SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Eluting Coronary Stent System

Device Trade Name: Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System

Device Procode: NIQ

Applicant's Name and Address: Medtronic Vascular
3576 Unocal Place
Santa Rosa, CA 95403

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160043/S012

Date of FDA Notice of Approval: December 14, 2018

The original PMA (P160043) was approved on April 28, 2017 and is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to de novo lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 5.0 mm. The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160043) and is incorporated by reference here. P160043/S001 was submitted to expand the indication for the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System to include reference vessel diameters of 2.0 mm was approved on November 16, 2017.
The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160043S001) The current supplement was submitted to expand the indication for the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System to include the treatment of *de novo* chronic total inclusions (CTO).

II. INDICATIONS FOR USE

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.0 mm to 5.0 mm. In addition, the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is indicated for treating *de novo* chronic total occlusions.

III. CONTRAINDICATIONS

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is contraindicated for use in:

- Patients with known hypersensitivity or allergies to aspirin, heparin, bivalirudin, clopidogrel, prasugrel, ticagrelor, ticlopidine, drugs such as zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum) or platinum-iridium alloy.
- Patients with a known hypersensitivity to the BioLinx polymer or its individual components

Coronary artery stenting is contraindicated for use in:

- Patients in whom anti-platelet and/or anticoagulation therapy is contraindicated.
- Patients 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (Resolute Onyx™ system) is a device/drug combination product comprised of the following device components:

- A Resolute Onyx™ Coronary Stent and delivery system. The delivery system is available in a rapid exchange (RX) and an over-the-wire (OTW) configuration.
- A drug/polymer coating component, which consists of a formulation of zotarolimus contained in a BioLinx polymer.

The characteristics of the Resolute Onyx™ product are described in **Table 1**.

Table 1: Device Component Description and Nominal Dimensions

Component		Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Rapid Exchange and Over-the-Wire			
		Stent Design 1 (Small Vessel)	**Stent Design 2 (Medium**	**Stent Design 3 (Large Vessel)**	**Stent Design 4 (Extra Large**
Available Stent Diameters (mm)		2.0, 2.25, 2.5	2.75, 3.0	3.5, 4.0	(RX Only) – 4.5, 5.0
Available Stent Lengths (mm)		8, 12, 15, 18, 22, 26, 30, 34*, 38* * 34, 38 mm lengths not available in 2.0	8, 12, 15, 18, 22, 26, 30, 34, 38	8, 12, 15, 18, 22, 26, 30, 34, 38	(RX Only) – 12, 15, 18, 22, 26, 30
Stent Material and Geometry		A continuous sinusoid pattern stent manufactured from a composite metal material, consisting of a cobalt-based alloy shell conforming to ASTM F562 and a platinum-iridium alloy core conforming to ASTM B684.			
Drug Component		A coating of polymers loaded with zotarolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.6 µg/mm^2 which results in a maximum nominal drug content of 317 µg on the stent with the largest surface area (4.0 x 38 mm).			
Delivery System Working Length		140 cm			
Delivery System Luer Adapter Ports	RX	Single access port to the inflation lumen. A guidewire exit port is located approximately 25 cm from the tip. Designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
	OTW	Y-Connector with side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
Stent Delivery Balloon		Single-layer Pebax balloon, wrapped over an inner member tubing with 2 radiopaque marker bands to locate the stent edges.			
Balloon Inflation Pressure		Nominal Inflation Pressure: 12 ATM (1216 kPa) Rated Burst Pressure: 2.0-4.0mm = 18 ATM (1824 kPa), RX only: 4.5-5.0mm = 16 ATM (1621kPa)			
Minimum Guide Catheter Inner Diameter		5 F (1.42 mm, 0.056 in)			
Catheter Shaft Outer Diameter	RX	Proximal Shaft OD, 2.0-5.0mm: 2.1 F (0.69 mm) Distal Shaft OD, 2.0-4.0mm: 2.7 F (0.91 mm) Distal Shaft OD, 4.5 and 5.0mm:			
	OTW	Proximal Shaft OD: 3.4 F (1.12 mm) Distal Shaft OD: 2.7 F			

A. Device Component Description

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (Resolute Onyx™ system) consists of a balloon-expandable, intracoronary, drug-eluting stent (DES) premounted on a stent delivery system (RX or OTW). The Resolute Onyx™ coronary stent is manufactured from a composite material of cobalt alloy and platinum- iridium alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The Resolute Onyx™ coronary stent is coated with a Parylene C primer, a Biolinx polymer, and the active pharmaceutical ingredient (API), zotarolimus with a nominal drug dose density of approximately 1.6 µg/mm^2.

The Resolute Onyx™ coronary stent utilizes the identical stent drug/polymer coating and coating application process as the commercially approved Resolute and Resolute Integrity coronary stents (P110013). The principal material difference between the Resolute Onyx™ coronary stent and the Resolute Integrity™ coronary stent is the stent wire material. The Resolute Onyx™ coronary stent is manufactured from a composite wire which has an outer shell and an inner core. The outer shell of the stent, which is in contact with the vessel, is of the identical cobalt alloy used for the predicate Resolute Integrity™ stent while the inner core material is a Platinum – Iridium alloy.

The Resolute Onyx™ stents are available 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. The stent is crimped on various sizes of delivery catheter balloons, which range from 2.0 mm to 5.0 mm. See **Table 1**, above, for full list of diameter ranges available on each delivery system (RX and OTW).

B. Drug Component Description

The drug coating of the Resolute Onyx™ System consists of the drug zotarolimus (the active ingredient) and BioLinx® polymer system (the inactive ingredient).

B1. Active Ingredient: Zotarolimus

The active pharmaceutical ingredient utilized in Resolute Onyx™ is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant.

The Chemical name of zotarolimus is: [3S-[3R*[S*(1R*,3S*,4R*)],6S*, 7E,9S*,10S*,12S*,14R*,15E,17E,19E, 21R*,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazoyl-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy- 6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown in **Figure 1**.

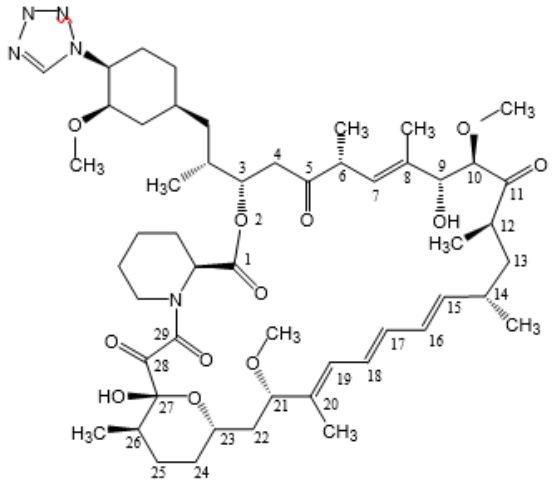

Figure 1: Chemical Structure of Zotarolimus

Zotarolimus has extremely low water solubility and is a lipophilic compound that is freely soluble in Propylene glycol, Acetone, Toluene, Acetonitrile, Ethanol, Benzyl alcohol and DMSO. The molecular formula of zotarolimus is C52H79N5O12 and its molecular weight is 966.2.

Zotarolimus does not have any ionizable group(s) in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

B2. Inactive Ingredient

Biolinx Polymer

Resolute Onyx™ coronary stent is covered with 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 and C19, and PVP (polyvinyl pyrrolidone).;

The structural formula of the BioLinx polymer subunits is show in **Figure 2**.

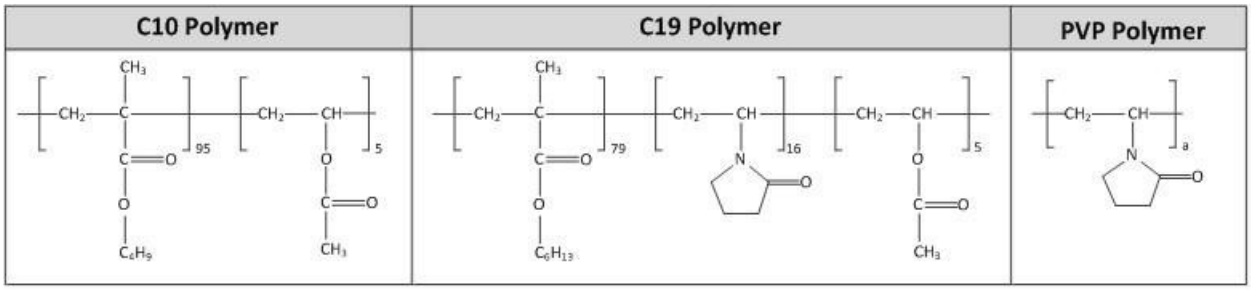

Figure 2: Chemical Structure of Biolinx Polymer Sub-units

Table 2: Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Content

Product Number Resolute Onyx RX	Product Number Resolute Onyx OTW	Nominal Expanded Stent ID RX (mm)	Nominal Unexpanded Stent Length RX & OTW	Nominal Zotarolimus Content RX (µg)	Nominal Zotarolimus Content OTW (µg)
RONYX20008UX	RONYX20008W	2.0	8	51	51
RONYX22508UX	RONYX22508W	2.25		51	51
RONYX25008UX	RONYX25008W	2.5		51	51
RONYX27508UX	RONYX27508W	2.75		67	67
RONYX30008UX	RONYX30008W	3.0		67	67
RONYX35008UX	RONYX35008W	3.5		77	77
RONYX40008UX	RONYX40008W	4.0		77	77
RONYX20012UX	RONYX20012W	2.0	12	70	70
RONYX22512UX	RONYX22512W	2.25		70	70
RONYX25012UX	RONYX25012W	2.5		70	70
RONYX27512UX	RONYX27512W	2.75		94	94
RONYX30012UX	RONYX30012W	3.0		94	94
RONYX35012UX	RONYX35012W	3.5		108	108
RONYX40012UX	RONYX40012W	4.0		108	108
RONYX45012UX	Not Available	4.5		132	Not Available
RONYX50012UX	Not Available	5.0		132	Not Available
RONYX20015UX	RONYX20015W	2.0	15	85	85
RONYX22515UX	RONYX22515W	2.25		85	85
RONYX25015UX	RONYX25015W	2.5		85	85
RONYX27515UX	RONYX27515W	2.75		117	117
RONYX30015UX	RONYX30015W	3.0		117	117
RONYX35015UX	RONYX35015W	3.5		132	132
RONYX40015UX	RONYX40015W	4.0		132	132
RONYX45015UX	Not Available	4.5		158	Not Available
RONYX50015UX	Not Available	5.0		158	Not Available
RONYX20018UX	RONYX20018W	2.0	18	104	104
RONYX22518UX	RONYX22518W	2.25		104	104
RONYX25018UX	RONYX25018W	2.5		104	104
RONYX27518UX	RONYX27518W	2.75		140	140
RONYX30018UX	RONYX30018W	3.0		140	140
RONYX35018UX	RONYX35018W	3.5		156	156
RONYX40018UX	RONYX40018W	4.0		156	156
RONYX45018UX	Not Available	4.5		188	Not Available
RONYX50018UX	Not Available	5.0		188	Not Available
RONYX20022UX	RONYX20022W	2.0	22	127	127
RONYX22522UX	RONYX22522W	2.25		127	127
RONYX25022UX	RONYX25022W	2.5		127	127
RONYX27522UX	RONYX27522W	2.75		171	171
RONYX30022UX	RONYX30022W	3.0		171	171
RONYX35022UX	RONYX35022W	3.5		186	186
RONYX40022UX	RONYX40022W	4.0		186	186
RONYX45022UX	Not Available	4.5		227	Not Available
RONYX50022UX	Not Available	5.0		227	Not Available
RONYX20026UX	RONYX20026W	2.0	26	146	146

Table 2: Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Content

Product Number Resolute Onyx RX	Product Number Resolute Onyx OTW	Nominal Expanded Stent ID RX (mm)	Nominal Unexpanded Stent Length RX & OTW	Nominal Zotarolimus Content RX (µg)	Nominal Zotarolimus Content OTW (µg)
RONYX22526UX	RONYX22526W	2.25		146	146
RONYX25026UX	RONYX25026W	2.5		146	146
RONYX27526UX	RONYX27526W	2.75		198	198
RONYX30026UX	RONYX30026W	3.0		198	198
RONYX35026UX	RONYX35026W	3.5		221	221
RONYX40026UX	RONYX40026W	4.0		221	221
RONYX45026UX	Not Available	4.5		265	Not Available
RONYX50026UX	Not Available	5.0		265	Not Available
RONYX20030UX	RONYX20030W	2.0	30	168	168
RONYX22530UX	RONYX22530W	2.25		168	168
RONYX25030UX	RONYX25030W	2.5		168	168
RONYX27530UX	RONYX27530W	2.75		225	225
RONYX30030UX	RONYX30030W	3.0		225	225
RONYX35030UX	RONYX35030W	3.5		252	252
RONYX40030UX	RONYX40030W	4.0		252	252
RONYX45030UX	Not Available	4.5		304	Not Available
RONYX50030UX	Not Available	5.0		304	Not Available
RONYX22534UX	RONYX22534W	2.25	34	187	187
RONYX25034UX	RONYX25034W	2.5		187	187
RONYX27534UX	RONYX27534W	2.75		257	257
RONYX30034UX	RONYX30034W	3.0		257	257
RONYX35034UX	RONYX35034W	3.5		282	282
RONYX40034UX	RONYX40034W	4.0		282	282
RONYX22538UX	RONYX22538W	2.25	38	206	206
RONYX25038UX	RONYX25038W	2.5		206	206
RONYX27538UX	RONYX27538W	2.75		284	284
RONYX30038UX	RONYX30038W	3.0		284	284
RONYX35038UX	RONYX35038W	3.5		317	317
RONYX40038UX	RONYX40038W	4.0		317	317

C. Mechanism of Action

In vitro, zotarolimus inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells, and also demonstrated binding affinity with FKBP-12 (binding protein). 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 activity results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. **Table 2,** above, lists the nominal drug content present on each product included in the Resolute Onyx™ matrix.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease including exercise, diet, smoking cessation counseling, drug therapy, percutaneous coronary interventions (such as balloon angioplasty, atherectomy, and replacement with bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass surgery (CABG). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is commercially available in the following countries:

Table 3: Resolute Onyx Commercial Availability

Albania	Ethiopia	Latvia	Qatar
Algeria	Fiji	Lebanon	Reunion
Argentina	Finland	Liechtenstein	Romania
Armenia	France	Lithuania	Russian Federation
Australia	Gabon	Luxembourg	Saudi Arabia
Austria	Georgia	Macedonia	Serbia
Azerbaijan	Germany	Malaysia	Singapore
Bahrain	Ghana	Malta	Slovakia
Bangladesh	Greece	Martinique	Slovenia
Belgium	Guatemala	Mexico	South Africa
Bolivia	Honduras	Moldova	Spain
Bosnia and Herzegovina	Hong Kong	Montenegro	Sri Lanka
Botswana	Hungary	Morocco	Sweden
Brunei Darussalam	Iceland	Namibia	Switzerland
Bulgaria	India	Nepal	Taiwan
Canary Islands	Iran	Netherlands	Tajikistan
Colombia	Iraq	New Zealand	Tanzania
Costa Rica	Ireland	Nicaragua	Thailand
Croatia	Israel	Norway	Trinidad And Tobago
Cyprus	Italy	Oman	Tunisia
Czech Republic	Japan	Pakistan	Turkey
Denmark	Jordan	Panama	United Arab Emirates
Dominican Republic	Kazakhstan	Paraguay	United Kingdom
Ecuador	Kenya	Philippines	United States
Egypt	Korea, Republic Of	Poland	Venezuela
El Salvador	Kuwait	Portugal	Vietnam
Estonia	Kyrgyzstan	Puerto Rico	Yemen

The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. Adverse events (in alphabetical order) which may be associated with coronary stent use in native coronary arteries include, but are not limited to:

- 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 migration or embolization

- Stent misplacement
- Stroke/transient ischemic attack
- Thrombosis (acute, subacute, or late)

Adverse events that have been associated with the intravenous injection of zotarolimus in humans include but are not limited to:

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

Potential adverse events related to BioLinx polymer include but are not limited to:

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

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies related to the Resolute family of products were performed and the pertinent data was leveraged from the previously approved PMAs P110013 and P160043. Because these previously collected data sufficiently represent the performance of the device for the new indications for use, no new non- clinical testing was conducted.

X. SUMMARY OF PRIMARY CLINICAL STUDY

A pre-specified subgroup analysis from an investigator-initiated clinical study (PERSPECTIVE) in the United States established reasonable assurance of safety and effectiveness of the Resolute DES for treatment of Chronic Total Occlusions (CTO). Data from this clinical study, in conjunction with data generated in the Global RESOLUTE Clinical Trial Program (See *Section XI – Summary of Supplemental Clinical Information*) were the basis for the PMA Supplement approval decision.

The Resolute Onyx™ stent is an iterative design update to the Resolute Integrity stent (P110013), utilizing the same continuous sinusoid manufacturing technology with slight modifications incorporated to provide a lower crossing profile. The clinical evaluations

assessed in the PERSPECTIVE Study and Global RESOLUTE Clinical Trial Program were performed on the Resolute MicroTrac or Resolute Integrity Stent. However, given the similarities between the Resolute stent system and the Resolute Onyx™ stent system, the findings from the RESOLUTE clinical studies are applicable to the Resolute Onyx™ stent system.

A summary of the clinical study is presented below.

A. Study Design

The PERSPECTIVE Study was an investigator-initiated, single arm, open label, single-center, observational study including approximately 250 prospective subjects undergoing attempted CTO revascularization and 250 retrospective subjects that had undergone CTO PCI all performed at the Piedmont Heart Institute in Atlanta, Georgia. This study was partially funded by Medtronic through its External Research Program. Medtronic did not have access to the clinical data prior to primary analysis.

Prospective subjects admitted for intended PCI of a CTO were screened for study eligibility and signed an IRB-approved informed consent form. Events were adjudicated by an independent Clinical Events Committee (CEC) constituted by interventional and/or non-interventional cardiologists who were not participants in the study. Criteria evaluated include death, myocardial infarction, target lesion revascularization, target vessel revascularization, bleeding, and stent thrombosis.

Patients receiving the Resolute Integrity™ stent in the PERSPECTIVE Study were treated between August 22, 2013 and February 17, 2016 and included 183 patients.

Assessment of use of the Resolute Integrity™ stent (P110013) in CTO revascularization was based on prospectively enrolled CTO patients compared to a pre-specified performance goal. Stent type selection for the prospective group was based on operator preference, and the number of enrolled subjects was set to meet the sample size required for the pre-specified RESOLUTE CTO Cohort analysis.

An estimated MACE rate was derived based on a weighted average of the reported rates for drug-eluting stents from the PRISON II[1] and EXPERT CTO[2] studies. Due to difference in the definition of myocardial infarction used in the PRISON II study, an adjustment for the MACE rate was made to approximate the MACE rate if the ARC definition of myocardial infarction had been applied. The weighted average produced an estimated MACE rate of 16.6% using the ARC definition of MI. The performance goal (PG) for the pre-specified RESOLUTE CTO Cohort analysis was 25.2% based on the estimated MACE rate of 16.6% and a one-sided 95% CI.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the PERSPECTIVE Study was limited to patients who met the following Key Inclusion Criteria:

   - Subjects experiencing clinical symptoms considered suggestive of ischemic heart disease (e.g., chest pain or discomfort or symptoms considered by the

investigator to represent anginal equivalents) or having evidence of myocardial ischemia (e.g., abnormal functional study) attributed to the CTO target vessel and scheduled for clinically indicated percutaneous CTO revascularization or are subjects with multi-vessel disease and/or Acute Coronary Syndrome (ACS) that are undergoing a staged CTO PCI procedure with the intent to achieve complete revascularization.

- Subject must have at least 1 target segment meeting non-acute total coronary occlusion as defined below. A CTO is any non- acute total coronary occlusion fulfilling the following angiographic characteristics and:
    a. High-grade native coronary stenosis
    b. Thrombolysis in Myocardial Infarction (TIMI) 0 or 1 antegrade flow
    c. Estimated in duration at least 3 months by clinical history and/or comparison with antecedent angiogram, functional study or electrocardiogram
    d. CTO segment may be *de novo* or previously treated via PCI

Patients were <u>not</u> permitted to be enrolled in the PERSPECTIVE Study if they met any of the following Key Exclusion Criteria:

- Any known allergy, hypersensitivity or contraindication to iodinated contrast that cannot be effectively managed medically
- Any known allergy, hypersensitivity or contraindication to clopidogrel bisulfate (Plavix®), prasugrel (Effient®) or ticagrelor (Brilinta®)—for which alternative agents cannot be used—or aspirin, heparin, nickel, stainless steel, zotarolimus, or everolimus
- Subjects with evidence of ongoing or active clinical instability including any of the following:
    a. Sustained systolic blood pressure <100 mmHg (if different from baseline) or cardiogenic shock
    b. Acute pulmonary edema that has not been medically stabilized
    c. Suspected acute myocarditis, pericarditis, endocarditis, or cardiac tamponade
    d. Suspected dissecting aortic aneurysm
- Subjects with known clinically significant abnormal laboratory findings
- Subjects with history of bleeding diathesis or coagulopathy or refusal of blood transfusions

2. <u>Follow-up Schedule</u>
All patients were scheduled for follow up contacts at six months (180 days ± 14 days) and one year (365 days ± 30 days) post procedure. The key timepoints are shown in **Table 4.**

Table 4: Schedule of Events for the Prospective Enrollment Group

	Baseline	Index Procedure	Discharge	6 Month Follow-Up	12 Month Follow-Up
Informed Consent	X				
Chart review of clinical history, medications, demographics	X				
Enrollment	X				
CTO PCI		X			
Standard Laboratory Testing (per Piedmont policy)	X				
CK-MB	X				
12-lead ECG (per Piedmont guidelines for PCI)	X		X[2]		
Quality of Life metrics (Seattle Angina Score, EQ-5D)	X		X		X[3]
Angina Status (CCSC)	X		X	X	X
Anti-Platelet, Anticoagulant and Anti-Ischemic Medications	X	X	X	X	X
SAE and MACE Assessment	X	X	X	X	X
LVEF% (if available)	X			X	X
AE Assessment	X	X	X	X[4]	X[4]
Angiographic Core Lab Analysis		X		X[5]	X[5]

[1] Subject contact includes phone call and/or clinic visit
[2] CK-MB obtained 6 – 12 hours post procedure, 18 – 24 hours post procedure or at discharged, if sooner
[3] EKG if available within ± 60 days of study visit
[4] Cardiovascular or cardiovascular-related AEs
[5] If applicable

3. Clinical Endpoints

Primary Endpoint
The pre-specified Primary Endpoint for Resolute Integrity stent in the PERSPECTIVE study was the occurrence of major adverse cardiac events (MACE), defined as: death, myocardial infarction (MI) (ARC defined), and clinically-driven target lesion revascularization (TLR) at one year post-procedure.

Key Secondary Endpoints

- In-hospital and one-year individual outcomes of death (cardiac and all-cause), MI (Q wave and Non-Q Wave), and TLR
- One-year event rate of all target vessel and non-target vessel revascularization
- One-year occurrence of stroke (cerebrovascular accident, CVA)
- Target lesion failure (TLF) defined as: cardiac death, target vessel-related MI and clinically-driven TLR and individual endpoint components during index hospitalization and at one-year post-procedure
- Target vessel failure (TVF) defined as: cardiac death, target vessel-related MI and clinically-driven target vessel revascularization in-hospital and at one-year post-procedure
- Acute Success (Device Success, Lesion Success, Procedural Success)
- Stent Thrombosis (ST): according to Academic Research Consortium criteria (all, definite, definite/probable, probable, possible) in-hospital and at one-year post-procedure
- Change in angina frequency and quality of life measures (Seattle Angina Questionnaire, EQ-5D) from baseline to one-year follow-up among revascularization and unsuccessful revascularization cohorts
- Frequency of both scheduled and PRN (as needed) anti-anginal medications during index hospitalization, at six months and at one year following attempted CTO revascularization
- Frequency and procedural success rate of second attempt CTO revascularization

B. Accountability of PMA Cohort

At the time of the database lock for this study, 176 subjects were eligible for the 12-month post-procedure contact. Although only 25.6% of subjects completed the 12-month follow-up within window, 96.2% (176/183) of subjects completed the study. Follow-up eligibility excludes a total of seven (7) subjects from the 12-month time frame; five (5) deaths, two (2) withdrawn consents (n=176). **Figure 3** provides an overview of the subject accountability for this study through the 12-month Follow-Up visit.

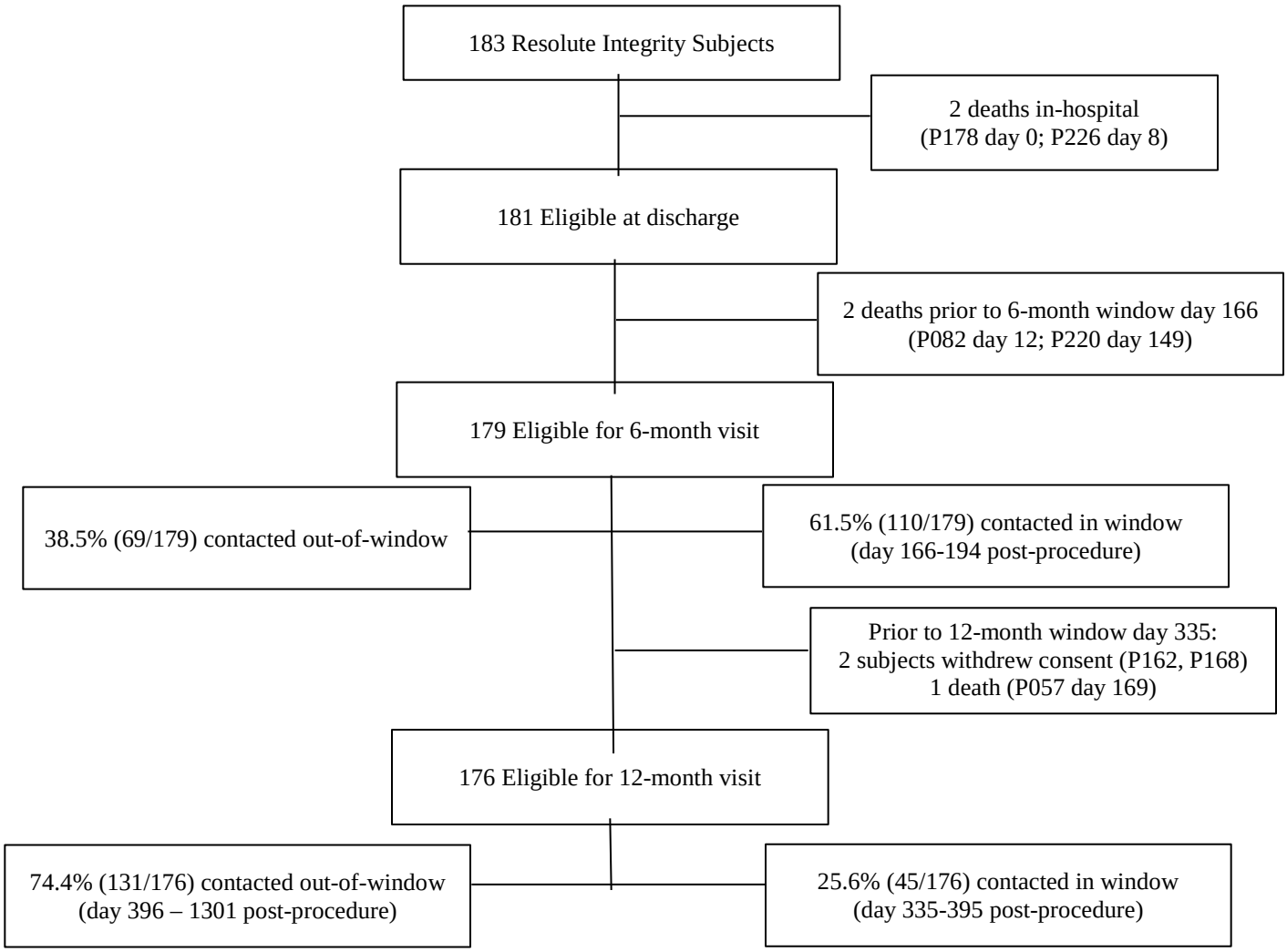

Figure 3: Accountability Flow Chart - PERSPECTIVE Study RESOLUTE CTO Cohort

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PCI study performed in the US.

The mean age of the study subjects was 63.4 years, with 79.8% (146/183) of subjects being male, 35.5% (65/183) diabetics, 18.0% (31/172) were current smokers, 33.3% (61/183) had prior MI, 51.4% (94/183) had prior PCI, 88.5% (162/183) had hypertension, and 98.4% (180/183) reported dyslipidemia. Baseline lesion characteristics include 56.3% (103/183) of RCA vessels with a CTO lesion, 95.1% (173/182) lesions were *de novo* in nature, and 87.7% (200/228) ACC/AHA type B2/C lesions. The mean RVD was 3.31 ± 0.77 mm.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on 181 subjects available for the 12-month evaluation.

The In-hospital rates for TLF, TVF, and MACE were similar at 15.3% (28/183). The cardiac death rate was 1.1% (2/183), and the peri-procedural (ARC defined) MI rate was 14.8% (27/183).

The one-year rates for TLF, TVF, and MACE were again similar at 18.2% (33/181), the TLR rate was 1.1% (2/181), the cardiac death rate was 2.2% (4/181), the (ARC defined) MI rate was16.0% (29/181) and the ARC definite or probable ST rate was 0.6% (1/181). There were no unanticipated adverse device effects (UADE), nor any device failures or malfunctions reported through 12 months.

2. Effectiveness Results

Effectiveness assessment included Clinical Success (defined as achievement of <50% residual stenosis with ≥TIMI 2 antegrade flow) and Technical Success (defined as successful guidewire crossing with placement in distal true lumen of CTO target lesion). Clinical Success was reported as 92.3% (169/183) and Technical Success was reported as 96.2% (175/182).

Principal safety and effectiveness results are reported in **Table 5**.

Table 5: Primary Safety and Effectiveness Results – The PERSPECTIVE Study

Safety and Effectiveness Measures	RESOLUTE CTO Cohort (N=183 Subjects) %(m/n)
Safety Measures (In-Hospital)	
TLF	15.3% (28/183)
TVF	15.3% (28/183)
MACE	15.3% (28/183)
Cardiac Death or MI	15.3% (28/183)
Death or MI	15.3% (28/183)
Death	1.1% (2/183)
Cardiac Death	1.1% (2/183)
Non-Cardiac Death	0.0% (0/183)
MI	14.8% (27/183)
TLR	0.0% (0/183)
TVR	0.0% (0/183)

Table 5: Primary Safety and Effectiveness Results – The PERSPECTIVE Study

Safety and Effectiveness Measures	RESOLUTE CTO Cohort (N=183 Subjects) %(m/n)
Safety Measures (to Six Months)	
TLF	17.5% (32/183)
TVF	17.5% (32/183)
MACE	17.5% (32/183)
Cardiac Death or MI	17.5% (32/183)
Death or MI	17.5% (32/183)
Death	2.7% (5/183)
Cardiac Death	2.2% (4/183)
Non-Cardiac Death	0.5% (1/183)
MI	15.8% (29/183)
TLR	0.5% (1/183)
TVR	0.5% (1/183)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.6% (3/183)
Stent Thrombosis ARC Definite/Probable	0.6% (1/183)
Stent Thrombosis ARC Possible	1.1% (2/183)
Early Stent Thrombosis (0 to 30 days)	0.6% (1/183)
Definite	0.6% (1/183)
Probable	0.0% (0/183)
Possible	0.0% (0/183)
Late Stent Thrombosis (31 days – 6 months)	1.1% (2/183)
Definite	0.0% (0/183)
Probable	0.0% (0/183)
Possible	1.1% (2/183)
Safety Measures (to One year)	
TLF	18.2% (33/181)
TVF	18.2% (33/181)
MACE	18.2% (33/181)
Cardiac Death or MI	17.7% (32/181)
Death or MI	17.7% (32/181)
Death	2.8% (5/181)
Cardiac Death	2.2% (4/181)
Non-Cardiac Death	0.6% (1/181)
MI	16.0% (29/181)
TLR	1.1% (2/181)
TVR	1.1% (2/181)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.7% (3/181)
Stent Thrombosis ARC Definite/Probable	0.6% (1/181)
Stent Thrombosis ARC Possible	1.1% (2/181)

Table 5: Primary Safety and Effectiveness Results – The PERSPECTIVE Study

Safety and Effectiveness Measures	RESOLUTE CTO Cohort (N=183 Subjects) %(m/n)
Early Stent Thrombosis (0 to 30 days)	0.6% (1/181)
Definite	0.6% (1/181)
Probable	0.0% (0/181)
Possible	0.0% (0/181)
Late Stent Thrombosis (31 days – 1year)	1.1% (2/181)
Definite	0.0% (0/181)
Probable	0.0% (0/181)
Possible	1.1% (2/181)
Effectiveness Measures	
Clinical success[1]	92.3% (169/183)
Technical success[2]	96.2% (175/182)

[1] Achievement of <50% residual stenosis with ≥TIMI 2 antegrade flow
[2] Successful guidewire crossing with placement in distal true lumen of CTO target lesion

The Intent-to-treat (ITT) population was defined as the primary analysis population for the RESOLUTE CTO Cohort. MACE at 1 year, defined as, a composite of death, myocardial infarction (ARC defined), and clinically-driven TLR was the primary safety endpoint. The MACE rate at one year for the RESOLUTE CTO Cohort was 18.2% (33/181) with the upper limit of 95% confidence interval of 23.6%. This is below the prespecified performance goal of 25.2%. Therefore, study success may be claimed for the primary safety endpoint.

Key outcomes for this study are presented below in **Table 6**.

Table 6: Primary Endpoint Analysis –PERSPECTIVE Study (RESOLUTE CTO Cohort)

Primary Endpoint	RESOLUTE CTO Cohort (N=183 Subjects)	One-side upper 95% Confidence Interval	Performance Goal
12-month MACE	18.2% (33/181)	23.6%	25.2%

3. Subgroup Analyses

The RESOLUTE CTO Cohort (i.e., patients who received a Resolute Integrity stent) was a pre-specified subgroup analysis of the PERSPECTIVE Study. A post hoc evaluation of the RESOLUTE CTO Cohort of the PERSPECTIVE Study for possible sex-based differences in the primary endpoint of MACE at 12 months is provided in **Table 7** below. Outcomes are similar.

Table 7: RESOLUTE CTO Cohort – MACE at 12 Months (Gender Analysis)

Primary Endpoint	Male Subjects RESOLUTE CTO Cohort (N=146 Subjects)	Female Subjects RESOLUTE CTO Cohort (N=146 Subjects)	P-Value
12-month MACE	18.8% (27/144)	16.2% (6/37)	0.815

4. Pediatric Extrapolation

In this premarket application, the clinical data summarized here will not be used to support approval of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System in a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included four (4) investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental information in support of this PMA application was presented from a pooled analysis of the Global RESOLUTE Clinical Program with CTO lesions treated with the Resolute DES. Subjects included in the analysis were pooled from three Resolute DES studies: one randomized trial, RESOLUTE China RCT (nCTO=15/198), and two single-arm studies, RESOLUTE International study (nCTO=186/2,349) and RESOLUTE China Registry (nCTO=157/1,800). All Resolute studies used uniform endpoint definitions, adjudication processes, and follow-up procedures. The RESOLUTE International Registry (R-Int) has completed the 3-year planned follow-up; RESOLUTE China RCT (R-China RCT) and RESOLUTE China Registry (R- China Registry) have completed the 5-year planned follow-up. These three studies contributed CTO subjects to make up the RESOLUTE Pooled CTO subset (n=358).

Event rates reported for the RESOLUTE Pooled CTO subset include MACE rate of 5.7% (20/352), cardiac death rate of 0.9% (3/352), TLR rate of 2.0% (7/352), and a stent thrombosis rate of 0.6% (2/352) at 1 year. Lesion-based effectiveness measures from the Global RESOLUTE Clinical Program report lesion success, defined as the attainment of <50% residual stenosis of the target lesion using any percutaneous method, and device success, defined as the attainment of <50% residual stenosis of the target lesion using only the assigned device. Subject-level effectiveness measures include procedure success, defined as the attainment of <50% residual stenosis of the target lesion and no in-hospital MACE. The RESOLUTE Pooled CTO subset reports lesion success at 100% (526/526), device success at 94.1% (496/527) and procedure success at 97.5% (348/357). See **Table 8** below.

Table 8: Safety and Effectiveness Results – RESOLUTE Pooled CTO

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n)[9]
Effectiveness Measures	
Lesion Success[6]	100.0% (526/526)
Device Success[7]	94.1% (496/527)
Procedure Success[8]	97.5% (348/357)
1 Year	
TLF[1]	4.5% (16/352)
TVF[2]	4.8% (17/352)
MACE[3]	5.7% (20/352)
Composite Endpoint[4]	12.2% (43/352)
Cardiac Death or TVMI	3.1% (11/352)
Death or TVMI	4.0% (14/352)
Death	1.7% (6/352)
Cardiac Death	0.9% (3/352)
Non Cardiac Death	0.9% (3/352)
TVMI (Extended historical definition)	2.3% (8/352)
Clinically Driven TLR	2.0% (7/352)
Clinically Driven TVR	2.3% (8/352)
Stent Thrombosis (ARC) Definite/Probable)	0.6% (2/352)
Early Thrombosis (<=30 days)	0.3% (1/352)
Late Thrombosis (>30 and <=360 days)	0.3% (1/352)
Significant Bleeding Complications[4]	1.1% (4/352)
Stroke	0.9% (3/352)
3 Years	
TLF[1]	8.9% (31/347)
TVF[2]	10.1% (35/347)
MACE[3]	10.1% (35/347)
Composite Endpoint[4]	18.4% (64/347)
Cardiac Death or TVMI	6.6% (23/347)
Death or TVMI	7.8% (27/347)
Death	5.5% (19/347)
Cardiac Death	4.3% (15/347)
Non Cardiac Death	1.2% (4/347)
TVMI (Extended historical definition)	3.2% (11/347)
Clinically Driven TLR	3.2% (11/347)
Clinically Driven TVR	4.3% (15/347)
Stent Thrombosis (ARC) Definite/Probable)	1.2% (4/347)
Early Thrombosis (<=30 days)	0.3% (1/347)
Late Thrombosis (>30 and <=360 days)	0.3% (1/347)
Very Late Thrombosis (>360 days)	0.9% (3/347)
Significant Bleeding Complications5	1.2% (4/347)
Stroke	1.7% (6/347)

Table 8: Safety and Effectiveness Results – RESOLUTE Pooled CTO

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n)[9]
1.Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. 2.Cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization. 3.Death, myocardial infarction, (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically driven/clinically indicated) by percutaneous or surgical methods. 4.The combined clinical outcome of (all cause) mortality, Myocardial Infarction (Q-wave and non Q-wave), or (any) revascularization. 5.Bleeding complication is defined as a procedure related hemorrhagic event that requires a transfusion or surgical repair. These may include a hematoma requiring treatment of retroperitoneal bleed. Significant Bleeding complication is defined as the bleeding complication that has at least one of the following • Bleedings that led to an interruption of anti-platelet medication; • Bleedings that require transfusion; • Intracerebral bleedings; or • Bleedings that resulted in substantial hemodynamic compromise requiring treatment 6.The attainment of <50% residual stenosis of the target lesion using any percutaneous method. 7.The attainment of <50% residual stenosis of the target lesion using only the assigned device. 8.The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE. 9.Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage () was calculated as 100 × Extended historical definition of MI is used for all the composite endpoints. TVMI is composed of both Q wave and non-Q wave MI which are not clearly attributable to a non-target vessel. Q wave MI defined when any occurrence of 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, or 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 clinical scenario and appropriate cardiac enzyme data. Non-Q Wave MI is defined as elevated CK ≥ 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves. [Note: Periprocedural MIs (events <48 hours post-PCI) that did not fulfill the criteria for Q-wave MI are included in Non-Q Wave MI category. Periprocedural MIs did not require clinical symptoms or ECG evidence of myocardial ischemia, and in the absence of CK measurements, were based on an elevated CKMB > 3 X the upper laboratory normal, an elevated troponin > 3 X the upper laboratory normal, or CEC adjudication of the clinical scenario.]	

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of the Resolute Onyx stent is based on the results of preclinical studies leveraged from the original Resolute Onyx PMA, including biocompatibility, *in vivo* pharmacokinetics (generated on the Resolute product); *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and a newly conducted clinical study (PERSPECTIVE Study – RESOLUTE CTO Cohort).

The PERSPECTIVE Study was an investigator initiated, single center study that evaluated procedural and one-year clinical outcomes among consecutive subjects undergoing attempted percutaneous chronic total occlusion (CTO) revascularization. The prospective arm (N=250) of this study included 183 subjects treated with the Resolute Integrity stent which constituted the RESOLUTE CTO Cohort. The primary endpoint for this study was the MACE rate at 1 year compared to a performance goal derived from previous studies of DES in CTO revascularization. In this study MACE is defined as the composite of death, myocardial infarction (ARC defined), and clinically-driven target lesion revascularization. Pooled patient-level data from the Global RESOLUTE Clinical Program (RESOLUTE Pooled CTO analysis) is also provided in support of long-term safety and effectiveness of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System.

A. Effectiveness Conclusions

Among patients enrolled in the RESOLUTE CTO Cohort of the PERSPECTIVE Study, clinical success (achievement of <50% residual stenosis with ≥TIMI 2 flow) was reported as 92.3% (169/183). TLF at one year was reported to be 18.2% (33/181) and was driven by an in-hospital MI rate of 14.8% (27/183; ARC definition of MI).

In the supplementary RESOLUTE Pooled CTO analysis, lesion-based effectiveness, defined as the attainment of <50% residual stenosis of the target lesion using any percutaneous method, was reported to be 100% (526/526). Device success, defined as the attainment of <50% residual stenosis of the target lesion using only the assigned device, was reported to be 94.1% (496/527). Procedure success, defined as the attainment of <50% residual stenosis of the target lesion and no in-hospital MACE (Extended historical definition of MI), was reported to be 97.5% (348/357).

B. Safety Conclusions

The primary endpoint for the RESOLUTE CTO Cohort of the PERSPECTIVE Study (MACE rate at 1 year in the ITT primary analysis set) was 18.2% (33/181) with an upper one-sided 95% CI of 23.6%. This is lower than the prespecified performance goal of 25.2% and therefore meets criteria for success.

The risks associated with use of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System have been evaluated in the clinical studies discussed above along with non-clinical laboratory and animal studies leveraged from the original Resolute

Onyx™ PMA approval. The biocompatibility, in vivo pharmacokinetics (data generated on the Resolute product), and in vivo performance characteristics of the product provide a reasonable assurance of safety and acceptability for clinical use.

In summary the leveraged nonclinical data along with the results from the PERSPECTIVE Study (RESOLUTE CTO Cohort), supported by the CTO data from the Global RESOLUTE Clinical Program demonstrate that the Resolute DES family of stents provide reasonable assurance of safety and effectiveness when used according to the proposed indications for the treatment chronic total coronary occlusions.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study conducted to support PMA Supplement approval as described above. The Resolute Onyx™ DES has been shown to be beneficial for improving luminal diameter in patients with symptomatic coronary artery disease. The primary endpoint of major adverse cardiac events (MACE) in the RESOLUTE CTO Cohort of the PERSPECTIVE Study ITT primary analysis set at 12-months was 18.2% (33/181), fulfilling the pre-specified performance criterion with an upper one-sided 95% CI of 23.6%, compared with the performance goal of 25.2%. Event rates reported at one year for the RESOLUTE Pooled CTO subset include MACE rate of 5.7% (20/352), cardiac death rate of 0.9% (3/352), TLR rate of 2.0% (7/352), and a stent thrombosis rate of 0.6% (2/352).

Additional factors to be considered in determining probable risks and benefits for the Resolute Onyx™ DES include characterization of the disease, availability of alternative treatments, quality of the study design and conduct, robustness of analysis of study results, and risk mitigations. Coronary artery disease (CAD) can be accompanied by symptomatic chest pain or silent ischemia which affects patients' quality of life. CAD is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms and the need for revascularization. Available treatments for CAD include medical therapy, percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. When treatment for coronary artery disease beyond medications and lifestyle changes is warranted, patients often choose stent deployment over surgical revascularization due to shorter recovery times and the less invasive nature of percutaneous coronary intervention. The risks associated with use of drug eluting stents are already well established, and in comparison to medical therapy, PCI has been shown to reduce the incidence of angina. Patient tolerance of the stent device in the PERSPECTIVE Study is in line with expectations. The study did not exclude any typical patient subgroups that would be expected to benefit from treatment.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In summary, given the available information, the data support the conclusion that the probable benefits of the Resolute Onyx™ Zotarolimus-Eluting Stent System outweigh the probable risks for the improvement coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.0 mm to 5.0 mm, including the treatment of *de novo* chronic total occlusions.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the RESOLUTE CTO Cohort of the PERSPECTIVE Study and the Global RESOLUTE Clinical Program support the safety and effectiveness of the Resolute Onyx™ Zotarolimus-Eluting Coronary System for the treatment of de novo chronic total occlusions.

XIV. CDRH DECISION

CDRH issued an approval order on December 14, 2018. The final conditions of approval cited in the approval order for this panel-track supplement are described below.

1. The RESOLUTE ONYX CTO Post-Approval Study – The objective of the RESOLUTE ONYX CTO Post-Approval Study (PAS) is to demonstrate the generalizability of the performance the Resolute family of drug-eluting stents for the treatment of chronic total occlusions (CTOs) in a real-world setting. The RESOLUTE ONYX CTO PAS will consist of lesion- and patient-level meta-analyses of approximately 100 subjects with CTOs treated with the Resolute Onyx stent system that are enrolled in the Primary, XLV and Bifurcation Cohorts of the RESOLUTE ONYX Post-Approval Study and the ONYX ONE outside of the US randomized controlled trial. Subjects will be followed according to the procedures in each respective study. The primary safety and effectiveness endpoint will be freedom from MACE (Death, Myocardial Infarction, and clinically-driven target lesion revascularization) at 30 days. Secondary endpoints will include acute success (device, lesion, and procedure), cardiac death, target vessel MI, TLR, TLF, TVF, and stent thrombosis. The RESOLUTE ONYX CTO PAS does not have a formal hypothesis, but descriptive statistics will be provided. You must collect and report clinical outcomes to FDA through 2 years post-procedure on all patients included in the RESOLUTE ONYX CTO PAS.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Suttorp MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. Circulation 2006; 114(9); 921 – 928.

2. Kandzari DE, Kini AS, Karmpaliotis D, et al. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results From the EXPERT CTO Multicenter Trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions). J Am Coll Cardiol Intv 2015; 8(6); 761 – 769.