Statistical Analysis 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

Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Yun Peng Principal Statistician
2.0	• Moved this plan into the new statistical analysis plan template • Added the bifurcation cohort • Added inclusion/exclusion criteria for bifurcation cohort • Added sample size for bifurcation • Added primary endpoint for bifurcation cohort • Added section 6.1 Pooling of Bifurcation Cohort and bifurcated lesions from Primary/XLV Cohorts • Added section 8.7 Analysis on Higher Complexity Bifurcation Sub-group • Deleted the paragraph "As supplementary analysis, to account for missing data, subjects who drop out prior to 330 days post procedure and do not experience TLG will have their 12 month TLF missing status (yes/no) imputed using the multiple imputation and worst case analysis using the same methods described above as those for Primary Cohort. " • Deleted the paragraph "The worst-case analysis will impute all the 12 month TLF missing status as "yes" then calculate the one side upper 95% confidence interval of 12 month TLF rate to compare to the performance goal of 13.2%. The above analysis on the primary endpoint will be performed on both the ITT and the PP analysis sets." *Note: Version 2.0 of this document may not align to the version of the document determined in the Medtronic Trial Master File (RAD)*	Te-Hsin Lung, Ph.D Principal Statistician
3.0	• Corrected the performance goal for tipping point analysis in Section 8.2.3. Changed the performance goal to 19.5%	Te-Hsin Lung, Ph.D Principal Statistician

Version	Summary of Changes	Author(s)/Title
	• Added Section 8.8 Analysis of Poolability and Homogeneity across Sites and Regions •	
4.0	• Section 2, added Third Universal Definition of Myocardial Infarction (3rd UDMI) • Section 5.3.1, updated performance goal to 17.5%, expected rate to 11.3%, power to 96%, and rationales of the performance goal and expected rate • Section 8.2.1, updated performance goal to 17.5%, expected rate to 11.3%, power to 96% • Section 8.5, updated the definitions of complex subset and long lesion subset	Te-Hsin Lung, Ph.D Principal Statistician
5.0	• Section 3.1 updated the sample size for bifurcation cohort to 200. • Section 3.3.3, updated performance goal to 24.5%, expected rate to 16.3%, power to 85%, sample size to 200 and the derivation of the expected rate. • Section 6.2.3, updated performance goal to 24.5% • Section 6.8, added a sentence about removing the only site with enrollment of 4 or less from poolability analysis	Te-Hsin Lung, Ph.D Principal Statistician
6.0	• Converted to the new version of Statistical Analysis Plan template to meet ISO 14155:2020 • Version History was moved to Section 1. • List of Abbreviations and Definitions of Terms was moved to Section 2. • Section 1 Introduction was moved to Section 3. • Section 2 Study Objectives was moved to Section 4. • Section 3.1 Treatment(s) and Subject Enrollment was moved to Section 5.1. • Section 3.2 Endpoints was moved to Section 6. • Section 3.3 Sample Size Justification was moved to Sections 6.1 – 6.3.	Te-Hsin Lung, Ph.D Principal Statistician

Version	Summary of Changes	Author(s)/Title
	1. Section 3.3.1 Primary Cohort was moved to Section 6.1. 2. Section 3.3.2 XLV Cohort was moved to Section 6.2. 3. Section 3.3.3 Bifurcation Cohort was moved to Section 6.3. • Section 4 Analysis Population, ITT and PP cohort definitions and the sentence "The primary endpoint will also be analyzed in PP population." were moved to Section 7.1.3 Analysis Sets. The following paragraph for the exclusion criteria for PP cohort were added to section 7.1.3. In addition to the general exclusion criteria listed above, Bifurcation subjects will be in the PP set only if all the Bifurcation target lesions meet the below criteria: 1. Proximal optimization technique was performed after provisional stenting 2. Baseline side branch diameters per site estimation are ≥ 2.0 mm 3. No planned two stent technique (main and side branch) of a bifurcation • Section 4.1 Pooling of Bifurcation Cohort and Bifurcated Lesions from Primary/XLV Cohorts moved Section 7.1.4. • Section 5 Interim Analysis was moved to Section 7.8. • Section 6.1 General Considerations was moved to Section 7.2. • Section 6.2 Analysis of the Primary Endpoints was moved to Section 7.9.1. • Section 6.3 Analysis of Secondary Endpoints was moved to Section 7.9.2. The sentence "Results for the components of composite endpoints will be tabulated" was added.	

Version	Summary of Changes	Author(s)/Title
	• Section 6.4 Analysis of Baseline Characteristics was moved to Section 7.6 Demographic and Other Baseline Characteristics. • Section 6.5 Analysis of Subgroups was moved to Section 7.9.3 Analysis of Subgroups. The analysis cohort for subgroup analysis was updated to include the ITT subjects recruited specifically for the Bifurcation Cohort and to revise the definition for bifurcation provisional stenting subgroups. Subgroups for the Bifurcation cohort were added. The following subgroups were added for the bifurcation cohort: • Male vs. Female • Age ≥ 65 vs. <65 • Race • Diabetes vs. Non-diabetes • Multiple vessels vs. Single vessel • True Bifurcation per Medina (111, 101, 011) vs non true bifurcation per Medina • Bifurcation – provisional: single stenting vs. 2 stent approach • Section 6.6 Handling of Missing Data was moved to the first paragraph of Section 7.4 Handling of Missing, Unused, and Spurious Data and Dropouts. • Section 6.7 Analysis on Higher Complexity Bifurcation Sub-group was moved to Section 7.9.4. • Section 6.8 Analysis of Poolability and Homogeneity across Sites and Regions was moved to Sections 7.3 Center Pooling • Section 7. Data Screening and Acceptance was moved to the second paragraph of Section 7.4 Handling of Missing, Unused, and Spurious Data and Dropouts.	

Version	Summary of Changes	Author(s)/Title
	• Section 8. Appendices was moved to Section 9 Statistical Appendices. • Added Section 7.1.1 to meet the new SAP template requirements. • Added Section 7.1.2 to meet the new SAP template requirements. • Added Section 7.5 to meet the new SAP template requirements. • Added Section 7.7 to meet the new SAP template requirements. • Added Section 7.10 to meet the new SAP template requirements. • Added Section 7.11 to meet the new SAP template requirements. • Added Section 7.12 to meet the new SAP template requirements.	
7.0	• Revised the referenced Clinical Investigational Plan to version 6 on the cover page.	Te-Hsin Lung, Ph.D Principal Statistician

2. List of Abbreviations and Definitions of Terms

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

Term	Definition
	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 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. **<u>I. PCI (PERCUTANEOUS CORONARY INTERVENTION)</u>** **Ia. Baseline Biomarkers of Myocardial Damage (CK and CKMB and Troponin < 1*URL) *and* not acute MI in progress.** **<u>Periprocedural <48 Hours Post PCI</u>** A. New pathologic q waves in ≥ 2 contiguous ECG leads ***AND***:

Term	Definition
	▪ 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** **<u>Myocardial Infarction, re-infarction (extension) <48 hours post PCI</u>** 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***

Term	Definition
	▪ 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 **<u>Spontaneous MI >48 hours (PCI)</u>** 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*** 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.** **<u>Periprocedural <72 hours post CABG</u>** 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***

Term	Definition
	▪ 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** **<u>Myocardial infarction, re-infarction (extension) <72 hours post CABG</u>** 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: ▪ 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	**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

Term	Definition
(peri-procedural) SCAI Definition	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.
Third Universal Definition of Myocardial Infarction (3rd UDMI)	**Criteria for acute myocardial infarction** The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI: • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: o Symptoms of ischemia. o New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). o Development of pathological Q waves in the ECG. o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. o Identification of an intracoronary thrombus by angiography or autopsy. • Cardiac death with symptoms suggestive of myocardial ischemia and presumed new

Term	Definition
	ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. **Criteria for prior myocardial infarction** Any one of the following criteria meets the diagnosis for prior MI: • Pathological Q waves with or without symptoms in the absence of non-ischemic causes.

Term	Definition
	• Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause. • Pathological findings of a prior MI.
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 * 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).

Term	Definition
	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 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.*

Term	Definition
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).
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. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of the RESOLUTE ONYX Post-Approval Study: A Post-Approval Study of the Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System. The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies. Specifically, the plan has the following purpose: To prospectively outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

4. Study Objectives

The primary objective of this study is 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. Investigation Plan

This study is designed as a single-arm, open-label multi-center study.

5.1 Treatment(s) and Subject Enrollment

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.

At least 510 subjects with ischemic heart disease due to stenotic lesions within coronary arteries that are amenable to treatment with a Resolute Onyx™ 2.0 mm – 5.0 mm stent, meet the eligibility criteria and sign the informed consent form will be included in this study. Subjects may receive treatment of more than one lesion (within a maximum of two target vessels).

The study will have three cohorts 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 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.

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.

Enrollment parameters are included in the study to avoid introduction of bias to the study results due to disproportionate enrollment. Enrollment at any individual site shall not exceed 25% (173 subjects) of the total planned subjects in the study. Enrollment in the US will be >50% of the total enrollment. (refer to Figure 1).

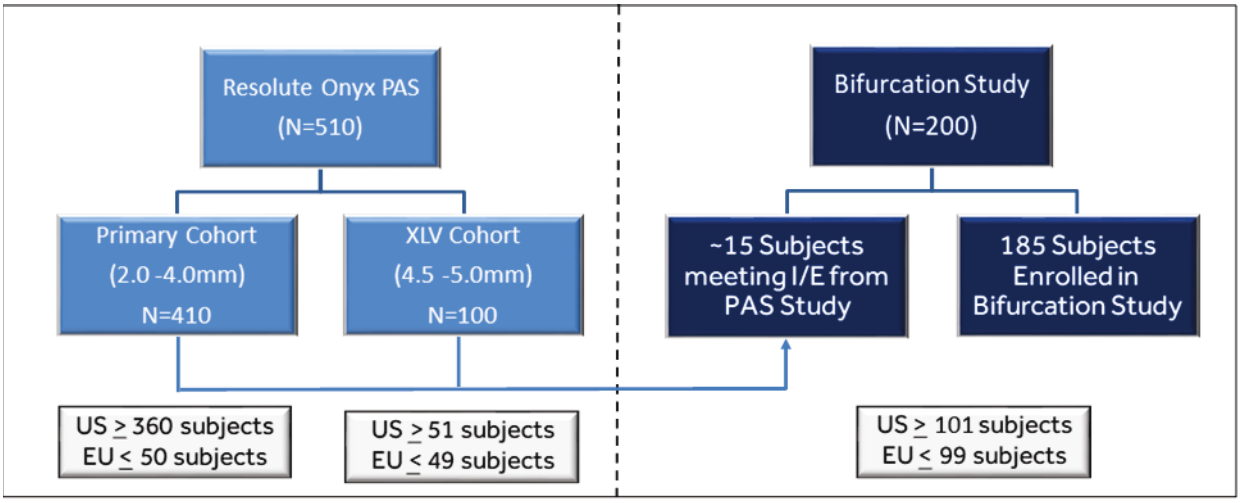

Figure 1: Subject Distribution

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 Intent-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.

5.1.1 Inclusion Criteria

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

1. Subject age is ≥ 18 years or minimum legal age as required by local regulations
2. Must have symptomatic 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

5.1.2 Exclusion Criteria

Subjects will be excluded from the trial 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

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%

6. Determination of Sample Size

The primary endpoint for all subjects participating in the Primary and XLV Cohorts 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.

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)
8. Target Lesion Failure (TLF)
9. Target Vessel Failure (TVF)
10. Stent Thrombosis (ST)

6.1 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:

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

$$H_1: P_{TLF} < 17.5\%$$

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%.

6.2 XLV Cohort

One hundred 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.

6.3 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:

$$H_0: P_{TVF} \geq 24.5\%;$$

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

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 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. The weighted average is shown in Table 1. Then the expected rate of 12-month TVF was modified upwards by 3.3% in order to account for the utilization of Third UDMI definition. Therefore, the expected rate of 12-month TVF is 16.3%.

Table 1: 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	11.60%
RAC (Xience V Arm) - single bifurcation treatment	EES	136	12.20%
TRYTON – Provisional Stenting Arm*	DES	339	13.9%**
Weighted Average		**13.00%**	
* 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			

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of enrolled subjects at each cohort, and the compliance at each scheduled visit will be summarized. The number of discontinuations (if any) and reason for discontinuation and whether they occurred before a specific scheduled visit will be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Summaries of major, minor, and COVID-19 impacted protocol deviations will be provided by cohort.

7.1.3 Analysis Sets

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 set excluding subjects who do not meet certain key entry criteria (for exclusion criteria below, if any answer is "yes", the patients are excluded from PP population):

1. Did not receive any study device
2. Received study device, and another type of DES
3. Did not meet the following inclusion criteria:
    a. Inclusion 2: Must have symptomatic coronary artery disease; chronic stable angina, silent ischemia, and acute coronary syndromes including non-ST elevation myocardial infarction and ST-elevation myocardial infarction.
    b. Inclusion 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
4. Did not meet the following exclusion criteria:
    a. Exclusion 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
    b. Exclusion 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)
    c. Exclusion 5: Subjects with planned PCI of three vessel disease (includes staged procedures)
    d. Exclusion 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.

In addition to the general exclusion criteria listed above, Bifurcation subjects will be in the PP set only if all the Bifurcation target lesions meet the below criteria:

1. Proximal optimization technique was performed after provisional stenting
2. Baseline side branch diameters per site estimation are ≥ 2.0 mm
3. No planned two stent technique (main and side branch) of a bifurcation

The primary endpoint will also be analyzed in both ITT and PP population.

7.1.4 Pooling of Bifurcation Cohort and bifurcated lesions from Primary/XLV Cohorts

It is intended to pool the two cohorts (Bifurcation Cohort and bifurcation subset from Primary/XLV cohorts). Comparability between the two cohorts on baseline characteristics and on the primary endpoint will be assessed.

- **Covariate homogeneity**

The first step will be to assess the homogeneity of the covariates between two cohort populations. The two-sample t-test or Fisher's exact test will be used depending on the distributions of the covariates. The covariates that will be considered include: lesion length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society angina class. Statistical non-significance (significance level set at 0.15) for any of the covariates is supportive evidence of the comparability of the cohorts without adjusting for that covariate. However, any covariate for which the group difference is deemed to be clinically and statistically significant could be adjusted by using propensity scores as discussed below to account for any covariate imbalances.

- **Outcome Comparability**

If any of the above baseline covariates is significantly different, then the outcome of 12 months TVF rate between the two cohorts will be compared as the following: for each individual a propensity score will be calculated using logistic regression, with indicator for cohort (Bifurcation cohort, bifurcation subset from Primary/XLV cohorts) membership as the dependent variable and the above mentioned covariates as the independent variables (covariates will be included regardless of whether or not they are deemed homogenous). Patients will then be categorized into quintiles based on this propensity score. The 85% confidence interval of propensity score quintile adjusted difference between cohorts in TVF at 12 months will be calculated. If the 85% confidence interval contains zero (0), then the two cohorts will be considered poolable.

If the two cohorts are deemed suitable for pooling based on this analysis, then combined data from the two cohorts will be used to compared to the performance goal. If the data from the two cohorts are not poolable, then Medtronic will discuss with FDA on the next steps.

7.2 General Methodology

All statistical analyses will be performed using Statistical Analysis Software (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.

All analyses will be based on "intent to treat" (ITT) principle, unless otherwise specified. For clinical events, the numerator of the event rate will be the number of "ITT" subjects having an event by the time of interest. The denominator will be the number of subjects who either have an event by the time of interest or have follow-up information beyond the lower window of the follow-up.

The Clinical Study Report will be available for the primary endpoint and for secondary endpoints annually through study close-out at 3 years.

7.3 Center Pooling

Given this is a multi-center trial, to account for the pooling of results across sites and regions the following analysis will be performed for primary endpoints of primary cohort, XLV cohort, and bifurcation cohort using complete data:

1. Pooling data of the small sites:
   The sites with enrollment of 5 subjects or more are reported individually. The sites with enrollment of 4 or less are pooled into super-sites according to their geographical closeness so that the combined super-sites would have five or more enrolled subjects. If a super-site is with 5 or more subjects, the pooling of this supersite will stop and the pooling of the next super-site will start.
2. Assessment of baseline characteristics across sites:
   Important baseline demographic and lesion characteristics (lesion-length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society Angina Class (CCSC)) will be tabulated for each site. Assessment of differences in baseline characteristics across sites will be performed using one-way analysis of variance for continuous parameters and logistic regression for categorical parameters.
3. Analysis on the primary endpoints across sites:

   For each primary endpoint, rate of the primary endpoint for every cohort will be presented by site and comparison across sites will be carried out using logistic regression to assess site homogeneity, with the primary endpoint as the dependent variable, and the sites as independent variable. If there is significant difference in baseline characteristics observed in step 2, then this comparison will be adjusted by adding the entire baseline variables listed above into the logistic regression model as additional independent variables.

To account for the pooling of results across regions (US vs. EU), the following analysis will be performed on all three cohorts using complete data:

1. Assessment of homogeneity of baseline characteristics between US and EU:

The two-sample t-test, Fisher's exact test or Cochran-Mantel-Haenszel (CMH) (Modified Ridit scores) will be used depending on the distributions of the baseline covariates. The covariates that will be considered include: lesion-length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society angina class. Statistical non-significance (significance level set at 0.15) for any of the covariates is supportive evidence of the comparability of Resolute arms without adjusting for that covariate. However, any covariate for which the group difference is deemed to be clinically and statistically significant could be adjusted by using propensity scores as discussed below to account for any covariate imbalances.

2. Assessment of Outcome Comparability:

   If any of the above baseline covariates is significantly different, then the outcome of primary endpoint between the US and EU will be compared as the following: For each individual a propensity score will be calculated using logistic regression, with indicator for cohort (US, EU) membership as the dependent variable and the above mentioned covariates as the independent variables (covariates will be included regardless of whether or not they are deemed homogenous). Subjects will then be categorized into quintiles based on this propensity score. The 85% confidence interval of propensity score quintile adjusted odds ratio of region will be calculated. If the 85% confidence interval contains one (1), then the US and EU data will be considered poolable.

Statistical non-significance in the primary endpoints for site and region comparisons will confirm that the sites and regions are homogeneous in this trial. Otherwise, the cause of the significant difference will be investigated and further analyses plan will be discussed with FDA.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing data. In time-to-event outcomes, drop-outs 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 characteristics and outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

Screening and acceptance testing of these data will be carried out in accordance with Data Management Plan. To this end, all data involved in the determination of endpoints will be screened for missing and unusual values. Any missing data that affect the ability to determine or analyze any endpoint will be queried by Data Management for confirmation of irretrievability. Unusual values, such as outliers, will also be queried, and if confirmed, will be used as recorded.

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be performed.

7.6 Demographic and Other 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.

7.7 Treatment Characteristics

All procedural data 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.

7.8 Interim Analyses

No interim analyses will be performed.

7.9 Evaluation of Objectives

7.9.1 Analysis of the Primary Endpoints

7.9.1.1 Primary Cohort

The primary endpoint 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 by percutaneous or surgical methods) at 12 months.

It is estimated that in average the TLF rate at 12 months post procedure is 11.3%. The performance goal (PG) is set to be 17.5%, which is approximately 55% above the expected TLF rate for Resolute Onyx.

If the 12 months TLF rate of the Resolute Onyx Post-Approval Study is shown to be significantly less than the PG, then the trial will be considered to have met its objective. In other words, the assessment of TLF at 12 months is a testing with the following null and alternative hypotheses:

$$H_0: p \geqslant 17.5\% \text{ vs. } H_1: p < 17.5\%,$$

where p is the true Onyx 12 months TLF rate.

The assessment of the null hypothesis will be carried out at the one-sided 0.05 level of significance. Rejection of the null hypothesis indicates the Onyx 12 months TLF rate is significantly below 17.5%.

The count and percentage of subjects with 12-month TLF will be presented. A one-sided upper 95% confidence interval of the Resolute Onyx stent 12-month TLF rate will be calculated through binomial (exact) method. If this upper limit is below 17.5%, the clinical objective will be considered to have been met. All ITT subjects in primary cohort with evaluable value will be included in the primary analysis.

As a supplementary analysis, to account for missing data, subjects who drop out prior to 330 days post-procedure and do not experience TLF will have their 12-month TLF-missing status ("yes"/"no") imputed using the multiple imputation and tipping point analysis.

The multiple imputation approach will use SAS V9 PROC MI. The covariates to be used in the imputation model are lesion-length, baseline RVD, age, sex, diabetes, history of MI, Canadian Cardiovascular Society Angina Class, and TLF status at visits prior to dropout. One hundred imputed data sets will be generated. An overall TLF rate and its one-sided upper 95% confidence intervals will be generated across the one hundred imputed data sets. For the subjects with 2 or more target lesions, the longest lesion length and the smallest baseline RVD will be used in the imputation model.

The tipping point analysis will impute the most 12-month TLF-missing status as "yes" so that the one-side upper 95% confidence interval will be less than or equal to the performance goal of 17.5%.

The survival analysis will be used on TLF to assess the censored subjects. The upper bound of 95% confidence interval through 12 months will be used to compare to the performance goal of 17.5%.

7.9.1.2 XLV Cohort

The count 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. All ITT patients in XLV cohort with evaluable value will be included in the primary analysis. The survival analysis will be used on TLF to assess the censored subjects.

7.9.1.3 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.

As a supplementary analysis, to account for missing data, subjects who drop out prior to 330 days post-procedure and do not experience TVF will have their 12-month TVF-missing status ("yes"/"no") imputed using the multiple imputation and tipping point analysis.

The multiple imputation approach will use SAS V9 PROC MI. The covariates to be used in the imputation model are lesion-length, baseline RVD, age, sex, diabetes, history of MI, Canadian Cardiovascular Society Angina Class, and TVF status at visits prior to dropout. One hundred imputed data sets will be generated. An overall TVF rate and its one-sided upper 95% confidence intervals will be generated across the one hundred imputed data sets. For the subjects with 2 or more target lesions, the longest lesion length and the smallest baseline RVD will be used in the imputation model.

The tipping point analysis will impute the most 12-month TVF-missing status as "yes" so that the one-side upper 95% confidence interval will be less than or equal to the performance goal of 24.5%. For all the three cohorts, the analysis of the primary endpoint will be repeated for PP set as a secondary analysis.

7.9.2 Analysis of 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 response variable may be presented by using the Kaplan-Meier methods. For the myocardial infarctions (MI) component of the endpoints, the extended historical MI definitions will be used if no specification. Results for the components of composite endpoints will be tabulated.

7.9.3 Analysis of Subgroups

For each of the subgroups below, principal safety and effectiveness results, demographic and baseline characteristics, and baseline angiographic characteristics will be provided. The subgroup analysis will be performed for all subjects in the ITT Cohorts.

- Male vs. Female
- Age ≥ 65 vs. <65
- Simple vs Complex

  For the purposes of stratification, subjects are considered "complex" if they have total occlusion, bifurcation, saphenous vein graft (SVG), target lesion in-stent restenosis (ISR), Acute MI (≤ 72 hrs), left ventricular ejection fraction (LVEF) < 30%, unprotected left main (LM), more than two vessels stented, renal insufficiency or failure (creatinine ≥ 140 umol/L), lesion length > 35 mm, more than one lesion per vessel, or pre-procedure thrombus. "Simple" subjects are all the subjects excluding "complex" subjects.
- Pre RVD <2.25 mm vs. Pre RVD ≥ 2.25 mm
- Pre RVD <2.5 mm vs. Pre RVD ≥ 2. 5 mm
- Diabetes vs. Non-diabetes
- Long lesion (lesion length > 35 mm) vs. Short lesion (lesion length ≤ 35 mm)
- Multiple vessels vs. Single vessel
- Multiple lesions vs. Single lesion
- Overlapping vs. Non-overlapping
- LAD vs. Non-LAD
- Bifurcation – provisional stenting: single vs. two-stent approach

Two-stent approach is stenting of main and side branch. Subjects reporting provisional single for one lesion and two-stent technique for another lesion will be included in the 2-stent approach subgroup.

Principal safety and effectiveness results will be provided for each of the below subgroups for the bifurcation cohort.

- Male vs. Female
- Age ≥ 65 vs. <65
- Race
- Diabetes vs. Non-Diabetes
- Multiple vessels vs. Single vessel
- True Bifurcation per Medina (111, 101, 011) vs non-true bifurcation per Medina
- Bifurcation – provisional stenting: single vs. two-stent approach

Two-stent approach is stenting of main and side branch. Subjects reporting both provisional single for one lesion and two-stent technique for another lesion will be included in the 2-stent approach subgroup.

7.9.4 Analysis on Higher Complexity Bifurcation Sub-group

Descriptive statistics for the important clinical outcomes for subsets of subjects 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.

7.10 Safety Evaluation

All site reported and CEC adjudicated adverse events will be summarized by count and percent as appropriate. A listing of device deficiencies and CEC adjudicated deaths will be provided.

7.11 Health Outcomes Analyses

Not applicable because the study does not collect health outcome data.

7.12 Changes to Planned Analysis

There are no deviations from planned analyses in CIP.

8. Validation Requirements

The tables, graphs, and listings for clinical study reports require level I validation (the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer).

9. Statistical Appendices

Appendix I: Incomplete Date of AE Onset

The table below is guiding on how to input missing dates for AE onset

Valid Portion	Missing Portion	Imputed Value for missing Portion
Month, Year	Day	Set Day = first day of that month and year, then set the day = later of (New onset date, procedure date).
Year	Day, Month	Set date = later of (January 1st of that year, procedure date).
None	Day, Month, Year	Date of Procedure

Appendix II: Follow-up Visit Windows for Endpoint Analyses

Follow-up interval	Study Time Window Post Procedure
30 days	30 ±5 days
6 months	180 ±14 days
12 months	360 ±30 days
24 months	720 ±30 days
36 months	1080 ±30 days