center's IRB approval letter and the IRB-approved Informed Consent Form.
- If applicable, approvals for the continuation of the study at each study center must be kept current in accordance with the IRB review schedule. All study center communications to and from the IRB must be forwarded to Medtronic as they are sent/received.
- The Sponsor will be informed by the IRB and/or the investigator in case any action is taken by an IRB with respect to this investigation.
- Study reimbursement is outlined in the Clinical Study Agreement. Indemnification will be done according to local laws. Reimbursement of travel cost will be considered if allowed by local regulations
- This study will be publicly registered on www.clinicaltrials.gov prior to first enrollment.
- Medtronic maintains appropriate clinical study liability insurance coverage if required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC.
- Study centers should follow their institutional procedures for maintenance of angiography, diagnostic, and laboratory equipment used for assessing the study variables

15. Study Administration

15.1. Investigator / Investigational Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

An investigator may be included in the clinical study if compliant with the following requirements:

- Investigator is qualified, educated and has experience in the interventional treatment of coronary arteries
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions.
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study. Each site must have a designated research coordinator assigned to the study.
- Investigator/site has access to an adequate number of eligible subjects.
- Investigator/site has the ability to comply with applicable IRB and regulatory requirements.
- Lack of potential conflict(s) of interest
- Anticipated study startup timeline, including contracting and IRB and regulatory submission and approval (if applicable) is acceptable.
- Anticipated competition for same subject population from competitive ongoing studies is at an acceptable rate.

A list of participating study centers, including contact information, and investigators, including titles, will be available as a separate document.

Prior to study start, a recent CV shall be collected from each principal investigator and key members of the study center team participating in this study (if required for the region), evidencing the required qualifications, including the year and where obtained, and shall include their current position at the study center.

15.2. Site Activation/Supply of Study Materials

Study centers will receive a formal letter of site activation upon receipt of or completion of the following:

- Curriculum vitae of the principal and sub-investigators and all key site staff (as required by the region)
- A signed trial agreement
- Financial disclosure from the investigators
- A copy of the IRB approval letter, along with the voting roster
- The IRB approved subject information and Informed Consent Form
- Documented training of the investigative team
- Delegated Task List
- Confirmation of calibration and maintenance of equipment and maintenance of facilities

Medtronic will control the supply of study materials and will only grant site activation when above activation criteria are met, and the site receives a formal activation letter from Medtronic.

15.3. Monitoring

Monitoring visits will be conducted during the course of the study in accordance with Medtronic SOPs and the Monitoring Plan. The monitor will be identified for each site and contact information will be provided as appropriate. The initiation visit will be performed before the first subject is enrolled once it has been verified that the site is prepared for the study and the requirements for starting subject enrollment are met. Subject-level data will be 100% monitored by a representative of Medtronic through the one-year primary endpoint, and a risk based plan will be in place for the remainder of the study.

Documentation of the training of site research personnel will be collected during the site initiation visit. In order to ensure a high degree of data quality, periodic monitoring will be performed at all recruiting clinical centers. Site monitoring will be conducted to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

The monitor will perform source data verification by reviewing subject documents through each subject's one-year time point. All Informed Consent Forms will be checked. The monitor will perform review of key variables for all enrolled subjects (including but not limited to, inclusion/exclusion criteria, endpoints and safety) on the eCRFs against subject's source documents per the Monitoring Plan. In addition, all available source documentation will be reviewed for potential serious adverse events and device effects. Any discrepancies will be noted and resolved. The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic study personnel during these visits or other times when questions arise regarding subject information.

15.4. Data Management

All records and other information about subjects participating in this study will be treated as confidential.

Medtronic will collect data and monitor study records. Auditors, IRB members, inspectors (governmental regulatory authorities) may also have access to the study records. Participating subjects will not be identified by name in any published reports about this study.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the subject medical file. Only authorized persons can complete eCRFs. eCRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

15.5. Direct Access to Source Data / Documents

The Investigator must be willing to give direct source data access to study monitors, auditors, EC members and inspectors, and have appropriate facilities to retain relevant study documents.

15.6. Confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. Every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (site number and subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

15.7. Liability

The sponsor and local sponsors are wholly own subsidiaries of Medtronic. Medtronic (including all wholly owned subsidiaries) maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Study Insurance statement or certificate will be provided to the IRB.

Medtronic will provide subject indemnification according to local laws where this study will be conducted.

15.8. Clinical Investigation Plan Amendments

All clinical investigation plan updates need to be approved by Medtronic and respective IRB. Medtronic is responsible for regulatory authority approval or notification of clinical investigation plan updates or amendments if applicable according to local regulations.

15.9. Record Retention

Medtronic records and reports will be stored at Medtronic during the course of the study. After the closure of the study, all records and reports will be archived by Medtronic permanently. Investigators' records will be retained for at least two years after the formal discontinuation of clinical development of the device, and according to the local requirements of the country.

15.10. Publication and Use of Information

Medtronic will form a Publications Committee with the purpose of providing direction and support for the development of the publication plan. The scientific validity and timing of all publications (manuscripts and presentations) will be evaluated in order to maximize the benefits derived from the publication of the clinical data of the study.

Members of the Publication Committee may include, but are not limited to, the principal investigators, members of the Executive Committee, the Clinical Program Director and other Medtronic personnel as appropriate.

Authorship selection for publications using multi-center data will be determined based on the International Committee of Medical Journal Editors (ICMJE) published guidelines. Specific authorship criteria required by the scientific journal or other forum for publication submission must also be met. Authors must meet the following four conditions:

- Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

At the conclusion of the study, a multi-center manuscript on the study primary results may be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the study is not allowed until the preparation and publication of the multi-center results. Investigators may submit publication ideas through the Publication Committee and may author publications approved by Medtronic and the Committee.

15.11. Suspension or Early Termination

Suspension: A temporary postponement of study activities related to enrollment. This is possible for the whole study or a single investigational site.

Early termination: Closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. If a center is terminated or suspended, no additional enrollments will be allowed at the center until, in the case of suspension, issues can be resolved. Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Non-compliance to obtain Informed Consent
- Non-compliance to the inclusion/exclusion criteria
- Failure to follow subjects per scheduled follow-ups
- Failure to submit data in a timely manner
- IRB approval expiration
- IRB suspension of the center

If the study is terminated prematurely or suspended:

- Medtronic will promptly inform the investigators of the termination or suspension and the reasons, and inform the regulatory authority(ies) (where required by applicable regulatory requirements)
- The IRB will also be promptly informed and provided with the reasons(s) for termination or suspension by the sponsor or by the clinical investigator
- The investigator will promptly inform the subjects if appropriate and assure appropriate therapy and follow-up for the subjects
- In the case of suspension, when Medtronic concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, Medtronic will inform the clinical investigator and the appropriate IRB of the rationale and provide relevant data to support this decision.
- In case of early termination, the investigator agreement will be terminated
- In case of early termination, the subjects need to be followed until at least 30 days after the index procedure

15.12. Organizations Involved in Study

Image Transfer:	Medidata Medical Imaging 700 W. Pete Rose Way, Suite 436 Cincinnati, OH 45202	**Data Safety Monitoring Board:**	Cardiovascular Research Foundation 1700 Broadway, Floor 8 New York, NY 10019
Clinical Events Committee:	Cardiovascular Research Foundation 1700 Broadway, Floor 8 New York, NY 10019	**Angiographic Core Lab:**	Cardiovascular Research Foundation 1700 Broadway, Floor 8 New York, NY 10019
Statistical Analysis (Independent Statistician)	BAIM Institute 930-W Commonwealth Ave Boston, MA 02215		

16. Version History

Version	Location of Change	Summary of Changes	Author
1.0	Not applicable	Not applicable – initial release	Lilian C Lee
2.0	See Summary of Changes Table – Onyx ONE Clear CIP v1.0 to v2.0	See Summary of Changes Table – Onyx ONE Clear CIP v1.0 to v2.0	Lilian C Lee
3.0	See Summary of Changes Table – Onyx ONE Clear CIP v2.0 to v3.0	See Summary of Changes Table – Onyx ONE Clear CIP v2.0 to v3.0	Lilian C Lee, Zhen Meng

Summary of Changes Table– Onyx ONE Clear CIP v1.0 to v2.0

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v1.0	New wording in Onyx ONE Clear v2.0		
Page 4 Glossary	--	• Antiplatelet Therapy: Prescription or intake of aspirin or a P2Y12 inhibitor (e.g. clopidogrel, ticlopidine, prasugrel, ticagrelor). Patients may or may not be on oral anticoagulant medication.	Addition of text	Antiplatelet therapy definition was added.
Page 6 Glossary	--	• Dual antiplatelet therapy (DAPT): Prescription/intake of two anti-platelet medications, with one being aspirin or an aspirin-containing drug and the other a P2Y12 inhibitor (e.g. clopidogrel, prasugrel, ticlopidine, ticagrelor).	Move and modification of text	Dual antiplatelet therapy definition was modified and moved on page 6.
Page 7 Glossary	--	• Major Bleeding: Hospitalization for bleeding that required transfusion or other related evaluation/treatment.	Move and modification of text	Major bleeding definition was modified moved from page 4 to page 7.
Page 9 Glossary	• Oral anticoagulant (OAC): Type of oral medication used to prevent or reduce coagulation of blood. Includes vitamin K antagonists and novel anticoagulants (NOACs)/ directly acting oral anticoagulants (DOACs)	• Oral anticoagulant (OAC): Type of oral medication used to prevent or reduce coagulation of blood. Includes vitamin K antagonists **(e.g. warfarin)** and novel anticoagulants (NOACs)/ directly acting oral anticoagulants (DOACs) **(e.g. apixaban, rivaroxaban, dabigatran, edoxaban)**	Addition of text	Added examples of oral anticoagulant
Page 10 Glossary	SAPT: Single Antiplatelet Therapy: prescription/intake of only one anti-platelet drug (aspirin or P2Y12 inhibitor). Patients may or may not be on OAC	• Single Antiplatelet Therapy (SAPT): Prescription/intake of only one anti-platelet drug (aspirin or P2Y12 inhibitor). Patients may or may not be on oral anticoagulant medication.	Modification	Modification of acronyms
Page 12 Glossary	--	• Triple therapy (TT): Prescription/intake of dual antiplatelet therapy plus an oral anticoagulant medication	Addition of text	Added triple therapy definition
Page 15 Synopsis	All Serious Adverse Events (SAEs) and endpoint-related events will be evaluated by the Medtronic.	All Serious Adverse Events (SAEs) and endpoint-related events will be evaluated by **Medtronic safety department**. **Quarterly progress reports on study enrollment status and rates of cardiac death, MI, cardiac death/MI and stent thrombosis will be provided to FDA.**	Addition of text	Added quarterly safety reports
Page 22 5.2 Rationale	The Onyx ONE Clear Study is a single-arm study that compares the Resolute Onyx stent with **objective performance criteria**.	The Onyx ONE Clear Study is a single-arm study that compares the Resolute Onyx stent with **a performance goal**.	Modification	Clarification

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v1.0	New wording in Onyx ONE Clear v2.0		
Page 25 6.1 Resolute Onyx Stent and Delivery System	The Resolute Onyx stent is mounted on a Rapid Exchange delivery system which incorporates design and process improvements to provide enhanced deliverability.	The Resolute Onyx stent is mounted on a Rapid Exchange **or Over-the-Wire** delivery system which incorporates design and process improvements to provide enhanced deliverability.	Addition of text	Description to match figures
Page 26 6.1 Resolute Onyx Stent and Delivery System Figure 1 caption	Figure 1. Delivery System and Resolute Onyx Stent	Figure 1. Resolute Onyx Rapid Exchange Delivery System (with Stent)	Modification	Added identification of delivery system
Page 28 6.9 Product Accountability	This study will use commercially available product and labeling with appropriate documentation of specific device identifiers, e.g. the **lot/batch** numbers of the used stent(s).	This study will use commercially available product and labeling with appropriate documentation of specific device identifiers, e.g. the **lot and reference/serial** numbers of the used stent(s).	Modification	Clarification of device identifiers to be recorded
Page 29 7.3 Inclusion Criteria	All subjects who are acceptable candidates for treatment with a DES in accordance with applicable guidelines for percutaneous coronary interventions, per manufacturer's Instructions for Use, who additionally meet pre-defined criteria for being high-bleeding risk and/or are candidates for 1-month DAPT can be considered.	All subjects who are acceptable candidates for treatment with a DES in accordance with applicable guidelines for percutaneous coronary interventions, per manufacturer's Instructions for Use, who additionally meet pre-defined criteria for being high-bleeding risk and/or are candidates for 1-month DAPT **and who in the opinion of the investigator, the potential benefit of 1-month DAPT to the subject outweighs the potential risk** can be considered.	Addition of text	Added additional emphasis on importance of risk-benefit assessment for one-month DAPT
Page 35 8.6 Medication Adherence	Subjects must also continue on single antiplatelet therapy (SAPT) after one month of DAPT through the end of the study.	Subjects must also continue on single antiplatelet therapy (SAPT) after one month of DAPT through the end of the study. **Subjects will be provided a medication reminder card and also instructed to inform the investigator and team on any changes in medication including medication stop date, reason for stopping medication, medication restart date, and medication dosage. Dual antiplatelet therapy compliance will be assessed in the clinic at the 1-month visit as well as in follow-up contacts and will be recorded in the eCRF.**	Addition of text	Added methods to track medication adherence to protect against DAPT interruption
Page 40 8.16 Sponsor record maintenance responsibilities	Competent Authority notification and approval documentation and correspondence	--	Deletion of text	Correction

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v1.0	New wording in Onyx ONE Clear v2.0		
Page 41 8.17 Sponsor reporting responsibilities Table 5. Sponsor Reporting requirements	--	Report: Study enrollment status and rates of cardiac death, MI, cardiac death/MI and stent thrombosis Submitted to: Progress reports will be provided to FDA on a quarterly basis	Addition of text	Added sponsor responsibility of submitting quarterly progress reports
Page 43 9.1 Potential Risks	This high-bleeding risk population in the LEADERS FREE study included **complex lesion subgroups such as in the senior and in ACS (STEMI/NSTEMI) patient population.** While rates of adverse clinical outcomes were higher in these subgroups as compared to treatment of simple lesions, the investigators did not find patients to be at higher risk in these subgroups that would trigger concern. These data were pre-specified and also published by the LEADERS FREE investigators.	This high-bleeding risk population in the LEADERS FREE study included **subjects who had clinical or anatomic features that posed a higher ischemic risk, including subjects who had multivessel disease (1493/2399 (62.2%)), ACS (659/2432 (27.1%)), diabetes (805/2427 (33.2%), hypertension (1913/2427 (78.8%)), bifurcation (15.5%), in-stent restenosis (2.5%) and chronic total occlusion (4.7%).** While rates of adverse clinical outcomes were higher in these subgroups as compared to treatment of simple lesions, the investigators did not find patients to be at higher risk in these subgroups that would trigger concern. These data were pre-specified and also published by the LEADERS FREE investigators. **Given that the Onyx ONE Clear Study inclusion/exclusion criteria are similar to that of LEADERS FREE, it is expected that similar proportions will be enrolled and have clinical or anatomic features that pose a higher ischemic risk.**	Modification	Added proportions of enrolled subjects who had clinical or anatomic features that pose a higher ischemic risk in LEADERS FREE study and an estimate of similar proportion of this population in the current study
Page 44 9.2 Risks Related to Devices	**Percutaneous Coronary Diagnostic and Treatment Procedures** Risks associated with using these products are those associated with percutaneous treatment procedures for a stenotic coronary artery. The complications relating to standard PTCA and stenting include, but are not limited to the following: • Abrupt stent / vessel closure • Access site pain, hematoma or hemorrhage	**Percutaneous Coronary Diagnostic and Treatment Procedures** Risks associated with using these products are those associated with percutaneous treatment procedures for a stenotic coronary artery. The complications relating to standard PTCA and stenting include, but are not limited to the following: • **Abrupt vessel closure** • Access site pain, hematoma or hemorrhage • Allergic reaction to anti-coagulation and/or anti-thrombotic therapy, contrast material, or stent	Modification	Correction of risk section to align with the Resolute Onyx US IFU

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v1.0	New wording in Onyx ONE Clear v2.0		
	• Acute myocardial infarction • Allergic reaction to anti-coagulation and/or anti-thrombotic therapy, contrast material, or stent and/or delivery system materials, drug, and polymer coating • Aneurysm, pseudoaneurysm, or arteriovenous fistula • Arrhythmias (including ventricular fibrillation and ventricular tachycardia) • Balloon rupture • Bleeding • Cardiac tamponade • Cardiogenic shock • Coronary artery occlusion, perforation, rupture, or dissection • Coronary artery spasm • Death • Damage to the stent or injury to the artery requiring emergency coronary artery bypass grafting (CABG) • Embolism, emboli (blockage), distal (air, tissue or thrombotic emboli) • Emergency surgery: peripheral vascular or coronary bypass • Failure to deliver the stent • Fever • Hemorrhage requiring transfusion • Hypotension / hypertension • Incomplete stent apposition • Increased risk of restenosis of stented segments	and/or delivery system materials, drug, and polymer coating • Aneurysm, pseudoaneurysm, or arteriovenous fistula • Arrhythmias (including ventricular fibrillation) • Balloon rupture • Bleeding • Cardiac tamponade • Coronary artery occlusion, perforation, rupture, or dissection • Coronary artery spasm • Death • **Embolism (air, tissue device or thrombus)** • Emergency surgery: peripheral vascular or coronary bypass • Failure to deliver the stent • Hemorrhage requiring transfusion • Hypotension / hypertension • Incomplete stent apposition • Increased risk of restenosis of stented segments • **Infection or fever** • **Myocardial infarction** • Pericarditis • Peripheral ischemia / peripheral nerve injury • Renal failure • Shock / pulmonary edema • Stable or unstable angina • Stent deformation, collapse, or fracture • Stent migration or embolization • Stent misplacement • Stroke or transient ischemic attack		

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v1.0	New wording in Onyx ONE Clear v2.0		
	• Infection and/or pain at catheter insertion site, fever • Pericarditis • Peripheral ischemia / peripheral nerve injury • Renal failure • Shock / pulmonary edema • Stable or unstable angina • Stent deformation, collapse, or fracture • Stent migration or embolization • Stent misplacement • Stent thrombosis or occlusion • Stroke or transient ischemic attack • Thrombosis (acute, sub-acute, late, or very late) • Total occlusion of coronary artery **Additional Potential Risks Related to Resolute Onyx stent** Additional potential adverse events that have been associated with zotarolimus include but are not limited to: • Anemia • Circumoral paresthesia • Diarrhea • Dry Skin • Headache • Hematuria • Pain (abdominal, arthralgia) • Rash	• **Thrombosis (acute, sub-acute, or late)** **Additional Potential Risks Related to Resolute Onyx stent** Additional potential adverse events that have been associated with zotarolimus include but are not limited to: • Anemia • Diarrhea • Dry Skin • Headache • Hematuria • **Infection** • **Injection site reaction** • Pain (abdominal, arthralgia) • Rash The types of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings. These additional risks may include, but are not limited to, the following: • Allergic reaction • Focal inflammation at the site of stent implantation • Restenosis of the stented artery		

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v1.0	New wording in Onyx ONE Clear v2.0		
	The types of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings. These additional risks may include, but are not limited to, the following: • Local inflammation at the site of stent implantation • Restenosis of the stented artery			
Page 43 Footnote	Morice MC, Talwar S, Gaemperli O, et al. Drug-coated versus bare-metal stents for elderly patients: A predefined sub-study of the LEADERS FREE trial. Int J Cardiol. 2017; 243:110-115.	Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. NEJM Oct 14, 2015.	Modification	Reference modification
Page 53 12.1.2 Hypothesis	--	Peri-procedural MIs will not exclude the patient from being considered as “one month clear”. For the secondary endpoints like TLF, all available biomarkers (including peri-procedural) will be forwarded to the CEC to be used towards the adjudication of events.	Addition of text	Clarification of the exclusion of peri-procedural MI from one-month clear
Page 57 15.3 Monitoring	Subject-level data will be 100% monitored by a representative of Medtronic through the one-year primary endpoint.	Subject-level data will be 100% monitored by a representative of Medtronic through the one-year primary endpoint, **and a risk based plan will be in place for the remainder of the study**.	Addition of text	Clarification that there is a rigorous monitoring plan in place through completion of study

Summary of Changes Table– Onyx ONE Clear CIP v2.0 to v3.0

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v2.0	New wording in Onyx ONE Clear v3.0		
Footer	Medtronic **Confidential** 056-F275 **v3.0** Clinical Investigation Plan Template	Medtronic **Controlled Information** 056-F275 **v A** Clinical Investigation Plan Template	Modification	Template update
Page 4 Glossary	AE	Adverse Event (AE)	Modification	Modification of acronyms
Page 21 5. Study Design	Subjects who are enrolled will be considered part of the **Intention**-to-Treat (ITT) population and followed through for two years.	Subjects who are enrolled will be considered part of the **Intent**-to-Treat (ITT) population and followed through for two years **if they receive Resolute Onyx stent only or exit after one year if they receive other non-study device (e.g. non-Resolute Onyx stent, POBA and drug-coated balloon)**.	Modification Addition	Typo This same information was previously only captured in Section 8.7 (p. 35); Added same information to section 5
Page 28 7.2. Subject Enrollment	Subjects who undergo consenting and have confirmation of coronary angiography anatomy eligibility and the Resolute Onyx stent was attempted but was not implanted will be considered part of the **intention**-to-treat (ITT) population.	Subjects who undergo consenting and have confirmation of coronary angiography anatomy eligibility and the Resolute Onyx stent was attempted but was not implanted will be considered part of the **intent**-to-treat (ITT) population.	Modification	Typo
Page 32 8.3. Subject Consent	Where a patient has initially verbally consented…, written consent should be sought **form** the patient as soon as, ...	Where a patient has initially verbally consented …, written consent should be sought **from** the patient as soon as, …	Modification	Typo
Page 33 8.3. Subject Consent	The consent process **should** be documented in the subject's medical record.	The consent process **must** be documented in the subject's medical record.	Modification	Emphasis on the requirement of consent process to increase to patient rights, safety or welfare
Page 35 8.8. Staged Procedure	Staging should be pre-specified at the time of the index procedure **and follow-up should be calculated from the date of index procedure**…. Lesions and vessels treated at the staged procedure are considered target lesions and vessels.	Staging should be pre-specified at the time of the index procedure. ... Lesions and vessels treated **with Resolute Onyx stent** at the staged procedure are considered target lesions and vessels.	Deletion Addition	Deletion of text since complete follow-up requirements are list in the following paragraph

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v2.0	New wording in Onyx ONE Clear v3.0		
				Clarification on target lesion and vessel definitions at staged procedure
Page 36 8.12. Assessment of Safety	Reports of all adverse events related to endpoint (including bleeding), SAEs, and device deficiencies, with the return of the device when possible, will be evaluated by Medtronic.	Reports of all adverse events related to endpoint (including bleeding), SAEs, **adverse device effects** and device deficiencies, with the return of the device when possible, will be evaluated by Medtronic.	Addition	"adverse device effects" was missing and added to aligned with other sections
Page 50 10.3. Recording and Reporting of Device Deficiencies	All reportable device deficiencies and malfunctions will be documented on the appropriate eCRF, one **more** each deficiency, and further reported to the IRB (if required) within the IRB required timeframe and local and national regulations.	All reportable device deficiencies and malfunctions will be documented on the appropriate eCRF, one **form for** each deficiency, and further reported to the IRB (if required) within the IRB required timeframe and local and national regulations.	Modification	Typo
Page 52 12.1.1. Primary Hypothesis	The primary endpoint of the study will be compared to a PG of **9.9%**. The study hypotheses are: H_0: $\pi \geq$ **9.9%** H_A: $\pi <$ **9.9%** … This one-sided test will be carried out at the 0.025 significance level using the **Fisher's** exact test.	The primary endpoint of the study will be compared to a PG of **9.7%**. The study hypotheses are: H_0: $\pi \geq$ **9.7%** H_A: $\pi <$ **9.7%** … This one-sided test will be carried out at the 0.025 significance level using the **binomial** exact test.	Modification	Updated performance goal and test name as consistent with Statistical Analysis Plan
Page 52 12.1.2. Hypothesis	As disproportionally higher rates of STEMI, unstable angina, and multi-vessel disease were identified in the ZEUS study population which could have led to a higher rate of cardiac death**. Hence**, the ZEUS rate was revised.	As disproportionally higher rates of STEMI, unstable angina, and multi-vessel disease were identified in the ZEUS study population which could have led to a higher rate of cardiac death, the ZEUS rate was revised.	Deletion	Typo
Page 52 12.1.2. Hypothesis	The performance goal incorporated a clinically acceptable margin of **3.1%** to the expected rate.	The performance goal **(9.7%)** incorporated a clinically acceptable margin of **2.9%** to the expected rate.	Modification	Updated the margin as consistent with Statistical Analysis Plan

Section/Page	Description of Change		Type of Change	Rationale for Change
	Previous wording in Onyx ONE Clear v2.0	New wording in Onyx ONE Clear v3.0		
Page 52 12.1.3. Sample Size Calculation and Methods	Assuming a one-sided alpha level of 0.025 and a true event rate of 6.8%, an effective sample size of 1360 subjects will yield a greater than **98%** power to reject the null hypothesis.	Assuming a one-sided alpha level of 0.025 and a true event rate of 6.8%, an effective sample size of 1360 subjects will yield a greater than **97%** power to reject the null hypothesis.	Modification	Updated the power as consistent with Statistical Analysis Plan
Page 53 12.4. Analysis of the Primary Endpoint	The CD/MI rate at one year in a one-month clear population [timeframe: one month to one year] will be compared with the performance goal of **9.9%**, with a one-sided **Fisher's** exact test at the 0.025 significance level.	The CD/MI rate at one year in a one-month clear population [timeframe: one month to one year] will be compared with the performance goal of **9.7%**, with a one-sided **binomial** exact test at the 0.025 significance level.	Modification	Updated performance goal and test name as consistent with Statistical Analysis Plan
Page 53 12.5. Analysis of Secondary Endpoints	For secondary endpoints, event/success rates, and 95% confidence interval will be provided.	For secondary endpoints, event/success rates, and 95% **two-sided** confidence interval will be provided.	Addition	Clarification on the confidence interval
Page 53 12.7. Analysis of Subgroups	Subgroup analyses of the primary endpoint include the following patient characteristics.	Subgroup analyses of the primary endpoint include **but are not limited to** the following patient characteristics.	Addition	Clarification on the subgroup analyses as consistent with Statistical Analysis Plan