

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Eluting Coronary Stent System

Device Trade Name: Resolute Integrity 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: P110013/S088

Date of FDA Notice of Approval: December 14, 2018

The original PMA (P110013) was approved on February 17, 2012 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 ≤ 27 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 4.2 mm. The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110013b.pdf.

P11013/S005 was submitted to expand the indication for the Resolute Integrity Zotarolimus-Eluting Coronary Stent System to include lengths of 34 and 38 mm was approved on February 22, 2013. The SSED to support the indication is available on the CDRH website: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110013S005B.pdf. The current supplement was submitted to expand the indication for the Resolute Integrity Zotarolimus-Eluting Coronary Stent System to include the treatment of *de novo* Chronic Total Occlusions.

II. INDICATIONS FOR USE

The Resolute Integrity 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 2.25 mm to 4.2 mm. In addition, the Resolute Integrity Zotarolimus-Eluting Coronary Stent System is indicated for treating *de novo* chronic total occlusions.

III. CONTRAINDICATIONS

The Resolute Integrity stent system is contraindicated for use in patients with:

- 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 known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with 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 Integrity Zotarolimus-Eluting Coronary Stent System labeling.

V. DEVICE DESCRIPTION

The Resolute Integrity Zotarolimus-Eluting Coronary Stent System (Resolute Integrity) is a device/drug combination products comprised of two regulated components:

- A device component, which consists of an Integrity Bare Metal Coronary Stent on the MicroTrac Delivery System. The MicroTrac 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 Integrity product are described in **Table 1**.

Table 1: Resolute Integrity Product Description

	Resolute Integrity RX	Resolute Integrity OTW
Available Stent lengths (mm) ¹	8, 9, 12, 14, 15, 18, 22, 26, 30, 34, 38	
Available stent diameters (mm) ²	2.25, 2.5, 2.75, 3.0, 3.5, 4.0	
Stent Material	A cobalt-based alloy (MP35N) – the Integrity stent	
Drug Component	A coating of polymers loaded with zotarolimus is applied to the stent at a dose of approximately 1.6µg of zotarolimus per mm ² of stent surface area. The maximum nominal drug content on the largest stent (4.0 x 38 mm) is 380µg.	
Delivery System Working Length (cm)	140 cm	
Delivery System Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25cm from tip. Designed for guidewires ≤0.014”.	Y-Connector (Side arm for access to balloon inflation/ deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewires ≤0.014”
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: 9 ATM; Rated Burst Inflation Pressure: 2.25-3.5 mm = 16 ATM, 4.0mm = 15 ATM	
Guide Catheter Compatibility	0.056” minimum (5F)	
Distal Section Outer Diameter	2.7F	
Proximal Outer Diameter	2.1F	3.4F
¹	2.25, 2.5 and 2.75 mm diameter stents are not available in lengths of 9, 15, 34, and 38 mm	
²	3.0, 3.5 and 4.0 mm diameter stents are not available in lengths of 8 and 14 mm	

A. Device Component Description

The Resolute Integrity device component consists of the Integrity Coronary Stent pre-mounted onto an RX or OTW MicroTrac Delivery System. The stent is made from a cobalt-based alloy and is coated with a drug/polymer coating, which consists of a Parylene C primer coat, a BioLinx polymer and the active pharmaceutical ingredient (API), zotarolimus. The Resolute Integrity stent has a drug density of 1.6 µg/mm². The MicroTrac Delivery System provides a means for delivering the stent through the coronary vasculature and, once in the desired location, expands the stent through balloon inflation.

The Resolute Integrity uncoated stent is identical to the Integrity bare metal stent (P030009/S039).

The Resolute Integrity stent utilizes the same API as the Endeavor (P060033) and Endeavor Sprint (P060033/S001) Zotarolimus-Eluting Stent (DES) Systems, but feature a different polymer coating (BioLinx). The BioLinx polymer coating is intended to provide extended elution characteristics compared to the Endeavor and Endeavor Sprint products.

The MicroTrac delivery system utilizes the same principle of operation and features a similar design as the Sprint delivery system utilized for the Endeavor Sprint product, and the Sprinter Legend RX (P790017/S96) and NC Sprinter RX (P790017/S95) Balloon Dilatation Catheters.

B. Drug Component Description

The drug coating on Resolute Integrity stents consists of a Parylene C primer coating, a BioLinx polymer blend (inactive ingredient), and the active pharmaceutical ingredient (API), zotarolimus. Zotarolimus is the same API used in the Endeavor Sprint Zotarolimus-Eluting Coronary Stent System (P060033/S001).

B1. Active Ingredient: Zotarolimus

The active pharmaceutical ingredient utilized in Resolute Integrity 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]oxaazacyclohentacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown in **Figure 1**. The nominal dose of zotarolimus per nominal stent length/diameter for the product matrix is shown in **Table 2**.

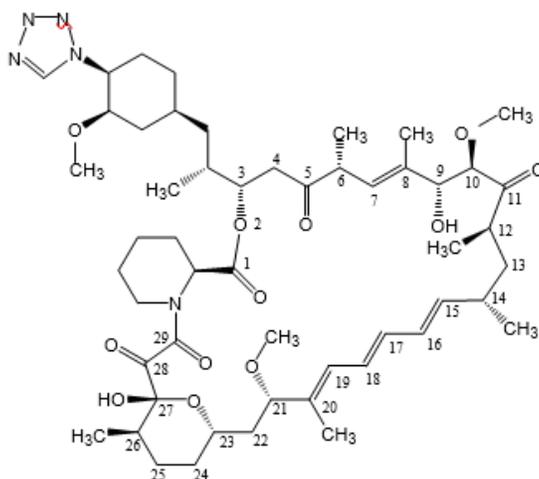


Figure 1: Chemical Structure of Zotarolimus

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 Integrity stents are covered with a Parylene C primer coating and a mixture of the drug zotarolimus and the BioLinx polymer. 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**.

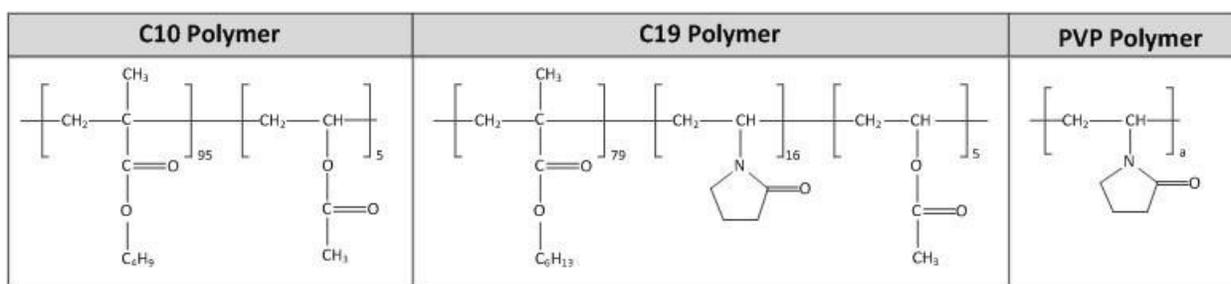


Figure 2: Chemical Structure of Biolinx Polymer Sub-units

Table 2: Product Matrix and Zotarolimus Content

Product Number Resolute Integrity OTW	Product Number Resolute Integrity RX	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSINT22508W	RSINT22508UX	2.25	8	59
RSINT25008W	RSINT25008UX	2.5	8	59
RSINT27508W	RSINT27508UX	2.75	8	59
RSINT30009W	RSINT30009UX	3.0	9	90
RSINT35009W	RSINT35009UX	3.5	9	90
RSINT40009W	RSINT40009UX	4.0	9	90
RSINT22512W	RSINT22512UX	2.25	12	85
RSINT25012W	RSINT25012UX	2.5	12	85
RSINT27512W	RSINT27512UX	2.75	12	85
RSINT30012W	RSINT30012UX	3.0	12	120
RSINT35012W	RSINT35012UX	3.5	12	120
RSINT40012W	RSINT40012UX	4.0	12	120
RSINT22514W	RSINT22514UX	2.25	14	102
RSINT25014W	RSINT25014UX	2.5	14	102
RSINT27514W	RSINT27514UX	2.75	14	102
RSINT30015W	RSINT30015UX	3.0	15	150

Table 2: Product Matrix and Zotarolimus Content

Product Number Resolute Integrity OTW	Product Number Resolute Integrity RX	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSINT35015W	RSINT35015UX	3.5	15	150
RSINT40015W	RSINT40015UX	4.0	15	150
RSINT22518W	RSINT22518UX	2.25	18	128
RSINT25018W	RSINT25018UX	2.5	18	128
RSINT27518W	RSINT27518UX	2.75	18	128
RSINT30018W	RSINT30018UX	3.0	18	180
RSINT35018W	RSINT35018UX	3.5	18	180
RSINT40018W	RSINT40018UX	4.0	18	180
RSINT22522W	RSINT22522UX	2.25	22	153
RSINT25022W	RSINT25022UX	2.5	22	153
RSINT27522W	RSINT27522UX	2.75	22	153
RSINT30022W	RSINT30022UX	3.0	22	220
RSINT35022W	RSINT35022UX	3.5	22	220
RSINT40022W	RSINT40022UX	4.0	22	220
RSINT22526W	RSINT22526UX	2.25	26	188
RSINT25026W	RSINT25026UX	2.5	26	188
RSINT27526W	RSINT27526UX	2.75	26	188
RSINT30026W	RSINT30026UX	3.0	26	260
RSINT35026W	RSINT35026UX	3.5	26	260
RSINT40026W	RSINT40026UX	4.0	26	260
RSINT22530W	RSINT22530UX	2.25	30	213
RSINT25030W	RSINT25030UX	2.5	30	213
RSINT27530W	RSINT27530UX	2.75	30	213
RSINT30030W	RSINT30030UX	3.0	30	300
RSINT35030W	RSINT35030UX	3.5	30	300
RSINT40030W	RSINT40030UX	4.0	30	300
RSINT30034W	RSINT30034UX	3.0	34	340
RSINT35034W	RSINT35034UX	3.5	34	340
RSINT40034W	RSINT40034UX	4.0	34	340
RSINT30038W	RSINT30038UX	3.0	38	380
RSINT35038W	RSINT35038UX	3.5	38	380
RSINT40038W	RSINT40038UX	4.0	38	380

C. Mechanism of Action

The mechanism (or mechanisms) by which Resolute Integrity stents affect neointimal production as seen in pre-clinical and clinical studies has not been established conclusively. *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.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of patients with coronary artery disease including exercise, diet, 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 Integrity Zotarolimus-Eluting Coronary Stent System is commercially available in the following countries:

Table 3: Resolute Integrity Commercial Availability

Albania	El Salvador	Lebanon	Romania
Algeria	Estonia	Libyan Arab Jamahiriya	Russia
Angola	Ethiopia	Liechtenstein	Saudi Arabia
Argentina	Fiji	Lithuania	Senegal
Armenia	Finland	Luxembourg	Serbia
Australia	France	Macao	Singapore
Austria	Georgia	Macedonia	Slovakia
Azerbaijan	Germany	Malaysia	Slovenia
Bahamas	Ghana	Malta	South Africa
Bahrain	Greece	Martinique	Spain
Bangladesh	Guadeloupe	Mauritius	Sri Lanka
Barbados	Guam	Mexico	Sudan
Belgium	Guatemala	Moldova	Sweden
Bolivia	Guyana	Montenegro	Switzerland
Bosnia & Herzegovina	Honduras	Morocco	Syrian Arab
Botswana	Hong Kong	Mozambique	Taiwan
Brazil	Hungary	Namibia	Tajikistan
Brunei Darussalam	Iceland	Nepal	Tanzania
Bulgaria	India	Netherlands	Thailand
Canada	Indonesia	New Zealand	Trinidad And Tobago
Canary Islands	Iran	Nicaragua	Tunisia
Cayman Islands	Iraq	Nigeria	Turkey
Chile	Ireland	Norway	Turkmenistan
China	Israel	Oman	Uganda
Colombia	Italy	Pakistan	United Arab Emirates
Costa Rica	Jamaica	Panama	United Kingdom
Cote D'Ivoire	Japan	Papua New Guinea	United States
Croatia	Jordan	Paraguay	Uruguay
Cyprus	Kazakhstan	Peru	Uzbekistan
Czech Republic	Kenya	Philippines	Venezuela
Denmark	Korea (South)	Poland	Vietnam

Table 3: Resolute Integrity Commercial Availability

Dominican Republic	Kosovo	Portugal	U.S. Virgin Islands
Dutch Antilles	Kuwait	Puerto Rico	Yemen
Ecuador	Kyrgyzstan	Qatar	
Egypt	Latvia	Reunion	

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 potential adverse effects (e.g., complications) associated with the use of Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems. 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 contract, 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 PMA (P110013). 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 STUDIES

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. 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 II¹ and EXPERT CTO² 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 not 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. Follow-up Schedule

All patients were scheduled for follow up contacts at six months (180 days \pm 14 days) and one year (365 days \pm 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 \pm 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.

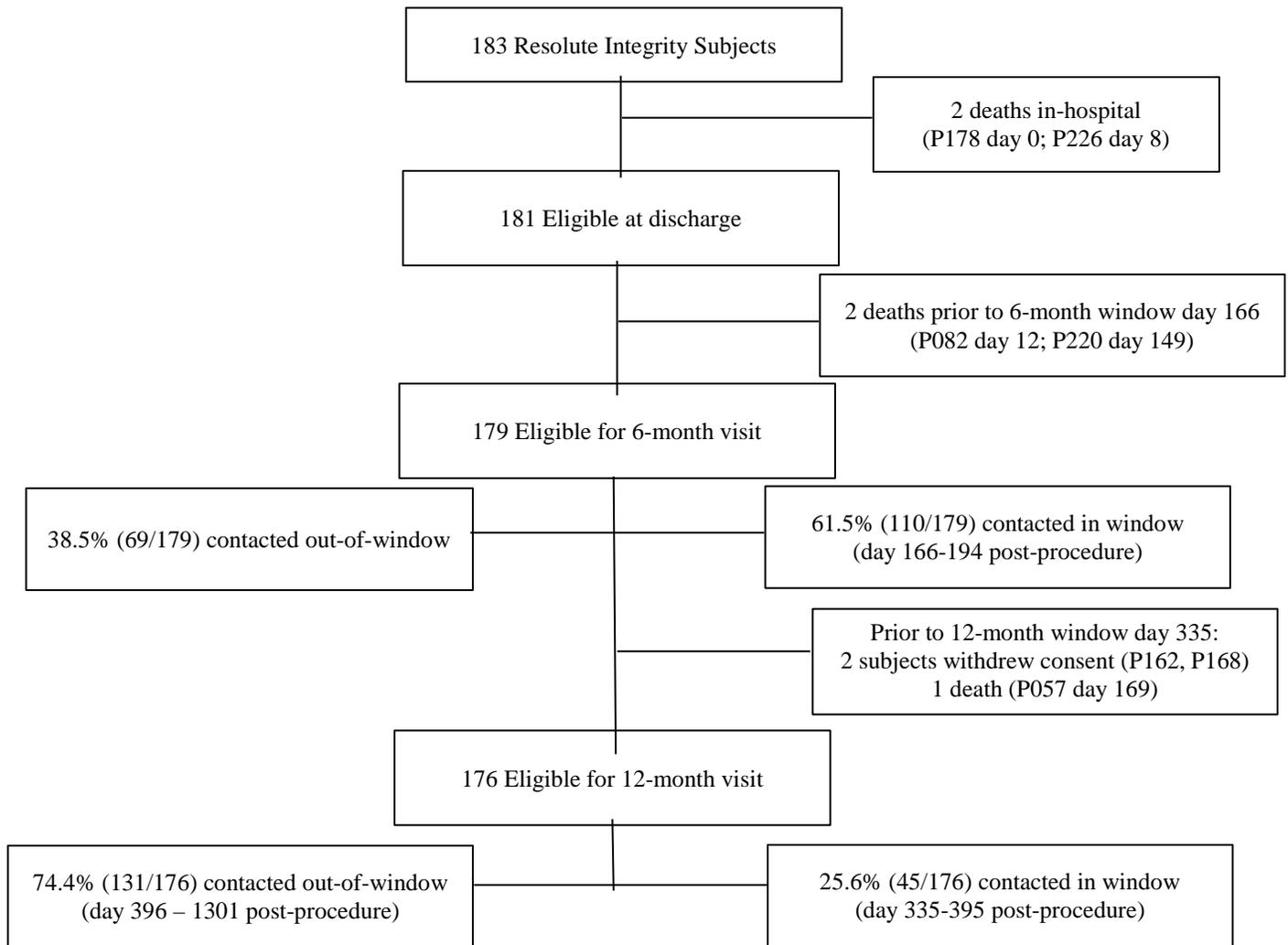


Figure 3: Accountability Flow Chart - PERSPECTIVE Study RESOLUTE CTO Cohort

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 was 16.0% (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 \geq 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)

¹Achievement of <50% residual stenosis with ≥TIMI 2 antegrade flow
²Successful 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 Integrity 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 Complications ⁵	1.2% (4/347)

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
Stroke	1.7% (6/347)
<p>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.</p> <p>2.Cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization.</p> <p>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.</p> <p>4.The combined clinical outcome of (all cause) mortality, Myocardial Infarction (Q-wave and non Q-wave), or (any) revascularization.</p> <p>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.</p> <p>Significant Bleeding complication is defined as the bleeding complication that has at least one of the following scenarios:</p> <ul style="list-style-type: none"> • 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 <p>6.The attainment of <50% residual stenosis of the target lesion using any percutaneous method.</p> <p>7.The attainment of <50% residual stenosis of the target lesion using only the assigned device.</p> <p>8.The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.</p> <p>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 $100 \times (m/n)$</p> <p>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 $\geq 2X$ 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.]</p>	

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 Integrity Zotarolimus- Eluting Coronary Stent System stent is based on the results obtained from biocompatibility, in vivo pharmacokinetics; 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 Integrity 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 \geq 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 Integrity 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

Integrity 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 Integrity™ 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 Integrity™ 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 Integrity™ 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 2.25 mm to 4.2 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 Integrity 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, Karpaliotis 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.