Clinical Investigation Plan

Clinical Investigation Plan A post-approval study of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (RESOLUTE ONYX Post-Approval Study)

BIFURCATION COHORT - NCT03584464

Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	A post-approval study of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (RESOLUTE ONYX Post-Approval Study)
Clinical Investigation Plan Identifier	MDT16025RES003
Study Product Name	Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System, sizes 2.0 mm – 5.0 mm (Resolute Onyx™ stent)
Sponsor/Local Sponsor	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA 95403 USA Medtronic Bakken Research Center (BRC) B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands
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2 Glossary

Term	Definition
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.
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.
Clinically-driven target lesion revascularization (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 (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.
Device success	Attainment of < 50 % residual stenosis of the target lesion using only the study device.
Lesion success	Attainment of < 50 % residual stenosis of the target lesion using any percutaneous method.
Major adverse cardiac events (MACE)	Death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically driven repeat target lesion revascularization by percutaneous or surgical methods.
Myocardial infarction (MI) Medtronic Extended Historical	All myocardial infarction data will be reported per Medtronic Extended historical protocol definitions. Medtronic Historical Definition of Q wave MI (QWMI): will require one of the following criteria: • Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous

Term	Definition
	ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data. • New pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data, the CEC may adjudicate Q wave MI based on the scenario and appropriate cardiac enzyme data. Medtronic Historical Definition of Non-Q Wave MI (NQWMI): • elevated CK ≥ 2X the laboratory upper limit of normal with the presence of an elevated CK-MB (any amount above the laboratory upper limit of normal) in the absence of new pathological Q waves. **I. PCI (PERCUTANEOUS CORONARY INTERVENTION)** **Ia. Baseline Biomarkers of Myocardial Damage (CK and CKMB and Troponin < 1*URL) *and* not acute MI in progress.** **PERIPROCEDURAL <48 HOURS POST PCI** A. New pathologic q waves in ≥ 2 contiguous ECG leads ***AND***: ▪ any CKMB > 1*URL ***or*** ▪ in the absence of CKMB: Troponin > 1*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 1*URL ***or*** ▪ in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario B. Appropriate cardiac enzyme data (respecting top-down hierarchy, b1 to b3): b1. CK ≥ 2*URL Confirmed by: ▪ - CKMB > 1*URL ***or*** ▪ - in the absence of CKMB, Troponin > 1*URL ***or*** ▪ - in the absence of CKMB and Troponin: CEC decision upon clinical scenario ***or*** b2. In the absence of CK: CKMB > 3*URL ***or*** b3. In the absence of CK and CKMB: Troponin > 3*URL Note: URL = upper reference limit, defined as 99th percentile of normal **Ib. If Baseline Biomarkers of Myocardial Damage: CK and/or CKMB > 1*URL or acute MI in progress** **MYOCARDIAL INFARCTION, RE-INFARCTION (EXTENSION) <48 HOURS POST PCI** A. If CK (or CKMB) from index MI has not yet reached its maximum level:

- Recurrent thoracic chest pain or ischemia equivalent >20 minutes (or new ECG changes consistent with MI) ***AND***
- Appropriate cardiac enzyme data:
  - A rise in CK within 24 hours of the index event >2*URL (confirmed by either CKMB or Troponin > 1*URL) and >50% above the previous level ***or***
  - In absence of CK: a (post PCI) rise in CKMB within 24 hours of the index event >3*URL and >50% above the previous level ***or***
  - In absence of CK and CKMB: a (post PCI) rise of Troponin within 24 hours of the index event >3*URL and > 50% above the previous level

B. If elevated CK (or CKMB) following the index MI has peaked AND CK level has returned < URL then any new rise in:

- CK >2*URL (confirmed by either CKMB > URL or Troponin >URL) ***or***
- in the absence of CK: CKMB > 3*URL ***or***
- in the absence of CK and CKMB, Troponin > 3*URL

C. If CK (or CKMB) following the index MI has peaked AND CK level has NOT returned to < URL:

- A rise in CK >50% above the previous level and > 2*URL confirmed by either CKMB > URL or Troponin > URL ***or***
- In absence of CK, when CKMB has NOT returned < URL, a rise in CKMB >50% above the previous level and > 3*URL ***or***
- In absence of CK, when CKMB and Troponin has not returned < URL a rise in Troponin > 50% above the previous level and >3*URL

SPONTANEOUS MI >48 HOURS (PCI)

A. Recurrent thoracic chest pain or ischemic equivalent ***AND***

- New pathologic q waves in ≥ 2 contiguous ECG leads AND any CKMB > 1*URL ***or***
- in the absence of CKMB: Troponin > 1*URL ***or***
- in the absence of CKMB and Troponin: CK > 1*URL ***or***
- in the absence of CKMB and Troponin and CK: CEC decision upon clinical scenario

B. Appropriate cardiac enzyme data (respecting top-down hierarchy):

b1. CK ≥ 2* URL Confirmed by:

- CKMB > 1*URL ***or***
- in the absence of CKMB: Troponin > 1*URL ***or***
- in the absence of CKMB and Troponin: CEC decision upon clinical scenario ***or***

b2. In the absence of CK: CKMB > 3*URL ***or***

Term	Definition
	b3. In the absence of CK and CKMB: Troponin > 3*URL *or* b4. In the absence of CK, CK-MB and Troponin, clinical decision based upon clinical scenario. **IIa. Baseline Biomarkers of Myocardial Damage (CK and CKMB and Trop < 1*URL) *and* not acute MI in progress.** **PERIPROCEDURAL <72 HOURS POST CABG** A. New pathologic q waves in ≥ 2 contiguous ECG leads or recurrent signs or symptoms consistent with myocardial ischemia ***AND*** ▪ CK-MB >5*URL *or* ▪ in the absence of CKMB: Troponin > 5*URL *or* ▪ in the absence of CKMB and Troponin: CK > 5*URL *or* ▪ in the absence of CKMB and Troponin and CK: CEC decision upon scenario B. Appropriate cardiac enzyme data ▪ CKMB ≥ 10* URL *or* ▪ In the absence of CKMB: Trop > 10*URL. *or* ▪ In the absence of CKMB and Troponin: CK > 10*URL **IIb. If Baseline Biomarkers of Myocardial Damage: CK and/or CKMB > 1*URL *or* acute MI in progress** **MYOCARDIAL INFARCTION, RE-INFARCTION (EXTENSION) <72 HOURS POST CABG** A. If Peak CK (or CKMB) from index MI has not yet reached its maximum level: ▪ signs or symptoms consistent with recurrent myocardial ischemia ***AND*** ▪ Appropriate cardiac enzyme data: - A rise in CKMB within 24 hours of the index event >10*URL and URL and ≥ 50% above the previous level. - In absence of CKMB: a rise in Troponin within 24 hours of the index event >10*URL and ≥ 50% above the previous level. - In absence of CKMB and Troponin: a rise in CK within 24 hours of the index event >10*URL and ≥ 50% above the previous level**.** B. If elevated CK (or CKMB) following the index MI has peaked ***AND*** CKMB level has returned < URL, any new rise in:

Term	Definition
	▪ CKMB >10*URL ***or*** ▪ in the absence of CKMB: Troponin > 10*URL ***or*** ▪ in the absence of CKMB and Troponin: CK > 10*URL C. If elevated CK (or CKMB) following the index MI has peaked ***AND*** CKMB level has NOT returned < URL: ▪ A rise in CKMB ≥50% above the previous level and > 10*URL ***or*** ▪ In absence of CKMB: a rise in Troponin ≥50% above the previous level and > 10*URL. ***or*** ▪ In absence of CKMB and Troponin: a rise in CK ≥ 50% above the previous level and >10*URL
Myocardial infarction (peri-procedural) SCAI Definition	**In subjects with normal baseline CK-MB:** The peak CK-MB measured within 48 hours of the procedure rises to ≥10 x the local laboratory ULN, or to ≥5 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, or in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70 x the local laboratory ULN, or ≥35 x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. **In subjects with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling:** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level. **In subjects with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling:** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.
Myocardial infarction Third Universal Definition (3rd UDMI)	**<u>Criteria for acute myocardial infarction</u>** 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: • Symptoms of ischemia. • New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB). • Development of pathological Q waves in the ECG.

Term	Definition
	• Imaging of evidence of new loss of viable myocardium or new regional wall motion 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 in 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.
Procedure success	Attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.
Stent thrombosis	All stent thrombosis data will be reported per the Academic Research Consortium (ARC) definition: 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. 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 – 1 year post stent implantation Very late stent thrombosis > 1 year post stent implantation

Term	Definition
	* Acute or subacute stent thrombosis can also be replaced by the term early stent thrombosis. Categories of evidence 1. Definite (either by angiographic or pathologic confirmation): a. Angiographic confirmation of stent thrombosis is considered to have occurred if: i. Thrombolysis In Myocardial Infarction (TIMI) flow is: 1. TIMI flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus 2. TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus ii. AND at least one of the following criteria has been fulfilled within a 48-hour time window: 1. New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes) 2. New ischemic ECG changes suggestive of acute ischemia 3. 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). b. Pathologic confirmation of stent thrombosis: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. 2. Probable: Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases: a. Any unexplained death within the first 30 days. b. 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. 3. 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.
Stroke	Sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain

Term	Definition
	such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists more than 24 hours.
Target lesion	Any lesion treated or attempted to be treated during the study procedure with the Resolute Onyx™ 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	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 TV related MI and TV Revasc assessments.*
Target vessel failure (TVF)	The composite endpoint comprised of cardiac death, target vessel myocardial infarction, or clinically-driven target vessel revascularization by percutaneous or surgical methods. 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.
Thrombus (intracoronary)	**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. **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).

Term	Definition
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.

3 Synopsis

Title	A post-approval study of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (RESOLUTE ONYX Post-Approval Study)
Clinical Study Type	Post-Approval
Product Name	Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System, sizes 2.0 mm – 5.0 mm (Resolute Onyx™ stent)
Sponsor	Medtronic Vascular, Inc.
Local Sponsor	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA 95403 USA Medtronic Bakken Research Center (BRC) B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands
External Organizations	Angiographic Core Lab Beth Israel Deaconess Medical Center, Inc. 375 Longwood Avenue, 3rd Floor Boston, MA 02215 USA Medidata Medical Imaging 700 W. Pete Rose Way, Suite 436 Cincinnati, OH 45202 USA 877-464-7473 www.intelemage.com MedStar Health Research Institute 6525 Belcrest Road, Suite 700 Hyattsville, Maryland 20782 USA
Indication under investigation	Symptomatic ischemic heart disease due to stenotic lesions of the coronary arteries Use of Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in the treatment of bifurcated lesions

Investigation Purpose	To observe the continued performance of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in a real-world more-comer population. To collect data on the safety and efficacy of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in bifurcated lesions
Product Status	The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (2.0 mm – 5.0 mm) has received CE Mark in Europe. The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (2.0 mm – 5.0 mm) is FDA approved in the United States; however the safety and efficacy in bifurcated lesions has not been established
Primary Objective(s)	To assess the continued safety and efficacy of the Resolute Onyx™ stent for the treatment of lesions in coronary arteries amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent. Subjects receiving stents 2.0 mm - 4.0 mm in diameter will be included in the Primary Cohort and subjects receiving stents 4.5 mm or 5.0 mm in diameter will be included in the Extra Large Vessel (XLV) Cohort. A Bifurcation Cohort will allow data collection to assess the safety and efficacy of the Resolute Onyx stent for the treatment of Bifurcated lesions in coronary arteries. The Bifurcation Cohort will include subjects receiving Resolute Onyx™ stents 2.0 mm – 5.0 mm in diameter for treatment of a bifurcation lesion with provisional stenting.
Primary Endpoint	The primary endpoint for all subjects in the Primary and XLV Cohorts participating in this study is 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, at 12 months. The primary endpoint for subjects participating in the Bifurcation Cohort is Target Vessel Failure (TVF) at 12 months.

Secondary Endpoint	The following secondary endpoints will be assessed for all subjects at hospital discharge, 30 days and 6, 12, 24, and 36 months post-procedure. 1. Acute Success (Device, Lesion, Procedure) 2. Cardiac Death 3. Target Vessel Myocardial Infarction (TVMI) 4. Target Lesion Revascularization (TLR) 5. Target Vessel Revascularization (TVR) 6. Cardiac Death and TVMI 7. Major Adverse Cardiac Event (MACE) • Defined as death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods 8. Target Lesion Failure (TLF) 9. Target Vessel Failure (TVF) 10. Stent Thrombosis (ST)
Study Design	Single arm, Non-Interventional, Open Label, Multicenter Study The enrollment period is anticipated to be approximately 10 months for the Primary Cohort and 12 months for the XLV Cohort. The Bifurcation Cohort enrollment is anticipated to be approximately 12 months. Subjects will remain in the study and continue with follow-up health status assessments through three years, study exit, or death, whichever comes first.
Sample Size	At least 410 in Primary Cohort (2.0 – 4.0mm) and 100 in XLV Cohort (4.5 – 5.0mm). The Bifurcation Cohort will consist of at least 200 subjects, of which approximately 15 subjects from the Primary and XLV Cohorts are anticipated to be included in the analysis, with an addition of approximately 185 subjects recruited specifically for the Bifurcation Cohort (2.0 – 5.0mm). Up to 25 United States (US) sites (at least 50% of subjects) and up to five European (EU) sites (up to 50 subjects participating in the Primary Cohort).
Duration	The study will be conducted to allow data collection and analysis through the 36-month follow-up assessment or until the study is formally terminated.

Inclusion/Exclusion Criteria	**Key Inclusion Criteria** • Symptoms and/or Evidence of coronary artery disease including subjects with chronic stable angina, silent ischemia, and acute coronary syndromes including non-ST elevation and ST-elevation myocardial infarction • Subject is an acceptable candidate for treatment with a drug eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions, manufacturer's Instructions for Use, and the Declaration of Helsinki **Key Exclusion Criteria** • Unprotected left main disease • Subjects with planned PCI of three vessel disease *Bifurcation Cohort (Additional Criteria)* **Key Inclusion Criteria** • Subject requires treatment of a single de novo bifurcated lesion amenable to treatment with Resolute Onyx using the provisional stenting technique • Target lesion(s) must have a stenosis of ≥ 50% and < 100% • Target vessel(s) must have a Thrombolysis In Myocardial Infarction (TIMI) flow ≥2 **Key Exclusion Criteria** • Planned two stent technique (main branch and side branch) of a bifurcation • Subjects with more than one bifurcation lesion • Impaired renal function (serum creatinine >2.5 mg/dl or 221 µmol/l) or on dialysis • Left ventricular ejection fraction (LVEF) ≤30% See Sections 9.3 and 9.4 for a detailed description of all Inclusion/Exclusion Criteria.
Study Procedures and Assessments	Screening and implant procedure, heath status assessments at 30 days and 6, 12, 24 and 36 months post-procedure.
Safety Assessments	All Serious Adverse Events (SAE) will be evaluated by Medtronic. The Clinical Events Committee (CEC) will adjudicate pre-defined clinical endpoint events.

Statistical Methods	For the Primary Cohort, the primary endpoint of TLF will be compared to a performance goal of 17.5%. The XLV Cohort analysis will descriptively evaluate the TLF rate with 95% confidence interval for the primary endpoint. The Bifurcation Cohort primary endpoint of TVF will be compared to a performance goal of 24.5%.

4 Introduction

4.1 Background

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 efficacy and are considered to be the current choice of treatment, Medtronic developed the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent to answer the demand for more flexible, and highly deliverable devices with enhanced radiopacity while maintaining the structural integrity needed to tackle complex disease.

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System represents Medtronic's fourth generation drug-eluting stent which incorporates thinner stent struts and increased radiopacity over predicate stents, while retaining the essential 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 1.6 µg/mm^2 remain the same. The BioLinx™ polymer, polymer thickness and drug coating formulation also remain the same.

The RESOLUTE ONYX Clinical Study program, including the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study and the RESOLUTE ONYX 2.0 mm Clinical Study, were designed to assess the safety and efficacy of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System for the treatment of lesions amenable to treatment with a Resolute Onyx™ 2.0 mm stent (RESOLUTE ONYX 2.0 mm Clinical Study) and a Resolute Onyx™ 2.25 mm – 4.0 mm stent (RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study) stent.

The RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study (75 subject premarket 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 outcomes are expected in 2017.

The Resolute Onyx™ 4.5 mm and 5.0 mm stents, a design extension of the remainder of the Resolute Onyx™ product matrix, achieve the required larger diameter at nominal pressure. The 4.5 mm and 5.0 mm stent design retains the equivalent elution profile (% released) and drug dose density as the remainder of the product matrix. The primary difference in the 4.5 mm and 5.0 mm stent design is the addition of one crown to create a 10.5 crown design (rather than the 9.5 crown design used on the 3.5 mm and 4.0 mm stents) and a marginally larger stent strut to achieve similar vessel scaffolding and metal to artery ratio in these larger vessels. The retention of key design attributes is essential to enable the utilization of the amassed clinical data from the RESOLUTE Clinical Trial Program to serve as the basis for supporting the efficacy and safety of the Resolute Onyx™ product, including the 4.5 mm and 5.0 mm stent diameters.

The safety and efficacy of DES in treating bifurcation lesions have been demonstrated acutely and in the long-term.[1-3] However, the safety and efficacy of Resolute Onyx™ in treating bifurcation lesions has not been demonstrated and will be investigated as part of the Bifurcation Cohort within this Post Approval Study. At present, there is general agreement that the majority of coronary bifurcation lesions should initially be treated using a single-stent strategy[4] (the Provisional Stenting Technique). 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. Both ACC/AHA[5] and ESC[6] revascularization guidelines currently recommend provisional stenting as the preferred procedure strategy for patients who are candidates for a bifurcation intervention.

The RESOLUTE ONYX Bifurcation Cohort will collect data to assess the safety and efficacy of the Resolute Onyx stent for the treatment of bifurcation lesions in native coronary arteries amenable to the treatment with Resolute Onyx stent sizes of 2.0 – 5.0 mm with provisional stenting.

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 patient population with the full size matrix of Resolute Onyx (2.0 mm - 5.0 mm diameter sizes).

The Resolute Onyx Zotarolimus-Eluting Coronary Stent System (sizes 2.0 mm – 5.0 mm) is commercially available in approximately 130 countries. To date, international commercial experience with Resolute Onyx has demonstrated a low complaint rate, comparable with the predicate Resolute Integrity product.

4.2 Purpose

The purpose of the RESOLUTE ONYX Post-Approval Study is to observe the continued performance of the Resolute Onyx™ stent in a real-world more-comer population.

The purpose of the RESOLUTE ONYX Bifurcation Cohort is to collect data to assess the safety and efficacy of the Resolute Onyx™ stent in the treatment of bifurcation lesions.

5 Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objective(s)

To continue the assessment of the safety and efficacy of the Resolute Onyx™ stent for the treatment of lesions in coronary arteries amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent.

The Bifurcation Cohort will assess the safety and efficacy of the Resolute Onyx Stent for the treatment of bifurcation lesions in native coronary arteries amenable to the treatment with Resolute Onyx Stent sizes of 2.0 – 5.0 mm utilizing the provisional stenting technique.

5.1.2 Primary Endpoint(s)

The primary endpoint for all subjects in the Primary and XLV Cohorts participating in this study is 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, at 12 months.

The primary endpoint for subjects participating in the Bifurcation Cohort is Target Vessel Failure (TVF) at 12 months.

5.1.3 Secondary Endpoint(s)

The following secondary endpoints will be assessed for all subjects at hospital discharge, 30 days and 6, 12, 24, and 36 months post-procedure.

1. Acute Success (Device, Lesion, Procedure)
2. Cardiac Death
3. Target Vessel Myocardial Infarction (TVMI)

4. Target Lesion Revascularization (TLR)
5. Target Vessel Revascularization (TVR)
6. Cardiac Death and TVMI
7. Major Adverse Cardiac Event (MACE)
    - Defined as death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods
8. Target Lesion Failure (TLF)
9. Target Vessel Failure (TVF)
10. Stent Thrombosis (ST)

6 Study Design

The Medtronic RESOLUTE ONYX Post-Approval Study is a single arm, open label, multi-center study evaluating approximately 710 subjects with ischemic heart disease attributable to stenotic lesions of the coronary arteries that are amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent. Subjects may receive treatment of more than one lesion (within a maximum of two target vessels).

The study will be conducted in two geographies, the United States (US) and Europe (EU). Up to 25 US sites (at least 50% of subjects) and up to five EU sites will participate in this study.

The study will have three cohorts; Primary, Extra Large Vessel and Bifurcation with specific and separate analyses (refer to Figure 1). The Primary Cohort will consist of at least 410 subjects who will be treated with at least one 2.0 mm – 4.0 mm diameter Resolute Onyx™ stent. No more than 50 subjects from European sites will be enrolled in the Primary Cohort. A maximum of 41 subjects will be treated with a 2.0 mm Resolute Onyx™ stent.

The Extra Large Vessel (XLV) Cohort will consist of at least 100 subjects who will be treated with at least one 4.5 mm - 5.0 mm diameter stent. Subjects will be enrolled in both the US and EU geographies, with no more than 49 subjects from European sites. Subjects in the XLV Cohort must have at least one lesion amenable to treatment with a 4.5 mm – 5.0 mm stent. Additional lesions may be treated with any available Resolute Onyx™ size stent but these subjects will be designated as a participant in the XLV Cohort as the primary analyses will be based on 4.5 and 5.0 mm stents.

The RESOLUTE ONYX Bifurcation Cohort is a single arm, multi-center study evaluating approximately 200 subjects with ischemic heart disease attributable to stenotic bifurcation lesions in native coronary arteries amenable to the treatment with Resolute Onyx Stent sizes of 2.0 – 5.0 mm utilizing the provisional stenting technique. The Bifurcation Cohort will consist of at least 200 subjects of which approximately 15 eligible subjects are expected to be included for analysis from the Primary and XLV cohorts, with an addition of approximately 185 subjects recruited specifically for the Bifurcation Cohort. Subjects will be treated with the full stent size matrix, 2.0 mm – 5.0 mm stents. Subjects will be enrolled in both the US and EU geographies, with no more than 99 subjects from European sites included in the analysis.

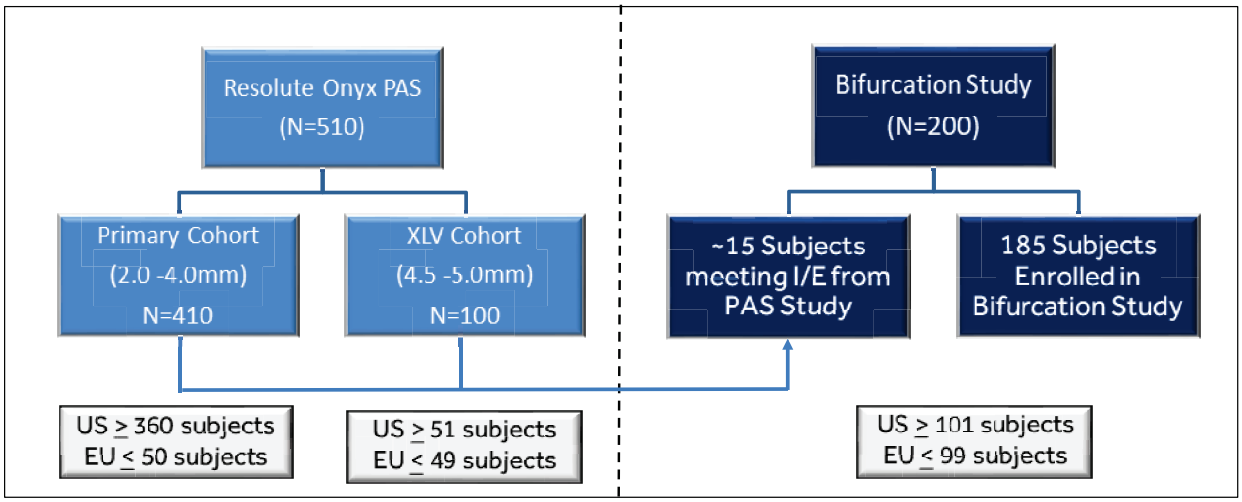

Figure 1: Subject Distribution

The study methods include the following measures to minimize potential sources of bias:

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and safety endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- An independent Angiographic Core Lab will evaluate all baseline and event-related angiograms.
- Study monitors will verify subject data and ensure compliance with the Clinical Investigational Plan and other study requirements.

6.1 Duration

The study will be conducted to allow data collection and analysis for a minimum of 36 months from treatment of the final subject or until the study has been formally terminated.

Health status assessments will be completed at 30 days and 6, 12, 24 and 36 months post-procedure.

As cohorts enroll at varying rates, not all Cohorts of the study will be open to enrollment at the same time.

6.2 Rationale

The rationale for this clinical study is to collect long-term clinical data to support the safety and efficacy profile of the 2.0 mm – 5.0 mm Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System including the treatment of bifurcation lesions with provisional stenting.

7 Product Description

7.1 General

The device being evaluated in this clinical study is the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (Resolute Onyx™ Stent System).

The following is a summary of the Resolute Onyx™ Stent System. Detailed information regarding clinical indications, contraindications, warnings and precautions, preclinical testing and materials in contact with tissues or body fluids, can be found in the 'Instructions for Use' (IFU).

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System consists of four components:

1. Resolute Onyx™ Bare Metal Stent: a premounted cobalt alloy and platinum-iridium alloy based stent
2. Delivery Systems:
   a. Resolute Onyx™ Rapid Exchange (RX) Delivery System, or
   b. Resolute Onyx™ Over-the Wire (OTW) Delivery System (only available in the US)
3. Polymer System
4. Zotarolimus: Anti-proliferative drug component/active pharmaceutical ingredient

All components of the Resolute Onyx™ Stent System (stent and delivery system) are packaged in one box represented by a model number per stent size available. For more information about stent sizes available, refer to Table 3.

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System received CE mark in September 2014 and the device will be used within its intended use as described in the approved Instructions for Use (IFU).

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System received FDA approval in April 2017, and the product will be used within its intended use as described in the Instructions for Use (IFU).

7.1.1 Stent

The Resolute Onyx™ Stent is manufactured from a composite material of cobalt alloy and platinum iridium alloy. The coronary stent is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are provided in multiple lengths and diameters. The delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014-inch (0.36-mm) guidewires and 1.42-mm (5-Fr/0.056-in) minimum inner diameter guide catheters.

Figure 2: Resolute Onyx™ Stent

7.1.2 Stent Delivery Systems

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent Systems consist of a balloon-expandable intracoronary drug-eluting stent pre-mounted on a stent delivery system. The Resolute Onyx™ RX delivery system (Figure 3) and the Resolute Onyx™ OTW delivery system (Figure 4) have an effective length of 140 cm. The OTW delivery system is only available in the United States.

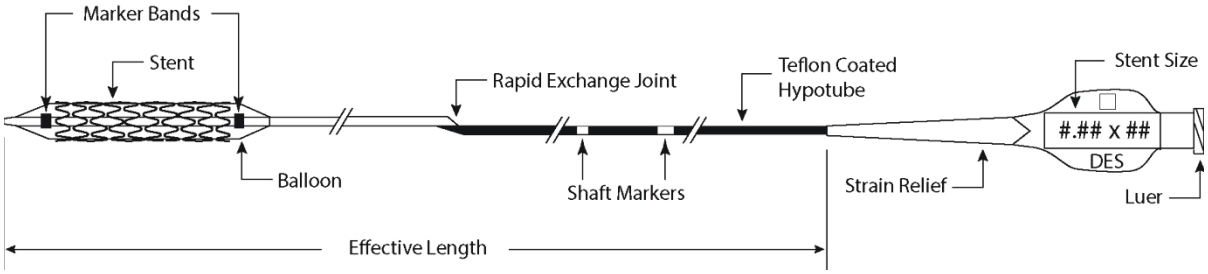

Figure 3: Resolute Onyx™ RX Delivery System (with Stent)

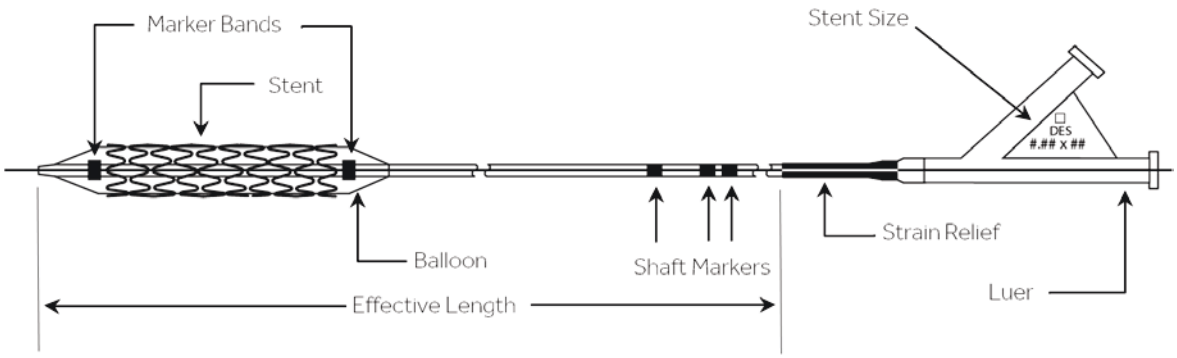

Figure 4: Resolute Onyx™ Over-the-Wire (OTW) Delivery System (with Stent)

7.1.3 Zotarolimus Drug Substance

The therapeutic agent utilized in the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is zotarolimus, a licensed proprietary chemical entity from Abbott Laboratories, and is identical to the predicate Resolute Integrity product. Zotarolimus is a tetrazole-containing macrocyclic immunosuppressant. 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), inhibiting its activity. Inhibition of mTOR results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. The zotarolimus drug in the Resolute Onyx™ stent is intended to reduce the incidence of restenosis in coronary interventions. The Resolute Onyx™ stent has a drug dose of approximately 1.6µg zotarolimus per mm^2 of the stent surface, which is identical to that of Resolute Integrity.

7.1.4 BioLinx™ Polymer

The Resolute Onyx™ stent is comprised of a bare metal stent with a Parylene C primer coat and a coating that consists of a blend of the drug zotarolimus and the BioLinx™ polymer system. BioLinx™ is a blend of the Medtronic proprietary components C10 (a copolymer of butyl methracrylate and vinyl acetate) C19 (a terpolymer containing hexyl methacrylate, vinyl pyrrolidinone, and vinyl acetate), and PVP (polyvinyl pyrrolidone). The Resolute Onyx™ stent uses the same drug coating formulation, drug dose density, and spray processing steps as the predicate Resolute Integrity product.

7.2 Manufacturer

Medtronic Inc.

710 Medtronic Parkway

Minneapolis, MN 55432

7.3 USA Packaging

The study will be conducted in geographies where the product is commercially available. The packaging and labeling is 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 Instructions for Use.

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

Storage: Store in the original container. Store between 15°C and 30°C.

7.4 Intended Population

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is intended to improve coronary luminal diameters in subjects with symptomatic ischemic heart disease due to stenotic lesion(s) amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent. This post-approval study will be conducted in a real-world more-comer population.

7.5 Equipment

Any test equipment critical to be used for assessing endpoints will be maintained/calibrated according to the study sites standard protocol.

7.6 Product Use

The device will be used in subjects meeting the inclusion and exclusion criteria according to the Instructions for Use.

7.7 Product Training Requirements

The stenting procedure should be performed according to the IFU. A representative of Medtronic will provide initial training on the Resolute Onyx Clinical Investigation Plan (CIP) requirements. Refer to Section 8.2 Study Site Activation for more details about training requirements.

7.8 Product Receipt and Tracking

The Resolute Onyx™ stent will be obtained by the centers according to routine hospital procedures for commercial products. Existing approved procedures for commercial product will be followed.

7.9 Product Storage

The Resolute Onyx™ stent will be stored by the centers according to routine hospital procedures for commercial products and IFU. Existing approved procedures for commercial product will be followed.

7.10 Product Return

Existing approved procedures for commercial product will be followed, according to hospital procedures for commercial products.

7.11 Product Accountability

The Resolute Onyx™ stent will be obtained by the centers according to routine hospital procedures for commercial products. Existing approved procedures for commercial product regarding distribution, shipment, storage, handling, of these devices will be followed. Devices used in the Bifurcation Cohort will be tracked.

8 Study Site Requirements

8.1 Investigator/Investigation Site Selection

All physicians must be experienced and trained in the handling of the investigational device.

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

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of the investigational device
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
    - Has the required number of eligible subjects needed within the recruitment period
    - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

8.2 Study Site Activation

Medtronic and/or its designees are responsible for the training of appropriate clinical site personnel. During the activation process (prior to subject enrollment), Medtronic or its designees will present a formal training session to review proper reporting of adverse events, device usage, uniform data collection and compliance with the Clinical Investigation Plan (i.e., protocol and consent processes), the device IFU, techniques for the identification of eligible subjects, instructions on data collection, schedules for follow-up, and applicable regulatory requirements. The site Principal Investigator is responsible for key center personnel to be appropriately trained to the tasks they have been delegated. The site Principal Investigator can conduct

full study training for site personnel who were not trained during the Site Initiation Visit. Ongoing assistance regarding completion and submission of CRFs as well as retraining (if necessary) will be provided by Medtronic and/or its designee. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB/EC approval (and voting list, as required by local law) of the current version of the CIP and IC.
- RA approval or notification (as required per local law)
- Fully executed CTA
- Financial disclosure
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 2 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Documentation of study training.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

8.3 Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Monitoring and auditing activities

9 Selection of Subjects

9.1 Study Population

Approximately 710 subjects with ischemic heart disease due to stenotic lesions with coronary arteries that meet the eligibility criteria and sign the informed consent form will be included in this study.

Enrollment parameters are included in the study to avoid introduction of bias to the study results due to disproportionate enrollment. Enrollment of participating subjects at any individual site shall not exceed 15% of the total planned subjects in each of the study cohorts and the Bifurcation Cohort. Enrollment of participating subjects in the US will be >50% of the total enrollment (refer to Figure 1).

9.2 Subject Enrollment

Subjects will be considered enrolled into the study after they have signed the Informed Consent Form (ICF). Subjects will be considered as participating in the study when the Resolute Onyx™ stent (study stent) is introduced into the guide catheter. The investigator will clearly mark the clinical records to indicate that the subject is participating in this clinical study.

If the study stent is introduced into the guide catheter but not implanted, the subject will be considered part of the Intention-to-Treat population (ITT) and will be followed through the 12-month endpoint and included in the primary analysis of this study. After the 12 month follow up, the subject will exit the study.

If the subject becomes unstable before a study stent is attempted (stent introduced into guide catheter), they will not be treated, a study exit form will be completed, the subject will not be followed, and will not be included in the primary analysis of this study.

9.3 Inclusion Criteria

Subject must meet ***all*** of the following criteria to be eligible for treatment in the study:

1. Subject age is ≥ 18 years or minimum legal age as required by local regulations
2. Must have symptoms and/or evidence of coronary artery disease; chronic stable angina, silent ischemia, and acute coronary syndromes including non-ST elevation myocardial infarction and ST-elevation myocardial infarction
3. Subject is an acceptable candidate for treatment with a drug eluting stent in accordance with the applicable guidelines on percutaneous coronary interventions, manufacturer's Instructions for Use and the Declaration of Helsinki
4. Subject is willing and able to cooperate with study procedures and required follow up evaluations
5. Subject or legal representative has been informed of the nature of the study and agrees to its provisions and has provided an Institutional Review Board (IRB)/ Ethics Committee (EC) approved written informed consent, including data privacy authorization
6. Female subjects of childbearing potential must have a negative pregnancy test within 7 days before the study procedure
7. Subject requires treatment of one or more target lesion(s) amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent in up to two separate target vessels

In addition to the general inclusion criteria listed above, subjects must meet ***all*** of the following criteria to be eligible for treatment in the Bifurcation Cohort:

1. The subject requires treatment of a **single de novo bifurcated lesion** amenable to treatment with provisional stenting technique
    a. All Medina classification types
    b. De novo lesion in native coronary artery
    c. Main branch ≥ 2.25 – 5.0 mm
    d. Side branch ≥ 2.0 mm
    e. Lesion length ≤ 35 mm

2. Target lesion(s) must have a stenosis of ≥ 50% and < 100%
3. Target vessel(s) must have a Thrombolysis In Myocardial Infarction (TIMI) flow ≥2

9.4 Exclusion Criteria

Subjects will be excluded from the study if ***any*** of the following criteria are met:

1. Known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, thienopyridines, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g. BioLinx™), anticoagulations or a sensitivity to contrast media, which cannot be adequately pre-medicated
2. History of an allergic reaction or significant sensitivity to drugs such as zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative
3. Subjects who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system
4. Unprotected left main coronary artery disease (no patent bypass graft(s) to one or more branches of the left coronary artery; the left anterior descending or circumflex artery, with an obstruction greater than 50% in the left main coronary artery)
5. Subjects with planned PCI of three vessel disease (includes staged procedures*)
6. Currently participating in an investigational drug or another device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints

Note: Studies requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational studies.

7. Planned surgery that would cause interruption in recommended DAPT duration per current guidelines

*Note: Subjects with planned PCI of three vessel disease are excluded from participating in the RESOLUTE ONYX Post Approval Study (PAS). This exclusion extends to staged procedures (even if started prior to study enrollment). Therefore, any subjects with a previous PCI may not participate if the intention is to treat two addition coronary vessels at a later date as part of RESOLUTE ONYX PAS. There are no exclusions for previous PCI or limits to timepoints on when a previous PCI was performed relevant to enrollment in RESOLUTE ONYX PAS as long all enrollment criteria are observed.

In addition to the general exclusion criteria listed above, subjects will be excluded from the Bifurcation Cohort if ***any*** of the following criteria are met:

1. Planned two stent technique (main branch and side branch) of a bifurcation
2. Subjects with more than one bifurcation lesion
3. Trifurcation lesions
4. Planned treatment of any additional lesion(s) in the bifurcation target vessel(s), inclusive of branches within 12 months
5. Target lesion(s) are located in native vessel(s) within 5 mm distal to anastomosis with a bypass graft (including but not limited to saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA)) and/or with more than 40% diameter stenosis anywhere within the graft
6. Impaired renal function (serum creatinine >2.5 mg/dl or 221 µmol/l) or on dialysis

7. Left ventricular ejection fraction (LVEF) ≤30%

10 Study Procedures

10.1 Schedule of Events

Subjects will be assessed by telephone, e-mail, and/or office visit at the intervals listed in Table 1.

Table 1: Schedule of Treatments and Assessments

Follow-up Interval	Window
30 days	± 5 days
6 months	±14 days
12 months	± 30 days
24 months	± 30 days
36 months	± 30 days

10.2 Data Collection

The clinical procedures that must be performed and laboratory tests that must be drawn for all subjects prior to the stenting procedure are listed below and in Table 2.

Table 2: Schedule of Treatments and Assessments

	Baseline	Procedure [1]	Discharge	Follow-up [2]
Eligibility criteria	●			
Informed Consent	●			
Medical & cardiac history	●			
Angina Status	●			●
Pregnancy Test [3]	●			
Angiogram	●	●		
SAE data [4]	●	●	●	●
Device deficiency data	●	●	●	●
Cardiac biomarkers [5]	●[6]		●[7]	
12 lead ECG [8]	●		●	
Anti-platelet medication	●	●	●	●
Serum Creatinine	●			
LV Ejection Fraction[9]	●			

1. End of procedure is defined as removal of the guide catheter
2. Follow-up subject contact is planned at 30 days, 6, 12, 24 and 36 months. Subject contact includes phone call, email or clinic visit (for radial access subjects, assess radial artery patency at the 30 day follow-up if completed as office visit)
3. For women of childbearing potential only
4. SAE collection will start when the subject has signed the Informed Consent or Data Release Form
5. CK values should be collected if standard hospital practice. In addition to CK values, CK-MB and/or Troponin values must be collected.
6. Cardiac biomarkers will be collected pre-procedure within 72 hours.
7. Post-procedure cardiac biomarkers will be collected at two times. The first collection must occur 3 or more hours post-procedure; the second collection must occur 4 hours after the first but prior to 24 hours post-procedure or at discharge whichever comes first.
8. A 12 lead ECG will be performed within 24 hours post-procedure.
9. LV Ejection fraction value (not a range) within 6-months prior to the index procedure

Relevant source documents including baseline ECG (screening and discharge), event ECG (most abnormal ECG and last ECG recorded), angiogram films and medical records (including admission, discharge notes, reports and biomarker values) will be requested for reported or suspected events including revascularizations, deaths or any (suspected) myocardial infarction or (suspected) stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Events Committee (CEC).

10.3 Scheduled Follow-up Visit Windows

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Follow up visit windows are listed in Table 1 and are based on days post-implant.

10.4 Subject Screening

All subjects evaluated for potential PCI of the coronary arteries should be screened for study eligibility. A qualified member of the investigational site's research team will review the subject's medical history and screen for study eligibility. A screening failure case report form (CRF) will be provided to the site to maintain a record of each subject screened by the site along with the reason(s) for study exclusion.

10.5 Prior and Concomitant Medications/Therapies

Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.

The following antiplatelet therapy is recommended:

A. A minimum of 75 mg of Aspirin daily (within 24 hours prior to the procedure) and continued indefinitely post procedure

B. A market approved antiplatelet loading dose within 24 hours prior to the procedure or immediately post procedure (within 30 minutes of last catheter removal). Antiplatelet should be prescribed as indicated by the current society guidelines and applicable Instruction for Use or longer as per physician's decision

C. During the index procedure, heparin or bivalirudin will be administered as per hospital standard of care. A GP IIb/IIIa receptor blocker may be administered at the Investigator's discretion

All other co-medication usage is at the Investigators discretion and should be done according to hospital routine.

10.6 Subject Consent

All subjects must complete the consent process prior to undergoing any study-related procedures. Sites must comply with local regulatory requirements (ISO14155: 2020 in Europe and 21 CFR 50 in the United States) and local IRB/EC policies for obtaining informed consent.

In advance of the consent discussion, the subject should receive the IRB/EC approved Subject Informed Consent Form. During the consent discussion, the investigator or his/her designee (only in geographies where allowed) must fully inform the subject of all pertinent aspects of the study. If a subject is illiterate, an impartial witness must be present during the entire informed consent discussion. All items discussed in the Subject Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable. Subject Informed Consent Forms should be made available in subject's native language.

Neither the investigator nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not appear to waive the subject's rights.

When the subject decides to participate in the clinical study, the site's current IRB/EC and Medtronic-approved Subject Informed Consent Form must be signed and personally dated by the subject (or their legally authorized representative) and investigator/or designee. If applicable, the witness shall also sign

and personally date the consent form to attest that the information in the Subject Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

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

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 Subject 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/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

Refer to Appendix 2: Subject Informed Consent for the IC template.

10.7 Enrollment

Refer to Section 9.2 Subject Enrollment. A log of all subjects enrolled in the study should be maintained. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

10.8 Baseline

Refer to section 10.2 Data Collection for the information collected at the baseline visit.

Treatment of the target lesion(s) will be in accordance with standard hospital policy for the care of interventional cardiology subjects unless otherwise specified in this Investigational Plan. Procedure start time is defined at the point of guide catheter insertion.

The angiography and stenting procedure should be performed according to the IFU for the Resolute Onyx™ stent and if applicable, the Angiographic Core Lab procedures in Appendix 6.

If the procedure involves treating a bifurcation lesion, a single-stent strategy[4] (the Provisional Stenting Technique provided under Appendix 7) will be followed.

Both ACC/AHA[5]and ESC[5] revascularization guidelines currently recommend provisional stenting as the preferred procedure strategy for patients who are candidates for a bifurcation intervention.

Bifurcation lesions in subjects enrolled in the Bifurcation Cohort should be treated with provisional stenting.

This provisional technique recommends stent placement in the Main Branch (MB), finalized with proximal optimization technique (POT), followed by placement of a second stent if inadequate results are found in the side branch (SB) such as:

- threatened closure of the side branch
- cases of Thrombolysis in Myocardial Infarction (TIMI) flow <3
- dissection type B or worse, or
- residual stenosis more than 80%, or
- abnormal assessment by fractional flow reserve (FFR) ≤ 0.80 or instant wave-free ratio (iFR) ≤0.89

All standard ancillary devices (e.g., guidewires, sheaths/guiding catheters, pre-dilatation balloons, etc.) used during the preparation and procedure should be used in accordance with the manufacturer's instructions.

When bailout is needed, and a second stent is required for the side branch, the recommended technique is culotte, however the anatomy characteristics and/or operator preference may dictate a different technique (e.g DK Crush or other)

Careful stent sizing is important to successful stenting. In general, the stent size should be chosen to match the diameter of the reference vessel and to correspond with the length of the lesion. The appropriate Resolute Onyx™ stent size selected for the target lesion must be ≥ 3 mm longer than the lesion length in order to provide 1.5 mm of stent coverage on either side of the lesion.

Available Resolute Onyx™ stent sizes are listed in Table 3.

Table 3: Resolute Onyx™ Stent Size Matrix

Nominal Expanded Inner Diameter (mm)	Stent Length (mm)								
	8	12	15	18	22	26	30	34	38
2.0	✓	✓	✓	✓	✓	✓	✓		
2.25	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.75	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.5		✓	✓	✓	✓	✓	✓		
5.0		✓	✓	✓	✓	✓	✓		

Post-dilatation may be performed at the Investigator's discretion 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 Resolute Onyx stent delivery system for post-dilatation.

The end of the procedure is defined as the time the guide catheter is removed from the subject.

10.8.1 Additional procedure criteria for bifurcation lesions

- Only one bifurcated lesion is allowed. An additional (non-bifurcated) lesion in a different epicardial vessel may be treated for a maximum of two treated vessels during index procedure. For subjects with planned treatment of two lesions, the first lesion (non-bifurcated) must be treated successfully and the subject must be clinically stable before treatment of the second lesion (bifurcated) is attempted.
- Any additional lesion(s) in the bifurcation target vessel(s), inclusive of branches, can only be treated after 12 months post-procedure.
- Any repeat revascularization should be clinically- driven, (e.g. positive stress test and or functional significance of the stenosis as evaluated by FFR)

10.8.2 Bailout

Bailout procedures should be avoided unless required for subject safety. If bailout procedures are performed, justification should be documented on the CRF.

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 electrocardiogram (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 study stents may be employed as a bailout treatment.

In this study, the 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 study stents may be employed to provide complete coverage.

It is recommended to overlap the Resolute Onyx stents 1-2 mm to avoid the potential for gap restenosis.

10.8.3 Staged procedures

Treatment of all target lesions with the Resolute Onyx stent(s) within a single PCI procedure is encouraged, if reasonable and safe. However, when staging is required for clinical reasons, it is recommended to perform the staged procedure using Onyx within 6 weeks from the index procedure.

- Staging should be pre-specified at the time of the index procedure
- 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

10.8.4 Treatment Failure

Following subject treatment, 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 CRF. Treatment failures should be followed-up for safety purposes through 12 months and will be included in the intent-to-treat (ITT) population.

10.9 Scheduled Follow-up Visits

Refer to section 10.2 Data Collection for the information collected at the follow-up visits.

10.10 Assessment of Efficacy

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.

10.11 Assessment of Safety

All serious adverse events and device deficiencies will be evaluated by Medtronic.

The Clinical Events Committee (CEC) will review and adjudicate all clinical events possibly related to study endpoints that need adjudication when the necessary data are available.

10.12 Recording Data

Data collected on each subject will be recorded on a web-based electronic Case Report Form (CRF). 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 required data on electronic case report forms. Study personnel delegated for CRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter provided with a user name and password to access the system. Passwords are individual and cannot be shared.

The CRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each CRF. The Oracle Clinical RDC system maintains an audit trail of entries, changes, and corrections in CRFs. If a person only authorized to complete CRFs makes changes to an already signed CRF, the investigator shall re-approve this CRF.

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 will be redacted and collected for events that need to be adjudicated by the CEC.

The CRFs 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 site may use technical worksheets if identified as source documents. Worksheets need to be signed and dated by the Principal Investigator or a delegated Investigator.

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.

10.13 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 Investigational Plan, applicable laws or regulations, or the Investigator Agreement.

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

Investigators are required whenever possible to obtain prior approval from the Medtronic Clinical Research Department before initiating changes in or deviations from the investigational 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. Prior approval is not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., subject did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.), however, the event, is still considered a deviation.

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 well-being of the subject in an emergency must be reported to Medtronic and the IRB/EC within five working days.

Subject-specific deviations will be reported on the non-compliance CRF. Deviations that are not subject-specific (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement, etc.) will be reported to Medtronic in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB/EC in accordance with their IRB/EC requirements.

The investigational site's compliance with the clinical investigational plan will be assessed on an ongoing basis. Corrective and preventive action plans will be developed and implemented to secure compliance. In case of serious noncompliance, the sponsor may decide to stop subject enrollment at an investigational site based on its assessment.

10.14 Subject Exit, 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 a subject decides to withdraw from the study, the investigator will document the reason for withdrawal and indicate any rationale for the withdrawal from the study in the subject's file. Subjects will be followed up per standard of care in case problems related to device safety or performance occur, if applicable. Subjects may decide to withdraw from study follow up visits/contacts but consent to continue to allow data collection from their medical records.

10.14.1 Study Exit

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject was not implanted with a (investigational) device
- Subject did not provide consent

- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

The following information is required to be collected at study exit:

- Reason for exit

If discontinuation is because of safety or lack of effectiveness, the subject shall be asked to be followed for collecting safety data outside the clinical investigation.

10.14.2 Study Completed

At the completion of the 36-month follow-up visit, subjects will be exited from the study. The 36-month follow-up visit and exit visit should be combined, and both a 36-month follow-up CRF and a Study Exit CRF need to be completed.

10.14.3 Lost to Follow-up

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. Contacting the subject's general practitioner or referring cardiologist should be considered in case the subject cannot be reached in order to obtain information about the subject's health status and documented in the subject's file. Continuous attempts (phone, email, certified letter etc.) throughout the 36-month 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 (SSDI) should be checked before subjects are considered LTFU. A subject is not considered LTFU until the subject's 36-month follow-up window has closed. Once a subject has completed their 36-month follow up visit, a study exit form must be completed.

10.14.4 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing EC/IRB.

10.14.5 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If an Investigator Withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Reason for subject withdrawal

11 Risks and Benefits

11.1 Potential Risks

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

Potential risks may also be referenced to in the *Instruction For Use* document.

11.1.1 Zotarolimus

Subjects' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The adverse events that have been associated with zotarolimus in humans include but are not limited to:

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

11.1.2 BioLinx Polymer Coating

The types of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings. These 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

11.1.3 Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks (in alphabetical order) may include but are not limited to the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- 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
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis
- Peripheral ischemia / peripheral nerve injury
- Renal Failure
- Restenosis of the stented artery
- Shock / pulmonary edema
- Stable or Unstable angina
- Stent deformation, collapse, or fracture
- Stent embolization
- Stent migration or embolization
- Stent misplacement
- Stroke / transient ischemic attack (TIA)
- Thrombosis (acute, sub-acute, late, or very late)

11.2 Risk Minimization

The potential risks associated with the investigational product were identified and have been successfully mitigated. Potential risks associated with this study are minimized by selecting qualified investigators and training study personnel on the CIP. All efforts will be made to minimize study specific 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.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the Resolute Onyx™ stent.

After implantation, subjects in the ONYX PAS study will be followed at regular intervals to monitor the condition of the implanted stent. At each protocol required follow-up, the investigator must collect data from the patient and assess any adverse events.

11.3 Potential Benefits

Participation in this clinical study will not result in a benefit to the subject. Study subjects implanted with a Resolute Onyx™ stent receive the same medical treatment as if they were not participating in this post-market study. Participation contributes to expansion the knowledge base with respect to the use of the Onyx stent system in a routine hospital setting.

11.4 Risk-Benefit Rationale

Appropriate risk management activities have been performed for the Onyx stent resulting in a positive risk-to-benefit rationale as confirmed by previous regulatory approvals in different global regions. Risks and potential benefits are similar for subjects being implanted as part of this study protocol compared to subjects implanted while not participating in this study.

11.5 Risk Determination

The study device is classified as a Significant Risk Device per 21 CFR 812.

12 Adverse Events and Device Deficiencies

Due to the nature and regulatory strategy of this study, the scope of Adverse Event reporting in this study has been limited to reporting of all serious adverse events (SAE) and device deficiencies. AEs not considered serious do not need to be reported. This is a deviation from ISO14155:2020.

12.1 Adverse Events

Adverse Events (AE) definitions are provided in Table 4. Reporting of these adverse events to Medtronic will occur on an AE Form. Each event must be reported separately.

For AEs that require immediate reporting (see Table 6), initial reporting may be done on the CRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of a reported SAE must also be reported.

Subject deaths are also required to be reported. Refer to Section 12.6 for Subject Death collection and reporting requirements.

12.2 Device Deficiency

The device deficiency (DD) definition is provided in Table 4. 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 [Ref. 21 CFR 803.3(m)]. Product labels, Instructions for Use, and User Manuals for this study are provided separately.

All device deficiencies and malfunctions will be documented on the appropriate case report form, reported to Medtronic, and reported to the IRB/EC (if required) within the IRB/EC required timeframe and local and national regulations. DD information will be collected throughout the study and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only. DD that did not lead to an Adverse Event should be reported on a Device Deficiency Form, one for each Device Deficiency. Please refer the Device Deficiency CRF for the information to be reported for each Device Deficiency that did not lead to an Adverse Event.

DD that did not lead to an AE but could have led to a 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 (see Table 6).

12.3 Processing Updates and Resolution

For any changes in status of a previously reported AE or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved system or procedure related AEs, as classified by the investigator, are resolved, or determined to be unresolved with no further actions planned. At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.4 Definitions/Classifications

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2020 (Table 4).

Where the definition indicates "device", it refers to any component of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System used in the study.

Table 4: **Adverse Event and Device Deficiency Definitions**

General	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated 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. (ISO 14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. NOTE 3: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Relatedness	

System Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the CIP)	An AE that results from the presence or performance of any component of the system. Device-related: An AE that results from the presence or performance (intended or otherwise) of the device. Lead-related: An AE that results from the presence or performance (intended or otherwise) of the lead. Implant tool-related: An AE that results from the presence or performance (intended or otherwise) of the implant tool.
Procedure Related	An AE that occurs due to any procedure related to the implantation or surgical modification of the system.
Medication Related	An AE that occurs due to the antiplatelet/anticoagulant medication.
Seriousness	
Serious Adverse Event (SAE)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, 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) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)

Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment NOTE 1: ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. (ISO 14155:2020, 3.51)
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals. (ISO 14155:2020, 3.46)

An event is not considered an SAE if it has been identified as a pre-existing condition, unless there is a change in nature, severity or degree of incidence of the event.

12.5 Reporting of Adverse Events

Investigators are required to report all serious adverse events and device deficiencies, regardless of seriousness observed in the study subjects, from the time point of signing the Informed Consent Form or Data Release Form until completion of follow-up.

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 (to the device, procedure and therapy Table 5where applicable), subsequent intervention required, resolution status and whether or not the adverse event resulted in the subject's discontinuation from the study. 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 CRF, as per the timeframes listed in Table 6 below.

UADE Evaluation and Reporting

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 Ethics Committees 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.

Device deficiencies that did not lead to an Adverse Event but could have led to an SADE (ISO 14155:2020)

a. if either suitable action had not been taken
b. if intervention had not been made, or
c. if circumstances had been less fortunate

require immediate reporting. Initial reporting may be done by will be done on the CRF by completing as much information as is available.

Investigators should contact their responsible monitor if they have any questions regarding reportable AEs and/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 protocol and provided to sites.

For reportable Adverse Events and/or Device Deficiencies that require immediate reporting (see Table 6), initial reporting shall be done by completing the appropriate CRF. If the CRF is not available, the reportable Adverse Event or Device Deficiency Form in the Investigator Site File must be completed and submitted to the rs.onyxpas@medtronic.com email box and/or to the responsible monitor. In due time, the Adverse Event or Device Deficiency needs to be entered in the CRF as well.

12.5.1 Adverse Event and Device Deficiency Classification

All AE and DD will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 6 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

For emergency contact regarding a UADE, USADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

AEs and Deaths will be classified according to the standard definitions as outlined below:

Table 5: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Procedure and antiplatelet therapy
	Sponsor	Device, Procedure and antiplatelet therapy
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE, DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

12.5.2 Adverse Event and Device Deficiency Reporting Requirements

All SAEs will be reviewed by Medtronic. 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. In case the SAE/Device Deficiency is related to a Medtronic commercially available device used during the study, the Medtronic employee who first becomes aware will immediately report this device related SAE/Device Deficiency to the Medtronic Product Experience Management (PXM) Galway, Ireland. The Medtronic Product Experience Management (PXM) Galway, Ireland will ensure prompt review, and appropriate reporting.

Table 6: Reporting Requirements

SAEs	
Investigator shall submit to:	
Medtronic	Submit to the sponsor immediately, but no later than 3 business days of the investigator's / site's first knowledge of the event
Sponsor shall submit to:	
RA	Submit to RA per local reporting requirement.
IRB/EC	Submit to IRB/EC per local reporting requirement.
ADEs	
Investigator shall submit to:	
Medtronic	Submit to the sponsor immediately, but no later than 3 business days of the investigator's / site's first knowledge of the event
Sponsor shall submit to:	
RA	Submit to RA per local reporting requirement.
IRB/EC	Submit to IRB/EC per local reporting requirement.
SADEs, UADEs, USADEs	
Investigator shall submit to:	
Medtronic	Submit to the sponsor immediately, but no later than 3 business days of the investigator's / site's first knowledge of the event
Sponsor shall submit to:	
RA	Submit to RA 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/EC	Submit to IRB/EC per local reporting requirement.
Investigators	Submit per local reporting requirement.
All other reportable AEs	

Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
DDs with SADE potential	
Investigator shall submit to:	
Medtronic	Submit to the sponsor immediately, but no later than 3 business days of the investigator's / site's first knowledge of the event
Sponsor shall submit to:	
RA	Submit to RA per local reporting requirement.
IRB/EC	Submit to IRB/EC per local reporting requirement.
All other Device Deficiencies	
Investigator shall submit to:	
Medtronic	Submit to the sponsor no later than 15 business days of the investigator's / site's first knowledge of the event

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their reviewing Ethics Board, Regulatory Authority and local regulations.

12.6 Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one AE with the outcome of death.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure

- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

12.6.1 Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Sudden Cardiac Death: Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, Sudden Cardiac Death will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Death Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 7: Subject death classification responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	System, procedure, and/or other protocol required categories
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The CEC will review deaths and provide a final adjudication of the primary cause of death and classification of death. Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

12.7 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the Medtronic clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:

- Life-threatening illness or injury
- Permanent impairment of a body function or permanent damage to a body structure
- A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

13 Data Review Committees

13.1 Clinical Events Committee Review

The Clinical Event Committee (CEC) is composed of multiple (minimum of three) cardiologists and qualified committee members 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 manual.

14 Statistical Design and Methods

14.1 General Aspects of Analysis

The Medtronic RESOLUTE ONYX Post Approval Study is a single arm, non-interventional, open label, multi-center study, evaluating approximately 710 subjects with ischemic heart disease attributable to stenotic lesions of the coronary arteries that are amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent.

At least 410 subjects will be treated in the Primary Cohort and will receive at least one 2.0 mm – 4.0 mm diameter Resolute Onyx™ stent, and at least 100 subjects will be treated in the XLV Cohort and will receive at least one 4.5 mm - 5.0 mm diameter stent.

At least 200 subjects will be analyzed in the Bifurcation Cohort and will receive at least one 2.0 mm – 5.0 mm diameter Resolute Onyx stent; approximately 15 subjects meeting the Bifurcation Cohort criteria and treated with provisional stenting, are expected to be included in analysis from the Primary and XLV Cohorts, with the remainder (approximately 185) recruited specifically for the Bifurcation Cohort

Subject disposition will be illustrated in a flowchart. Subject visits will be tabulated and compliance to visit windows will be summarized. Attrition will be identified and summarized.

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate SAP under a separate cover. Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate.

14.1.1 Analysis Populations

Intent-to-Treat (ITT): For this study, all subjects who sign the written informed consent and also have the study stent (Resolute Onyx stent™) introduced into the guide catheter will be counted in the ITT set,

which will be the primary analysis set.

Per-Protocol (PP): The ITT population excluding subjects who do not meet certain key entry criteria. The analysis of the primary endpoint will be repeated for PP set as a secondary analysis. The primary endpoint will also be analyzed in PP population.

14.1.2 Derivation of Performance Goals

14.1.2.1 Primary Cohort

In the Primary Cohort, the primary endpoint of Target Lesion Failure (TLF) at 12 months post-procedure will be compared to a performance goal.

Based on literature, it is expected that Onyx stent will have a 12-months TLF rate of 8.5%. The performance goal is set at 17.5%, which is about 55% above the expected TLF rate in the Primary Cohort.

14.1.2.2 Bifurcation Cohort

In the Bifurcation Cohort, the primary endpoint of Target Vessel Failure (TVF) at 12 months post-procedure and will be compared to a performance goal.

Based on literature, it is expected that the Onyx stent will have a 12-month TVF rate of 16.3% in treating bifurcated lesions with provisional stenting. The performance goal is set at 24.5%, which is 50% above the expected TVF rate in the Bifurcation Cohort.

14.2 Sample Size Justification

14.2.1 Primary cohort

If the 12-month TLF rate of the Resolute Onyx stent™ is shown to be significantly less than 17.5%, then the Primary Cohort will be considered to have met its primary endpoint. In other words, the null and the alternative hypotheses are:

H_0: $P_{TLF} \geq 17.5\%$;

H_a: $P_{TLF} < 17.5\%$

where P_{TLF} is the true primary endpoint rate for the study stent. Rejection of the null hypothesis will signify that the PG is met.

Assuming a one-sided alpha level of 0.05 and a true event rate of 11.3%, an effective sample size of 369 subjects will yield 96% power to reject the null hypothesis. Assuming a 10% loss to follow-up rate, a total sample size of 410 RESOLUTE ONYX Post-Approval Study subjects will be enrolled in the Primary Cohort. An expected event rate of 7.95% was derived from both arms of the RESOLUTE All-Comers (RAC) trial (excluding unprotected left main (UPLM) and PCI of 3 vessels). Modification of 3.31% was added to the expected rate to adjust the difference in MI reporting per third UDMI. This resulted in the expected event rate of 11.3%. The performance goal 17.5% is a 55% extension from the expected event rate of 11.3%.

14.2.2 XLV cohort

In addition to the Primary Cohort, 100 subjects will be treated with 4.5 mm or 5.0 mm stents and enrolled in the XLV Cohort. There is no formal hypothesis for the XLV Cohort, and descriptive statistics will be provided.

14.2.3 Bifurcation cohort

If the 12-month TVF rate is shown to be significantly less than 24.5% for the RESOLUTE ONYX Bifurcation Cohort, then the Bifurcation Cohort will be considered to have met its primary endpoint. Therefore, the null and the alternative hypotheses are:

H0: $P_{TVF} \geq 24.5\%$;

Ha: $P_{TVF} < 24.5\%$

where P_{TVF} is the true primary endpoint rate for the study stent. Rejection of the null hypothesis will signify that the PG is met. This PG is based on review of clinical evidence from published literature.

Assuming a one-side alpha level of 0.05 and a true event rate of 16.3%, an effective sample size of 180 subjects will yield 85% power to reject the null hypothesis. Assuming 10% loss to follow-up rate, a total sample size of 200 subjects will be needed; hence data on a total of 200 subjects will be generated.

The expected rate for the RESOLUTE ONYX Bifurcation Cohort was obtained by utilizing the weighted average of outcomes from the RESOLUTE All-Comers (RAC) study[8] in patients with single bifurcations treated with single or double stents (excluding unprotected left main lesions and patients with three vessel disease), and the from the provisional stenting arm of the TRYTON study.[9] The weighted average is shown in Table 8.

Table 8: Expected 12-month TVF rate for the RESOLUTE ONYX Bifurcation Cohort

Study/Arm	Stent Used	N	12m TVF Rate
RAC (Resolute Arm) - single bifurcation treatment	ZES	133	11.6%
RAC (Xience V Arm) - single bifurcation treatment	EES	136	12.2%
TRYTON – Provisional Stenting Arm*	DES	339	13.9%**
Weighted Average		**13.0%**	

* Data from TRYTON SSED

**Adjusted downwards from 15.3% to 13.9% to account for the difference in true versus non-true bifurcated lesions per Medina Classification that were treated in the Resolute All comer study and the provisional stenting arm of the TRYTON study

The performance goal of the RESOLUTE ONYX Bifurcation Cohort of 24.5% represents a clinically acceptable 50% extension from the expected rate as shown in Table 9.

Table 9:Performance Goal

Sample Size	Expected Rate	Margin (50%)	PG	Power
200 (180 evaluable)	16.3%	8.2%	24.5%	≥ 85%

14.3 Analysis Execution

Analysis for the primary endpoints of the three cohorts of the Onyx PAS will occur when subjects in the cohort have reached their one-year endpoint. Analysis will include both primary and all secondary endpoints. A final report will be prepared once all data collection has ended and all subjects have completed the three-year visit or have ended the study participation. The analysis for the secondary endpoints will be descriptive in nature. All analysis defined in this plan will be formed by Medtronic statisticians.

All statistical analyses will be performed using SAS for Windows (version 9.1 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of results will be provided.

14.4 Interim Analysis

No interim analyses are planned for this study.

14.5 Analysis of the Primary Endpoint

For Primary Cohort, the count and percentage of subjects with 12-month TLF will be provided. A one-sided upper bound of the 95% CI of the observed 12-month TLF rate will be calculated through binomial (exact) method. If this upper limit of the 95% CI is below 17.5%, the clinical objective will be considered to have been met for the Primary Cohort.

For XLV Cohort, the number and percentage of the primary endpoint will be presented. In addition, the two-sided 95% confidence interval of the observed 12-month TLF rate will be calculated through binomial (exact) method. Further, the time to the primary endpoint will be evaluated using Kaplan-Meier method.

For Bifurcation Cohort, the count and percentage of subjects with 12-month TVF will be provided. A one-sided upper bound of the 95% CI of the observed 12-month TVF rate will be calculated through binomial (exact) method. If this upper limit of the 95% CI is below 24.5%, the clinical objective will be considered to have been met for the Bifurcation Cohort.

The analysis of the primary endpoint will be repeated for PP set as a secondary analysis.

14.5.1 Analysis on Higher Complexity Bifurcation Sub-group

Descriptive statistics for the important clinical outcomes for subsets of patients treated for true bifurcation lesions per Medina classification will be provided for the RESOLUTE ONYX Bifurcation Study Cohort. Categorical variables will be reported using counts and percentages and continuous variables will be reported by giving the number of known values, mean, standard deviation, minimum and maximum. The time-to-event data may be presented by using the Kaplan-Meier methods.

14.6 Analysis of the Secondary Endpoints

Descriptive statistics for the secondary endpoints will be provided. 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. The time to event variables may be displayed by using a Kaplan-Meier plot.

14.7 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.

14.8 Pooling Bifurcation cohort

To minimize selection bias, consecutively enrolled subjects with bifurcation treated with Resolute Onyx 2.0mm- 5.0mm stents in the RESOLUTE ONYX PAS study will be considered for inclusion. Comparability between RESOLUTE ONYX Bifurcation Cohort and subjects treated for bifurcation lesions and meeting the same inclusion and none of the exclusion criteria in the RESOLUTE ONYX PAS on baseline characteristics and on the primary endpoint will be assessed.

Pooling details are listed in the Statistical Analysis Plan under a separate cover.

14.9 Missing Data

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.

15 Ethics

15.1 Statement(s) of Compliance

- The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), the 21 CFR 50, 21 CFR 803 and 21 CFR 812.46(b) and the ethical principles that have their origin in the Declaration of Helsinki, ISO 14155 2020, and applicable laws and regulations of the country in which the clinical study is being conducted, and hospital requirements. The principles of the Declaration of Helsinki have all been implemented in this study by means of the subject informed consent process, IRB/EC approval, study training, clinical study registration, preclinical testing, risk benefit assessment, publication policy, etc
- A written approval from the IRB/EC with authority for the participating center will be obtained prior to commencing subject enrollment. Any additional requirements imposed by the IRB/EC and regulatory authority shall be followed if required/applicable
- If any action is taken by a IRB/EC with respect to the investigation, that information will be forwarded to the sponsor

- The RESOLUTE ONYX Post-Approval Study will not start enrollment in a geography until applicable national regulatory approvals for the Resolute Onyx™ stent have been obtained. The device should be used within the intended approved indication
- 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
- Study reimbursement is outlined in the Clinical Study Agreement. Indemnification will be done according to local laws
- Study sites should follow their institutional procedures for maintenance and calibration of angiography and laboratory equipment used for assessing the study variables. Documentation supporting compliance with these procedures should be available for assessment upon request.
- Subjects will not receive any compensation for participation in this study
- Reimbursement of travel cost will be considered if allowed by local regulations

16 Study Administration

16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site or remotely wherever it is allowed per local regulations in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

16.1.1 Monitoring Visits

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. 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. All informed consent forms of assigned subjects per Risk Based Monitoring will be checked. The monitor will perform review of key variables for all assigned (per Risk Based Monitoring) subjects (including but not limited to, inclusion/exclusion criteria, endpoints and safety) on the CRFs 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.

Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions

to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

16.2 Data Management

All records and other information about subjects participating in this study will be treated as confidential. Medtronic and/or CRO will collect data and monitor study records. Auditors, IRB/EC 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 CRFs and in all other required reports. Data reported on the CRFs 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 CRFs. CRFs shall be signed by investigators (physicians only) as specified on the Delegated Tasks List included in the Investigator Site File.

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

16.3 Direct Access to Source Data/Documents

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

16.4 Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. A unique subject identification code will be assigned to maintain confidentiality. Medtronic and/or CRO will collect data and monitor study records. Auditors, IRB/EC 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. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation.

16.5 Liability/Warranty/Insurance Information

16.5.1 Warranty

Warranty information is provided in the product packaging for the commercially released Resolute Onyx™ and additional copies are available upon request.

16.5.2 Insurance (Europe)

Medtronic Bakken Research Site B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC.

16.6 CIP Amendments

All clinical investigation plan (CIP) updates need to be approved by Medtronic. Medtronic is responsible for regulatory authority approval or notification of CIP updates or amendments if applicable according to local regulations. In the US, the investigator is responsible for approval or notification submission to the IRB and obtaining the required approvals if needed before implementing the amendment. In Europe, the Sponsor might be responsible for submission to the Ethics Committees if allowed by local regulation.

16.7 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.

16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after the date on which the investigation is terminated.

- All correspondence between the EC, sponsor, monitor, FDA, RA and the investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
  - Signed and dated IC (In U.S. signed by subject. In Europe signed by subject and investigator)
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Implant and follow-up data (if applicable)
  - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation study sites
- FD
- Subject screening log & ID log
- Normal value(s)/range(s) for clinical laboratory test
- Lab certificate
- All approved versions of the CIP and IC
- Signed and dated CTA
- CV, signed and dated in Europe only, of principal investigators and key members of investigation study site team as required by applicable regulations
- Documentation of delegated tasks

- IRB/EC approval documentation. Written information that the investigator or other study staff, when member of the EC, did not participate in the approval process. Approval documentation must include the ECs composition, where required per local law
- RA notification, correspondence and approval, where required per local law
- Study training records for study site staff
- Insurance certificates (as applicable)
- Any other records that FDA and local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

16.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- Signed Investigator Trial Agreements, FD and current signed and dated (Europe only) CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB/EC approval letters and relevant IRB/EC correspondence and IRB/EC voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- RA correspondence, notification and approval as required by national legislation
- Insurance certificates (where applicable)
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, IB/Report of Prior Investigations summary and study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

16.8 Reporting Requirements

16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, serious adverse events and device deficiencies and any deviations from the clinical investigation plan. If any action is taken by an IRB/EC with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 12. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 10: Additional Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Progress report	IRB/EC	The investigator must submit this report to the IRB/EC at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/EC, and the FDA/applicable RA. If the deviation does not affect these issues then only Medtronic must approve it. (21 CFR 812.150(a)(4))
Failure to obtain IC prior to investigational device use	Sponsor and IRBs/ECs	If an investigator uses a device without obtaining IC, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	IRBs/ECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or completion or termination of the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB/EC and FDA	An investigator shall, upon request by a reviewing IRB/EC, FDA or any other RA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

Table 11: Investigator reports applicable to Europe per ISO 14155

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor	Report if required by local law.
Progress Report	Sponsor and IRB/EC	Provide if required by local law or IRB/EC.
Study Deviations	Sponsor, Competent Authority and IRB/EC	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees, CAs or the appropriate RAs should be informed. (ISO 14155:2020)
Failure to obtain IC	Sponsor and IRBs/ECs	IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2020)

16.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of the reviewing EC, RA or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 12.

Table 12: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Investigators, IRB/EC, FDA, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators, IRB/EC, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(3))
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. (21 CFR 812.150(b)(4))
Progress Reports	IRB/EC and FDA	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f)

Report	Submit to	Description/Constraints
Recall and device disposition	Investigators, Head of Institution, IRB/EC, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Final report	Investigators, IRB/EC, RAs upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/ECs within six months after completion or termination of this clinical study. (21 CFR 812.150(b)(7))
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Study site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))
Premature termination or suspension of clinical study	IRB/EC, Investigators, and regulatory authorities, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB/EC and RAs.

Table 13: Sponsor reports for Europe

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Investigators, Head of Institution, IRB/EC and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Withdrawal of CA approval	Investigators, Head of Institution, IRB/EC, and relevant authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Progress Reports	IRB/EC and RAs	This will be submitted to the IRB/EC only if required by the IRB//EC).
Final report	Investigators, IRB/EC, and RAs if required	For studies with study sites complying to ISO 14155: • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal Investigator in each study site should be obtained. (ISO 14155:2020)
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

16.9 Publication Policy and Use of Information

16.9.1 Publication Committee

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 Steering Committee, the Clinical Program Director and other Medtronic personnel as appropriate.

The Publication Committee's role is to: 1) Refine and finalize the Publication Plan and its subsequent updates; 2) Review, approve, and prioritize publication ideas; 3) Provide input on the scientific merit and clinical relevance of ancillary publications; 4) Apply and enforce the authorship criteria guidelines set forth in the Publication Committee Charter; 5) Facilitate the timely submission of key publications to the most preferred scientific platform; 6) Review abstracts and manuscripts according to established timelines; 7) Determine whether or not any study related information (e.g., study design and preliminary results) will be publicly released prior to publication of the primary manuscript, as well as the criteria for doing so.

Membership in the Publication Committee does not guarantee authorship. The committee will meet at regular intervals as needed. Clinical investigators will not be financially compensated for writing abstracts, presentations or manuscripts.

The Publication Committee will be disbanded at the discretion of Medtronic when input in developing, reviewing and prioritizing publication requests is no longer necessary. At such time, the priority of analyses and publications last established by the committee will be implemented to the degree feasible. While Medtronic will make every attempt to support all remaining publication requests, no guarantee can be made that all requests can or will be accommodated.

16.9.2 Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the CIP.

An ancillary publication is any publication that does not address the study objectives identified in the CIP. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this study, and clinicians not participating in this study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual study site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

16.9.3 Criteria for Determining Authorship

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 all of 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

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic ONYX PAS Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

At the conclusion of the RESOLUTE ONYX Post-Approval 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.

16.9.4 Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and CAs of participating countries when required by local law
- Registering and posting the study results on a publicly accessible database, e.g., ClinicalTrials.gov based on the posting rules stipulated
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study site's study data accessible to the corresponding investigator after the completion of the study, if requested

16.10 Suspension or Early Termination

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/EC 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 and assure appropriate therapy and follow-up for the subjects
- 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.

16.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete.

16.10.2 Early Termination or Suspension

Study Suspension: A temporary postponement of study activities related to enrollment and distribution of the product if applicable. This is possible for the whole study or a single investigational site.

Early Termination of the Study: Closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single investigational site.

16.10.2.1 Study-wide termination or suspension

Possible reasons for considering study-wide suspension or termination of the study include but are not limited to:

- AEs associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or RA (where the study is operating under RA)

16.10.2.2 Investigator/study site termination or suspension

If a center is terminated or suspended, no additional enrollments will be allowed at the center. Possible reasons for clinical Investigator or center termination or suspension include but are not limited to:

- Non-compliance to obtain subject informed consent
- Non-compliance to the inclusion/exclusion criteria
- Lack of enrollment
- Failure to follow subjects per scheduled follow-ups
- Failure to submit data in a timely manner
- IRB/EC approval expiration
- IRB/EC suspension of the center
- Investigator request (e.g. no longer able to support the study)

16.10.3 Procedures for Termination or Suspension

16.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed at least 30 days after the index procedure out of consideration of their safety, rights and welfare
- In case of early termination, the investigator agreement will be terminated

16.10.3.2 **Investigator-initiated**

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the EC
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

16.10.3.3 **Ethics Committee-initiated**

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

17 References

1. Routledge HC, Morice MC, Lefevre T, et al. 2-year outcome of patients treated for bifurcation coronary disease with provisional side branch T-stenting using drug-eluting stents. JACC Cardiovasc Interv 2008;1:358-65.
2. Ferenc M, Gick M, Kienzle RP, et al. Long-term outcome of percutaneous catheter intervention for de novo coronary bifurcation lesions with drug-eluting stents or bare-metal stents. Am Heart J 2010;159:454-61.
3. Colombo F, Biondi-Zoccai G, Infantino V, et al. A long-term comparison of drug-eluting versus bare metal stents for the percutaneous treatment of coronary bifurcation lesions. Acta Cardiol 2009;64:583-8
4. Hildick-Smith D, Lassen JF, Albiero R, et al. Consensus from the 5th European Bifurcation Club meeting. EuroIntervention 2010; 6(1): 34
5. 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.
6. 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
7. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. New England Journal of Medicine 2017;376:1813-23.

8. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46.
9. Genereux P, Kumsars I, Lesiak M, et al. A randomized trial of a dedicated bifurcation stent versus provisional stenting in the treatment of coronary bifurcation lesions. J Am Coll Cardiol 2015;65:533-43.

18 Appendices

Appendix 1: Study Contact Information

Sponsor: - Project & Site Management - Statistical Analysis	Medtronic 3576 Unocal Place Santa Rosa, CA 95403 USA
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Product Experience Management:	CVG Product Experience Management Medtronic Ireland Parkmore Business Park West Ballybrit, Galway Ireland
Angiographic Core Lab:	Beth Israel Deaconess Medical Center, Inc. 375 Longwood Avenue, 3rd Floor Boston, MA 02215 USA
Image Transfer:	Medidata Medical Imaging 700 W. Pete Rose Way, Suite 436 Cincinnati, OH 45202 USA 877-464-7473 www.intelemage.com
Clinical Events Committee:	MedStar Health Research Institute 6525 Belcrest Road, Suite 700 Hyattsville, Maryland 20782 USA

Appendix 2: Subject Informed Consent

Refer to the most current version of the sample Subject Informed Consent provided under a separate cover.

Appendix 3: Instructions for Use

Refer to the most current version of the Instructions for Use (IFU) approved for use in your geography provided under a separate cover or packaged with the device.

Appendix 4: Case Report Forms

Refer to the most current version of the Case Report Forms (CRFs) provided under a separate cover.

Appendix 5: List of Participating Investigators, Institutions and Ethics Committees

The listing of participating investigators, institutions and Ethics committees to be provided under a separate cover.

Appendix 6: Angiographic Core Lab Procedures

Refer to the most current version of the Angiographic Core Laboratory Procedures provided under a separate cover.

Appendix 7: Provisional Stenting and Culotte Technique

Refer to the most current version of the instructions for Provisional Stenting and Culotte Technique provided under a separate cover.

19 Version History

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	Not Applicable, New Document	NA	NA	NA	Donna Corum, Clinical Study Manager
2.0	Addition of Bifurcation Sub-study; added language throughout document Glossary: Added term 'Target vessel failure' and clarified 'Target Vessel' definition Synopsis: Product status - update to approved product in US Inclusion criteria: Removed 'symptomatic' add 'symptoms and/or evidence of' for clarification Exclusion criteria: Added note clarifying exclusion of subject with planned PCI of three vessels Treatment schedule: Added LV Ejection fraction and Serum Creatinine requirements Procedure: Added language for clarification; Procedure start time is	NA	NA	NA	Patrice Lerum, Clinical Study Manager

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	defined at the point of guide catheter insertion Appendix 7: added to include provisional stenting and culotte technique Correction of grammatical errors throughout document				
3.0	**Bailout procedure (sub-study):** section 10.2 added recommended culotte technique or additional technique when bailout is required **Synopsis:** section 4.0 updated Statistical method (sub-study) performance goal to 19.5% from 19.65% **Performance goal:** section 14.1.2 update TVF rate to 13.0% from 13.1% The performance goal update to 19.5% from 19.65% Section 14.2.3: hypothesis update to 19.5% from 19.65%. Power updated to 80% from 83%	NA	NA	NA	Patrice Lerum, Clinical Study Manager

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
4.0	Removed 'Sub-study', added Bifurcation Cohort throughout document **Synopsis:** Section 4, updated device sizes approved in the US (2.0mm) Added clarity that Bifurcation Cohort is concurrent with the Primary and XLV Cohorts **Background:** section 5.1: Added language to clarify use for Bifurcation is investigational. Data obtained from Resolute ONYX PAS for bifurcation lesions will be utilized to support safety and efficacy. **Purpose:** section 5.2: defined the Bifurcation Cohort assess the safety and efficacy of the Resolute Onyx™ stent in the treatment of bifurcation lesions. **Study design:**				Alissa Anderson, Clinical Study Manager

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	Section 7 & synopsis; clarification on the defined PAS study. PAS refers to the Primary, XLV and Bifurcation Cohorts **Duration:** Section 7.1; added clarification that due to varying enrollment times, enrollment may not be open in all cohorts at the same time. **Product accountability:** section 8.6 added clarity that devices used in the Bifurcation Cohort will be tracked. **Procedure:** Section 10.2 added FFR recommendation guideline **Performance Goal:** section 14.2.3 added clinical study information and clarity on performance goal calculations				

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	Pooling of Bifurcation Cohort: section 14.3.110; added justification of pooling data **Analysis on higher complexity bifurcation sub-group:** section 14.10 added Added references				
5.0	Glossary: Added 3rd UDMI definition Section 4.0 Sample Size and Statistical Methods: Performance goals updated Section 7.0 Study Design/Figure 1: Bifurcation Cohort sample size updated Section 9.1 Study Population: Revised total planned bifurcation subjects per site Section 14: Adjusted performance goal for Primary and Bifurcation Cohorts Table 7: Adjusted for Bifurcation performance goal rationale	NA	NA	NA	Alissa Anderson, Clinical Study Manager

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	Table 8: Adjusted for Bifurcation performance goal Section 14.5: Analysis for primary and bifurcation cohorts adjusted to reflect modified performance goals				
6.0	Implementation of new ISO compliant CIP template. Details of the changes are available under a separate cover. **Header and Footer:** updated to new template with version 6.0 information **Cover page:** Addition of "Vascular Inc." in 'Sponsor/Local Sponsor', change of version number from 5.0 to 6.0, addition of field of version date and replacement of 'Coordinating' with 'Lead Principal' per new CIP template **Section 3 Synopsis** • Addition of "Vascular Inc." to "Sponsor" and "Local Sponsor" • Addition of line and details for External Organizations • Addition of Secondary Endpoint	Transfer to new template to incorporate new ISO14155: 2020 requirements	No	CSMP CSMPCP DM MP SAP CRF	Maria Alepaki, aCRS Zhen Meng, Sr. CRS

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	Section 4.1 Background: The Resolute Onyx marketing information was updated **Section 7 Product Description:** Added new subsections and information per new ISO requirements per new CIP template **Section 8 Study Site Requirements was added:** Added new subsections and information per new ISO requirements per new CIP template **Section 10 Study procedures:** Added new subsections and information per new ISO requirements per new CIP template **Section 11 Risks and Benefits:** Added new subsections and information per new ISO requirements per new CIP template **Section 12 Adverse Events and Device Deficiencies:** Added new subsections and information per new ISO requirements per new CIP template				

Version	Summary of Changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	Section 14 Statistical Design and Methods: Sections were reordered per new template **Section 15.1 Statement(s) of compliance:** summarized the regulations mentioned throughout the document; Updated ISO 14155:2011 to 2020 **Section 16 Study Administration:** Added new subsections and information per new ISO requirements per new CIP template				