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, Inc.
3576 Unocal Place
Santa Rosa, CA 95403
USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160043

Date of FDA Notice of Approval: April 28, 2017

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 2.25 mm to 5.0 mm.

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 Delivery Systems			
	Stent Design 1 (Small Vessel)	**Stent Design 2 (Medium Vessel)**	**Stent Design 3 (Large Vessel)**	**Stent Design 4 (Extra Large Vessel)**
Available Stent Diameters (mm)	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	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			

Table 1: Device Component Description and Nominal Dimensions

Component		Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Rapid Exchange and Over-the-Wire Delivery Systems			
		Stent Design 1 (Small Vessel)	**Stent Design 2 (Medium Vessel)**	**Stent Design 3 (Large Vessel)**	**Stent Design 4 (Extra Large Vessel)**
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: 2.25-4.0mm = 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, 2.25-5.0mm: 2.1 F (0.69 mm) Distal Shaft OD, 2.25-4.0mm: 2.7 F (0.91 mm) Distal Shaft OD, 4.5 and 5.0mm: 3.2 F (1.07 mm)			
	OTW	Proximal Shaft OD: 3.4 F (1.12 mm) Distal Shaft OD: 2.7 F (0.91 mm)			

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™ cornary 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 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 2.25 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**.

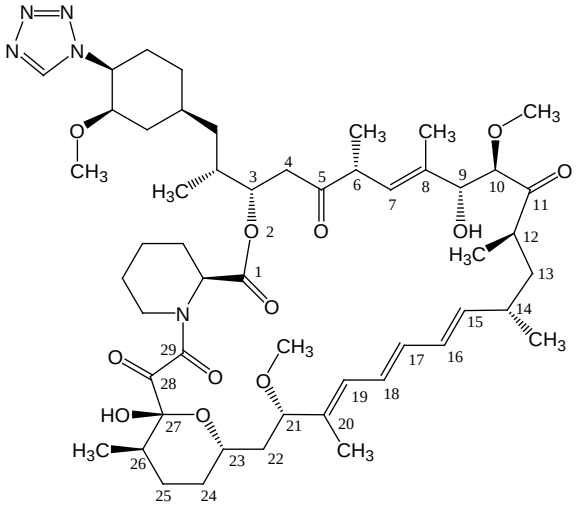


Figure 1: Chemical Structure of Zotarolimus

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 $C_{52}H_{79}N_5O_{12}$ 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**.

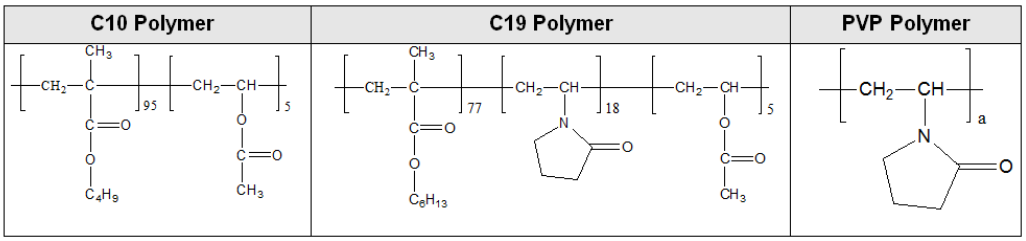


Figure 2: Chemical Structure of Biolinx Polymer Sub-units

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 (mm)	Nominal Zotarolimus Content RX (µg)	Nominal Zotarolimus Content OTW (µg)
RONYX22508UX	RONYX22508W	2.25	8	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
RONYX22512UX	RONYX22512W	2.25	12	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
RONYX22515UX	RONYX22515W	2.25	15	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
RONYX22518UX	RONYX22518W	2.25	18	104	104
RONYX25018UX	RONYX25018W	2.5		104	104

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 (mm)	Nominal Zotarolimus Content RX (µg)	Nominal Zotarolimus Content OTW (µg)
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
RONYX22522UX	RONYX22522W	2.25	22	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
RONYX22526UX	RONYX22526W	2.25	26	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
RONYX22530UX	RONYX22530W	2.25	30	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 leads to inhibition of cell cycle progression from the G1 to the S phase. **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:

Algeria	El Salvador	Kyrgyzstan	Romania
Argentina	Estonia	Latvia	Russian Federation
Armenia	Finland	Lebanon	Saudi Arabia
Australia	France	Lithuania	Singapore
Austria	Germany	Malaysia	Slovakia
Azerbaijan	Greece	Mexico	Slovenia
Bahrain	Guatemala	Morocco	South Africa
Bangladesh	Honduras	Namibia	Spain
Belgium	Hong Kong	Nepal	Sri Lanka
Bolivia	Hungary	Netherlands	Sweden
Botswana	Iceland	New Zealand	Switzerland
Brunei Darussalam	India	Norway	Tajikistan
Bulgaria	Iran	Oman	Tanzania
Colombia	Ireland	Pakistan	Thailand
Costa Rica	Israel	Panama	Trinidad And Tobago
Croatia	Italy	Paraguay	Tunisia
Czech Republic	Jordan	Philippines	Turkey
Denmark	Kazakhstan	Poland	United Arab Emirates
Dominican Republic	Kenya	Portugal	United Kingdom
Ecuador	Korea, Republic Of	Qatar	Venezuela
Egypt	Kuwait	Reunion	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

For the specific adverse events that occurred in the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study, please see **Section X** below.

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies related to the Resolute Onyx™ system were performed. Studies included those performed on the bare metal stent (Onyx or Integrity stent mounted on the respective delivery system), the coated stent alone, the polymer-only coated stent alone, or the finished combination products. These evaluations included animal studies, *in vivo* pharmacokinetics, biocompatibility studies, *in vitro* engineering tests, coating characterization, chemistry, manufacturing, and controls (CMC) testing, sterilization, stability and shelf life.

A. Laboratory Studies

A1. Biocompatibility

A biocompatibility evaluation was conducted to ensure the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System met the requirements of the international standard ISO 10993-1 (Biological Evaluation of Medical Devices) and that its

associated materials, manufacturing processes, and sterilization resulted in a safe and biocompatible product.

Biological evaluation of the Resolute Onyx™ product took into account the chemical characteristics of the product materials and the nature and duration of their exposure in the body. The tests described in this section were selected in accordance with the guidance provided in ISO 10993-1 and were performed in compliance with Good Laboratory Practices (GLP), which are contained in Medtronic's biocompatibility testing guidelines and satisfy the requirements of international guidelines for blood contact/implant materials.

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); therefore the biocompatibility testing previously performed on the drug/polymer component of the Resolute and Resolute Integrity coronary stents is representative of the Resolute Onyx™ product. 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. Accordingly, biocompatibility evaluation for the Resolute Onyx™ product was performed with non-coated, bare-metal stents.

Table 3 outlines the biocompatibility testing performed to support the biologicalsafety of the Resolute Onyx™ bare metal stent and the Resolute Onyx™ RX delivery system. **Table 4** outlines the biocompatibility testing performed to support the biological safety of the drug/polymer coating. **Table 5** outlines the biocompatibility testing performed to support the biological safety of the Resolute Onyx OTW delivery system.

Table 3: Summary of Resolute Onyx™ Biological Safety Evaluation of Onyx Bare™ Metal Stent and RX Delivery System

Test Name per ISO 10993-01	Test Description	Test Article	Result
Cytotoxicity	MHLW Cytotoxicity using the Colony Assay	S, DS	PASS
	ISO Direct Contact Cytotoxicity	S, DS	PASS
Sensitization	ISO Maximization Sensitization	S, DS	PASS
Intracutaneous Reactivity	ISO Intracutaneous Reactivity	S, DS	PASS
Systemic Toxicity (Acute)	MHLW Acute Systemic Toxicity	S	PASS
	ISO Acute Systemic Toxicity	DS	PASS
	USP Material Mediated Pyrogen	S, DS	PASS
Subacute/Subchronic Toxicity	4 Week Systemic Toxicity	S	PASS
	13 Week Systemic Toxicity	S	PASS
Genotoxicity	In-vitro Bacterial Reverse Mutation	S	PASS
	In-vitro Chromosomal Aberration	S	PASS
	In-vivo Mouse Peripheral Blood Micronucleus	S	PASS
Haemocompatibility	ASTM *In-vitro* Hemolysis, Direct and Indirect	S, DS	PASS
	C3a & SC5b-9 Complement Activation	S, DS	PASS

Table 3: Summary of Resolute Onyx™ Biological Safety Evaluation of Onyx Bare™ Metal Stent and RX Delivery System

Test Name per ISO 10993-01	Test Description	Test Article	Result
	In-vivo Thromboresistance	S, DS	PASS
S = Stent Testing DS = Delivery System Testing			

Table 4: Summary of Previous Resolute Stent Testing (Supports Biological Safety of Drug/Polymer Coating)

Test Category per 10993-01	Test Description	Results
Cytotoxicity	MHLW Cytotoxicity using the Colony Assay	PASS
	ISO Direct Contact Cytotoxicity	PASS
Sensitization	ISO Maximization Sensitization	PASS
	Murine Local Lymph Node Assay	PASS
Intracutaneous Reactivity	ISO Intracutaneous Reactivity	PASS
Systemic Toxicity (Acute)	MHLW Acute Systemic Toxicity	PASS
	ISO Acute Systemic Toxicity	PASS
	USP Material Mediated Pyrogen	PASS
Subacute/Subchronic Toxicity	4wk & 13wk Systemic Toxicity following Subcutaneous Implantation	PASS
Genotoxicity	In-vitro Bacterial Reverse Mutation	PASS
	In-vitro Chromosomal Aberration	PASS
	In-vivo Mouse Peripheral Blood Micronucleus	PASS
Implantation	12wk Muscle Implant	PASS
Hemocompatibility	ASTM In-vitro Hemolysis, Direct and Indirect	PASS
	C3a & SC5b-9 Complement activation	PASS
	In-vivo Thromboresistance	PASS

Table 5: Summary of Supportive Biological Safety Evaluation from Resolute Integrity OTW Delivery System

Test Category per ISO 10993-01	Test Description	Results
Cytotoxicity	MHLW Cytotoxicity using the Colony Assay	PASS
Sensitization	MHLW Sensitization	PASS
	Murine Local Lymph Node Assay	PASS
Intracutaneous Reactivity	ISO Intracutaneous Reactivity	PASS
Systemic Toxicity (Acute)	ISO Acute Systemic Toxicity	PASS
	USP Material Mediated Pyrogen	PASS
Haemocompatibility	ASTM *In-vitro* Hemolysis, Indirect	PASS
	C3a & SC5b-9 Complement Activation	PASS

A2. *In-Vitro* Testing

In vitro engineering testing has been completed in accordance with the following:

- FDA Guidance: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 2010
- Guidance for Industry and Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, 13 January 2005 and
- FDA recommendation
- 21CFR §814.20(b)(6)(i),
- 21 CFR §820.30(f),
- 21 CFR§210/211

Testing was conducted on devices representative of Resolute Onyx™ (both RX and OTW delivery systems), except in cases in which testing could be leveraged from Resolute Integrity.

The *in-vitro* engineering studies, which support the performance of Resolute Onyx™, are provided in **Table 6**. "Pass" denotes that the test results met product specifications and/or the recommendations in the above-referenced guidance documents.

Table 6: *In Vitro* Testing Supporting the Performance of Resolute Onyx

Test	Description of Test	Results
Material Characterization		

Table 6: *In Vitro* Testing Supporting the Performance of Resolute Onyx

Test	Description of Test	Results
Material Composition (Stent)	This test verified that stents are produced from material that conforms to the chemical composition requirements of ASTM F562 and B684.	PASS
Material Composition (Delivery System)	This test verified that the delivery system materials were documented.	PASS
Stent Corrosion – Galvanic	This test evaluated whether galvanic coupling Resolute Onyx with 316L stainless steel may promote accelerated corrosion of either stent. The testing conducted with consideration of methods described in ASTM G71. Stents were tested after simulated use by tracking through a tracking fixture based on ASTM F2394-04.	PASS
Stent Corrosion – Pitting Crevice	This test determined the relative susceptibility of the stent to localized corrosion. Testing was conducted with consideration of the methods described in ASTM F2129. Testing was conducted on as-manufactured stents as well as post-fatigue stents. As-manufactured stents were tested after simulated use by tracking through a tracking fixture based on ASTM F2394-04.	PASS
Stent Corrosion - Fretting	This test evaluated the risk of stent failure caused by fretting corrosion of the Resolute Onyx stent with overlapped stents.	PASS
Physicochemical Testing of Plastics	This test confirmed that the materials for Resolute Onyx on the Delivery System that come in direct contact with the drug meet the acceptance criteria for USP physicochemical testing for plastics. The test assessed the physical and chemical properties of the materials by evaluating an extraction of the plastic material. Samples were tested for non-volatile residue, residue on ignition, heavy metals, and buffering capacity per USP <661>.	PASS
Stent Dimensional and Functional Testing		
Cell Perimeter	This test quantified the cell perimeter within a stent. Cell perimeter gives an indication of maximum side branch opening possible.	PASS
Inscribed Circle	This test quantified the maximum inscribed circle diameter of the cells. Maximum inscribed circle diameter is used to characterize the ease of side branch access with a guidewire or a secondary device.	PASS
Deployed Stent Length	This test demonstrated that the stent length is consistent with labeling when deployed at nominal pressure.	PASS

Table 6: *In Vitro* Testing Supporting the Performance of Resolute Onyx

Test	Description of Test	Results
Stent Foreshortening at Nominal Diameter	This test measured the change in stent length from the catheter-loaded condition to deployment at nominal pressure. Testing was conducted with consideration of the methods described in ASTM F2081.	PASS
Stent Foreshortening at Maximum Diameter	This test determined the change in length as a function of stent inner diameter. Testing was performed at maximum labeled diameter. Testing was conducted with consideration of the methods described in ASTM F2081.	PASS
Metal to Artery Ratio	The metal to artery ratio relates the amount of vessel wall that is supported by the stent to the amount that is not for all stent diameters.	PASS
Stent Crossing Profile	This test verified that the stent crossing profiles of Resolute Onyx is consistent with label claims. Testing was conducted with considerations of the methods described in ASTM F2081. All samples met product specifications.	PASS
Strut Thickness	Strut thickness was quantified on the Resolute Onyx stent.	PASS
Stent Integrity	This test determined if the stress and strain experienced by the stent when expanded from the undeployed diameter to the final maximum deployed diameter can result in fractures.	PASS
Accelerated Stent Durability	This test evaluated the risk of stent failure caused cyclical loading of Resolute Onyx stents deployed in an overlapped configuration on a 1.5cm radius bend after a simulated 10 year period.	PASS
Stent Distortion	This test evaluated the force required to deform a stent after catching a post dilation balloon catheter while attempting to cross the stent.	PASS
Stent Recoil	This test quantified the elastic recoil of the stent. Testing was conducted with consideration of the methods described in ASTM F2079.	PASS
Stent Radial Stiffness	This test determined the stents resistance characteristics when exposed to radial loading. Both the diameter and the loading force were captured for this evaluation.	PASS
Stent Radial Strength (Stent Crush Resistance)	This test determined the change in stent diameter as a function of circumferential pressure equivalent to expected *in-vivo* loading.	PASS
Stent Retention	This test measured the force required to remove a stent proximally and distally from a balloon.	PASS

Table 6: *In Vitro* Testing Supporting the Performance of Resolute Onyx

Test	Description of Test	Results
MRI Safety and Compatibility (MRI Conditional)	This test characterized the interaction of the stent during MR Imaging with respect to: -Force Displacement -Torque Displacement -RF Induced Heating -Image Artifact Generation Where appropriate testing was conducted at 1.5 and/or 3.0 Tesla on single and overlapped with consideration of the methods described in ASTM guidelines F2052, F2213, F2119, F2182 as appropriate.	PASS
Compliance	This test characterized the stent inner diameter as a function of balloon inflation pressure.	PASS
FEA (Finite Element Analysis)	This test analyzed each stent design using finite element analysis model. The stress analysis identified critical stress locations and magnitudes and the fatigue analysis plotted the calculated stresses on a combined Goodman and Gerber diagram.	PASS
Stent ID	This test quantified the stent inner diameter, when deployed to Nominal pressures, along the stent length.	PASS
Stent ID Delta	This test quantified the maximum difference in stent ID along the length of the stent, when deployed at Nominal pressure.	PASS
Stent to Markerband Gap (proximal and distal)	This test characterized the gap between the proximal marker band the proximal longest crown, as well as the distal marker band and the distal longest crown of the stent.	PASS
Balloon Overhang	This test characterized the distance between the end of the stent to the end of the balloon working length on both proximal and distal ends.	PASS
Delivery System Dimensional and Functional Testing		
Balloon Bond Tensile	This test demonstrated that each delivery system met the design requirements for balloon bond tensile.	PASS
Balloon Bond Yield	This test demonstrated that each delivery system met the design requirements for balloon bond yield.	PASS
Exchange Joint Tensile	This test demonstrated that the delivery system met the design requirements for exchange join tensile.	PASS
Hypotube Bond Tensile	This test demonstrated that the delivery system met the design requirements for hypotube bond tensile.	PASS

Table 6: *In Vitro* Testing Supporting the Performance of Resolute Onyx

Test	Description of Test	Results
Stiffening Wire to Hypotube Tensile	This test demonstrated that the delivery system met the design requirements for stiffening wire to hypotube tensile.	PASS
Luer to hypotube Tensile	This test demonstrated that the delivery system meets the design requirements for luer to hypotube tensile.	PASS
Catheter Effective Length (Catheter Tip to Strain Relief)	This test measured the length of the catheter from the distal tip to the strain relief.	PASS
Exchange Joint Distance	This test measured the distance from the balloon bond to the exchange joint for the delivery systems.	PASS
Distal Shaft to Marker Distance	This test measured the distance from the balloon bond to the distal end of the distal exit marker.	PASS
Balloon Fatigue	This test demonstrated the repeatability of successful unconstrained balloon inflation to the rated burst pressure (RBP).	PASS
Kink Resistance	This test demonstrated that the catheter can conform to a minimum radius without kinking.	PASS
Catheter Torque Strength	This test demonstrated the number of rotations the catheter can withstand prior to fracture	PASS
Balloon Deflation and Inflation Time	This test characterized the inflation time to RBP and the time required for the product to deflate from RBP.	PASS
Hydrophilic Coating Presence and Visual Integrity	This test evaluated the hydrophilic coating presence and the condition of coating pre- and post- tracking.	PASS
Maximum Catheter Profile: -Distal Tubing OD -Tip Seal OD -Balloon Bond OD -Exchange Joint OD -Hypotube Bond OD -Proximal Shaft OD	This test verified that the crossing profile of the delivery system is consistent with the labeling.	PASS
Stent Movement (Lesion Crossability)	This test characterized the ability of the stent to resist shifting/dislodgement while passing through a simulated lesion.	PASS

Table 6: *In Vitro* Testing Supporting the Performance of Resolute Onyx

Test	Description of Test	Results
Pull Back	This test evaluated stent dislodgement by reverse motion when the stent is withdrawn into a guide catheter with a minimum guide catheter inner diameter in accordance with labeling.	PASS
Rated Burst Pressure (RBP)	This test demonstrated that the delivery system (with mounted stent) does not experience loss of integrity of balloon, shaft, proximal adapter or proximal/distal seal at or below the pressure required to expand the stent to the Rated Burst Pressure (RBP). The results demonstrated with 95% confidence that at least 99.9% of devices would not rupture below the rated burst pressure.	PASS
Compatibility with existing catheterization lab accessories and equipment	This test demonstrated the ability of the delivery system to be prepared and tracked through a tortuous path and simulated vessel. Retraction forces of the delivery system post deployment from the stent were also measured.	PASS
Compatibility with existing catheterization lab accessories and equipment (KBT)	This test assessed the ability to track a balloon dilation catheter, while the stent delivery system is in position, through a 6F guide, a tortuous path and deploy/inflate in a vessel. Tracking and Retraction forces of the balloon dilation catheter as it passes the stent delivery system pre- and post- deployment were recorded.	PASS
OTW specific Delivery System Testing		
Maximum Catheter Profile - Proximal Shaft OD- Trans Bond OD	This test verified that the crossing profile of the delivery system for Resolute Onyx OTW is consistent with label claims.	PASS
Transition Bond Tensile	This test demonstrated that the delivery system meets the design requirements for Transition Bond tensile.	PASS
Bifurcate/Proximal Shaft Bond Tensile	This test demonstrated that the delivery system meets the design requirements for Bifurcate/Proximal Shaft Bond tensile.	PASS
Proximal/Distal Inner Shaft Tensile	This test demonstrated that the delivery system meets the design requirements for Proximal/Distal Inner Shaft tensile.	PASS

A3. Coating Characterization and Analytical Testing

The coating characterization testing conducted includes the tests summarized in **Table 7**.

Table 7: Coating Characterization and Analytical Testing

Test	Description of Test
Chronic Coating Durability	This test characterizes the stent coating integrity after being subjected to simulated 10 years of heated radial fatigue post tracking and deployment in an overlapped configuration.
System Particulate	This test quantified particulate matter after a single stent had been tracked through a tortuous fixture and deployed in a bent configuration.
System Particulate (Simulated Use)	This test quantified particulate matter after 2 stents had been tracked through a tortuous fixture and deployed in a bent and overlapped configuration (simulated use).
SEM Surface Imaging (coated stent): • Pre-Deploy • Track & Deploy at maximum labeled diameter	This test visually assessed the coating integrity of a crimped stent and a single stent deployed to maximum labeled diameter in a mock vessel after tracking through a tortuous fixture (simulated use)
Coating Durability	This test quantified particulate matter after deployment of a single stent in an aqueous solution in 2 configurations: -to nominal (baseline) -to maximum labeled diameter (over expansion)
Drug Dose Density	This test measured the uniformity of the drug content along the length of the finished Resolute Onyx stent un-tracked.

A4. Analytical (CMC) Release Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines are followed for the testing routinely performed on the Resolute Onyx stents as part of CMC. This testing is summarized in **Table 8**. All testing met the specifications established for finished goods release. Information to support the stability of the Resolute Onyx stent is summarized separately in Section B6 – Stability.

Table 8: Analytical Release (CMC) Testing

Test	Description of Test
Determination of Total Drug Content (Potency and Content Uniformity)	The objective of this test is to identify and quantify zotarolimus in the Resolute Onyx stent.
Determination of Total Drug Degradants and Impurities	The objective of this test is to quantify degradants or impurities on the finished Resolute stents.
Determination of Butylated Hydroxytoluene (BHT)	The objective of this test is to quantify the BHT content of the finished Resolute stent

Table 8: Analytical Release (CMC) Testing

Test	Description of Test
Determination of Residual Solvents	The objective of this test is to quantify the residual solvents, used in manufacturing of finished Resolute stents,
Elution Testing	The objective of this test is to characterize the *in vitro* elution profile of Resolute stents.
Particulate Testing	The objective of this test is to use the light obscuration particle count method for the determination of particulate matter on Coronary Stent Systems that have been tracked, deployed and expanded to rated burst pressure (RBP), simulating clinical procedure.

A5. Sterilization

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (RX and OTW) is sterilized using ethylene oxide sterilization, and has been validated per AAMI/ISO 11135-1:2007 "Sterilization of health care products-Ethylene Oxide – Part 1:Requirements for development, validation and routine control of a sterilization process for medical devices" and EN556-1:2002 "Sterilization of Medical Devices – Requirements for medical devices to be designated STERILE – Part 1: Requirements for terminally sterilized medical devices". Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

A6. Stability and Shelf Life

Manufacturing site-specific aging and stability studies were conducted to establish an expiration date for the Resolute Onyx™ product. Appropriate engineering tests were performed on aged product to ensure that Resolute Onyx™ product performed acceptably. Testing in support of package integrity of the stent systems was also conducted on aged product. Stability testing included evaluation of drug identity, drug content, degradants/impurities, related substances/BHT, elution, particulates, sterility, BET, drug content uniformity and residual solvents. The data generated from the *in vitro* shelf life studies, coupled with the data generated from the stability studies supports a 24-month label claim and associated shelf life for the product.

B. Animal Studies

B1. Preclinical Testing

Three GLP Preclinical studies were performed to support the deliverability, deployment, and safety of the Resolute Onyx product in a porcine coronary artery model. All animal testing was performed in compliance with the Good Laboratory Practice regulations., as set forth in 21 CFR Part 58, These were multi-site studies and selected phases at the test sites were monitored to ensure GLP compliance. **Table 9** provides a summary of the preclinical studies conducted for the Resolute Onyx™ product.

Table 9: Summary of Resolute Onyx™ Preclinical Testing

Study ID	No. of Animals	Type of Animals	Duration	Test and Control Article	Stent Size	Major Endpoints
FS222 5 Day Safety Study and Acute Deliverability	22	Yucatan mini Swine	5 Days	Test: Medtronic Resolute Onyx Drug Eluting Stent System Control: Medtronic Integrity Bare Metal Stent on the MicroTrac RX Stent System	3.0 x 18 mm; single stent implants 3.0 x 12 mm; overlapping implants	Acute Performance, Angiographic Performance, Morphometric Analysis, Histopathology, SEM Analysis
FS223 28 Day Safety Study	24	Yucatan mini Swine	28 days	Test: Medtronic Resolute Onyx Drug Eluting Stent System Control: Medtronic Integrity Bare Metal Stent on the MicroTrac RX Stent System	3.0 x 18 mm; single stent implants 3.0 x 12 mm; overlapping implants	Angiographic Performance, Morphometric Analysis, Histopathology, SEM Analysis
FS224 90 Day Safety Study	23	Yucatan mini Swine	90 Days	Test: Medtronic Resolute Onyx Drug Eluting Stent System	3.0 x 18 mm; single stent implants 3.0 x 12 mm;	Angiographic Performance, Morphometric Analysis, Histopathology, SEM Analysis

Table 9: Summary of Resolute Onyx™ Preclinical Testing

Study ID	No. of Animals	Type of Animals	Duration	Test and Control Article	Stent Size	Major Endpoints
				Control: Medtronic Integrity Bare Metal Stent on the MicroTrac RX Stent System	overlapping implants	

B2. *In Vivo* Pharmacokinetics

No new *in vivo* pharmacokinetic studies were performed on the Resolute Onyx™ product as the *in-vivo* Pharmacokinetics data (provided in support of the commercial Resolute Integrity product) are directly applicable to the Resolute Onyx™ product. Pharmacokinetic data on the Resolute Integrity product can be found in the Resolute Integrity (P110013) SSED.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study in the United States to establish a reasonable assurance of safety and effectiveness of percutaneous coronary intervention with the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System 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 under IDE G140178. Data from this clinical study, in conjunction with data generated in the Global RESOLUTE Clinical Trial Program were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between July 7, 2015 and November 4, 2015. The database for this PMA reflected data collected through August 19, 2016 and included 75 patients. There were eleven enrolling investigational sites.

The Medtronic RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study was a single arm, open label, multi-center trial enrolling at least 75 subjects with ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with stenting. Subjects were to receive treatment of one or two lesions with stent diameters 2.25 mm - 4.0 mm, one lesion per target vessel, for a maximum of two target vessels. Only one lesion was to be treated in a

single target vessel. All treatment with the study stents was to be performed during a single index procedure.

If a subject became unstable before a study stent was attempted (stent introduced into guide catheter), the subject was not to be enrolled, or followed, and would not be included in the primary analysis of this trial. Another subject was to be enrolled to replace this subject for the primary analysis. If treatment with the Resolute Onyx stent was attempted (stent introduced into guide catheter) but not implanted, the subject would be considered part of the Intention-to-Treat population (ITT), followed through the 8 month endpoint, and included in the primary analysis of this trial. After the 8 month follow up, these subjects would exit the study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study study was limited to patients who met the following Key Inclusion Criteria:

- Must be an acceptable candidate for percutaneous coronary intervention (PCI), stenting, and emergent coronary artery bypass graft (CABG) surgery
- Must have clinical evidence of ischemic heart disease, stable or unstable angina, and/or a positive functional study
- Must require treatment of either
  - a single target lesion amenable to treatment OR
  - two target lesions located in separate target vessels
- Target lesion(s) must be *de novo* lesion(s) in native coronary artery(ies)

Patients were not permitted to enroll in the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study if they met any of the following Key Exclusion Criteria:

- Known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, thienopyridines, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g. BioLinx) or a sensitivity to contrast media, which cannot be adequately pre-medicated
- History of an allergic reaction or significant sensitivity to drugs such as zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative
- History of a stroke or transient ischemic attack (TIA) within the prior 6 months
- Active peptic ulcer or upper gastrointestinal (GI) bleeding within the prior 6 months
- History of bleeding diathesis or coagulopathy or will refuse blood transfusions
- Concurrent medical condition with a life expectancy of less than 12 months

- Currently participating in an investigational drug or another device trial that has not completed the primary endpoint
- Documented left ventricular ejection fraction (LVEF) < 30% at the most recent evaluation

2. Follow-up Schedule

   All patients were scheduled for follow up contacts at 30 days (± 5 days), 6 months (± 14 days), and then annually (1, 2, and 3 years ± 30 days) postoperatively. All patients were to return for angiographic assessment at 8 months (± 14 days) including IVUS assessment if participating in the IVUS subset. The key timepoints are shown in **Table 10**.

Table 10: Schedule of Treatments and Assessments

Index Hospitalization						Follow-up Assessments			
Event	**Screening/Pre-procedure**			**Proced.**	**Post-proced.[1]**	**30 Day, 6 Month**	**8 Month**	**12 Month**	**24, 36 Months**
	Screen	**Prior to procedure within:**				**Subject Contact[2]**	**Clinic Visit**	**Subject Contact[2]**	**Subject Contact[2]**
		7 days	**72 hours**						
Informed Consent signed	X								
Medical and cardiac history	X								
Angina	X				X	X	X	X	X
Pregnancy		X							
Creatinine		X							
WBC[6] with Plts		X							
12 lead ECG[6]		X			X Within 24 hours				
CK[4,6] and Troponin			X		X 1st: >3hrs 2nd: >4 hrs after 1st, < 24 hrs				
QCA[6]				X			X		
IVUS[5,6]				X			X		
AE[6] monitoring				X	X	X	X	X	X SAEs[6] only

Antiplatelet medications	X Within 24 hours				X	X	X	X	X

1. End of procedure is defined as removal of the guide catheter
2. Subject contact includes phone call, email or clinic visit
3. For women of childbearing potential only
4. If it is not standard hospital practice to measure CK values, CK-MB values are sufficient. All subjects should have Troponin values.
5. IVUS subset only
6. Definitions: WBC (White Blood Cell), ECG (Electrocardiogram), CK (Creatine Kinase), QCA (Quantitative Coronary Angiography), IVUS (Intravascular Ultrasound), AE (Adverse Event), SAE (Serious Adverse Event).

3. Clinical Endpoints

Primary Endpoint(s)

In-stent late lumen loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA).

Key Secondary Endpoint(s)

Secondary endpoints of the trial include the following:

Clinical Endpoints:

- Acute Success (Device, Lesion, Procedure)
- The following secondary endpoints will be assessed at hospital discharge, 30 days, 6 months, 8 months and 12 months post-procedure, and annually thereafter through year 3:
    - Cardiac Death
    - Target Vessel Myocardial Infarction (TVMI)
    - Cardiac Death and TVMI
    - Target Lesion Revascularization (TLR)
    - Major Adverse Cardiac Event (MACE)
        - Defined as death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically-driven repeat target lesion revascularization by percutaneous or surgical methods
    - Target Lesion Failure (TLF)
    - Target Vessel Failure (TVF)
    - Stent Thrombosis (ST)

Angiographic Endpoints at 8 Months:

- In-segment Late Lumen Loss (LL)
- Binary Angiographic Restenosis (BAR)

- Percent Diameter Stenosis (%DS)

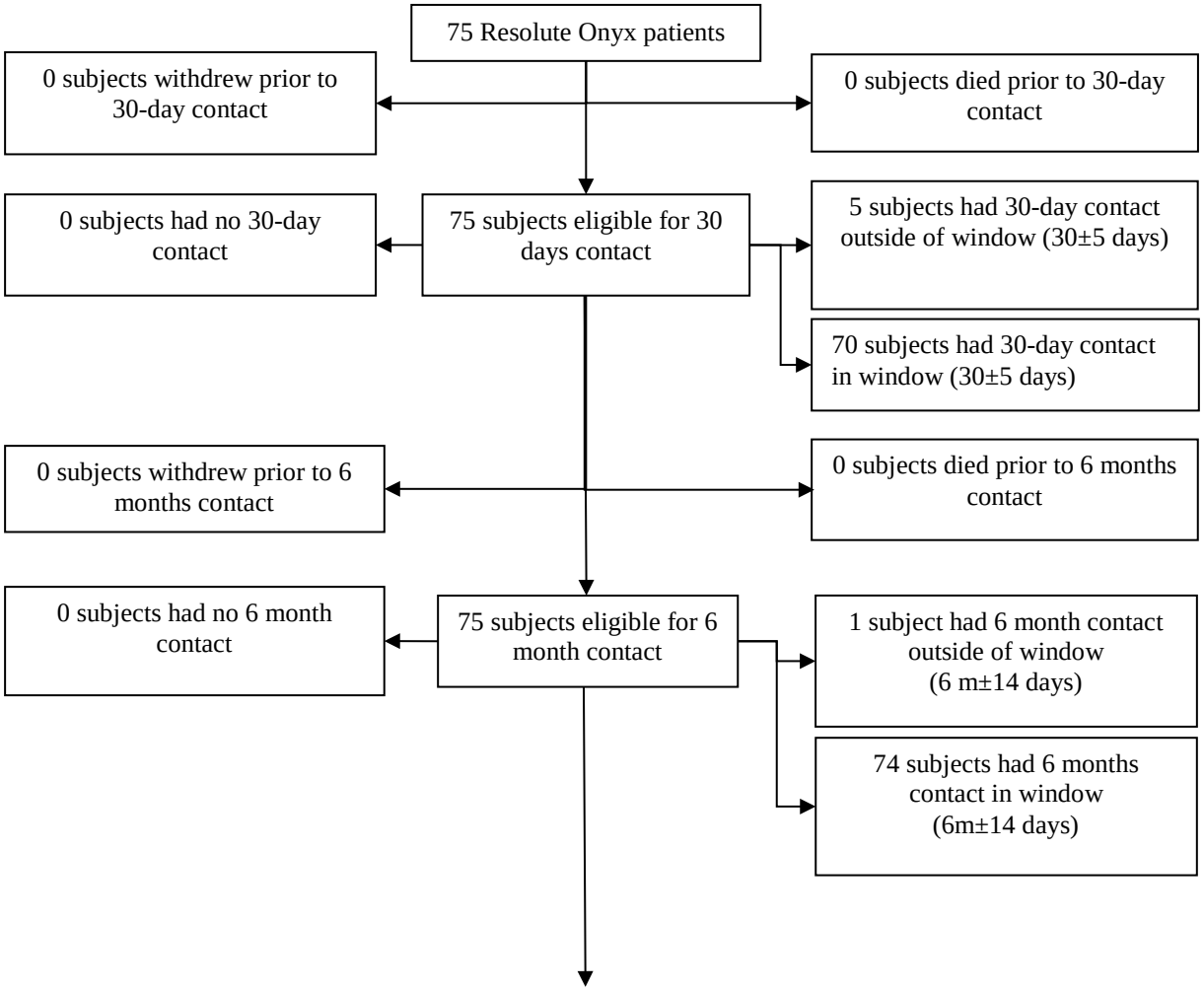
Intravascular Ultrasound (IVUS) Endpoints at 8 Months:

- Incomplete stent apposition, categorized as persistent or late

Neointimal hyperplastic volume and percent volume obstruction (%VO)

B. Accountability of PMA Cohort

At the time of the database lock for this study, 74 subjects were eligible for the eight (8) month post-procedure quantitative coronary angiography (QCA) assessment. **Figure 3** provides an overview of the subject accountability for this study through the 8-month Follow-Up visit.



Continue to next page for 8 month

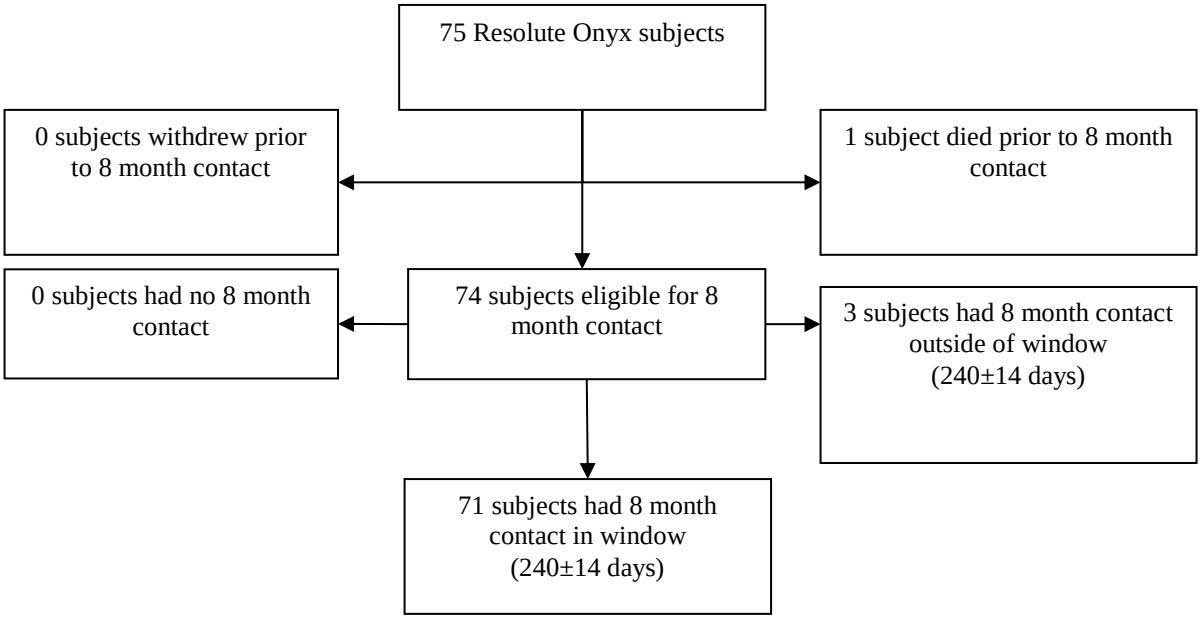


Figure 3: RESOLUTE ONYX Core (2.25 mm -4.0 mm) Clinical Study Subject Accountability out to 240 Days Post-Procedure

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 was 66 years with 73.3% (55/75) of subjects being males. Of the subjects enrolled, 32.0% (24/75) had diabetes mellitus, 16.0% (12/75) were current smokers, 23.0% (17/74) had prior MI, 40.0% (30/75) had prior PCI, 73.3% (55/75) had hypertension, and 85.3% (64/75) reported hyperlipidemia. Baseline lesion characteristics include 49.3% (37/75) of subjects with LAD lesions, a mean lesion length of 14.28 ± 6.68 mm, and 85.9% (73/85) ACC/AHA type B2/C lesions. The mean RVD was 2.57 ± 0.48mm and the percentage diameter stenosis was 62.98 ± 10.75%.

D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the Primary cohort of 75 subjects available for the 8-month evaluation. There were no Unanticipated Adverse Device Effects (UADE), nor any device failures or malfunctions reported through 8 months. Adverse effects are reported in **Table 11** to **Table 14**.

Adverse effects that occurred in the PMA clinical study:

Table 11: All Site Reported Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
Any Adverse Event	88.0% (66/75)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4.0% (3/75)
ANAEMIA	4.0% (3/75)
COAGULOPATHY	1.3% (1/75)
THROMBOCYTOPENIA	2.7% (2/75)
CARDIAC DISORDERS	34.7% (26/75)
ACUTE MYOCARDIAL INFARCTION	4.0% (3/75)
ANGINA PECTORIS	9.3% (7/75)
ANGINA UNSTABLE	1.3% (1/75)
ARRHYTHMIA	2.7% (2/75)
ATRIAL FIBRILLATION	5.3% (4/75)
ATRIAL FLUTTER	1.3% (1/75)
BRADYCARDIA	1.3% (1/75)
CARDIAC FAILURE CONGESTIVE	1.3% (1/75)
CARDIAC FLUTTER	1.3% (1/75)
CORONARY ARTERY DISEASE	5.3% (4/75)
CORONARY ARTERY DISSECTION	2.7% (2/75)
CORONARY ARTERY PERFORATION	1.3% (1/75)
CORONARY ARTERY STENOSIS	1.3% (1/75)
CORONARY ARTERY THROMBOSIS	1.3% (1/75)
IN-STENT CORONARY ARTERY RESTENOSIS	2.7% (2/75)
MYOCARDIAL INFARCTION	2.7% (2/75)
MYOCARDIAL ISCHAEMIA	1.3% (1/75)
PALPITATIONS	1.3% (1/75)
SINUS BRADYCARDIA	1.3% (1/75)
SUPRAVENTRICULAR EXTRASYSTOLES	1.3% (1/75)
SUPRAVENTRICULAR TACHYCARDIA	2.7% (2/75)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1.3% (1/75)
HYDROCELE	1.3% (1/75)

Table 11: All Site Reported Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
EAR AND LABYRINTH DISORDERS	1.3% (1/75)
DEAFNESS	1.3% (1/75)
ENDOCRINE DISORDERS	1.3% (1/75)
THYROID DISORDER	1.3% (1/75)
GASTROINTESTINAL DISORDERS	22.7% (17/75)
ABDOMINAL DISTENSION	1.3% (1/75)
ABDOMINAL PAIN	2.7% (2/75)
ABDOMINAL PAIN UPPER	2.7% (2/75)
CONSTIPATION	2.7% (2/75)
DIARRHOEA	4.0% (3/75)
DYSPEPSIA	1.3% (1/75)
EPIGASTRIC DISCOMFORT	1.3% (1/75)
GASTRITIS	1.3% (1/75)
GASTROOESOPHAGEAL REFLUX DISEASE	1.3% (1/75)
INGUINAL HERNIA	1.3% (1/75)
NAUSEA	6.7% (5/75)
PARAESTHESIA ORAL	1.3% (1/75)
RECTAL HAEMORRHAGE	1.3% (1/75)
VOMITING	2.7% (2/75)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	34.7% (26/75)
CHEST DISCOMFORT	2.7% (2/75)
CHEST PAIN	21.3% (16/75)
FATIGUE	5.3% (4/75)
NON-CARDIAC CHEST PAIN	1.3% (1/75)
OEDEMA PERIPHERAL	2.7% (2/75)
PAIN	1.3% (1/75)
PUNCTURE SITE HAEMORRHAGE	1.3% (1/75)
PUNCTURE SITE REACTION	2.7% (2/75)
VESSEL PUNCTURE SITE PAIN	1.3% (1/75)

Table 11: All Site Reported Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
HEPATOBILIARY DISORDERS	2.7% (2/75)
BILE DUCT STONE	1.3% (1/75)
CHOLECYSTITIS	1.3% (1/75)
INFECTIONS AND INFESTATIONS	24.0% (18/75)
BRONCHITIS	2.7% (2/75)
CELLULITIS	4.0% (3/75)
FOLLICULITIS	2.7% (2/75)
HERPES ZOSTER	1.3% (1/75)
INFLUENZA	1.3% (1/75)
PNEUMONIA	2.7% (2/75)
SEPSIS	1.3% (1/75)
SINUSITIS	1.3% (1/75)
UPPER RESPIRATORY TRACT INFECTION	6.7% (5/75)
URINARY TRACT INFECTION	1.3% (1/75)
VIRAL INFECTION	1.3% (1/75)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16.0% (12/75)
BACK INJURY	1.3% (1/75)
CONTUSION	4.0% (3/75)
FALL	2.7% (2/75)
HEAD INJURY	1.3% (1/75)
IN-STENT ARTERIAL RESTENOSIS	4.0% (3/75)
LACERATION	1.3% (1/75)
POST PROCEDURAL HAEMATOMA	1.3% (1/75)
INVESTIGATIONS	20.0% (15/75)
BLOOD CHOLESTEROL INCREASED	1.3% (1/75)
BLOOD POTASSIUM INCREASED	1.3% (1/75)
CARDIAC ENZYMES INCREASED	10.7% (8/75)
LIVER FUNCTION TEST ABNORMAL	1.3% (1/75)
OCCULT BLOOD POSITIVE	1.3% (1/75)
TRANSAMINASES INCREASED	1.3% (1/75)

Table 11: All Site Reported Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
TROPONIN I INCREASED	1.3% (1/75)
TROPONIN INCREASED	1.3% (1/75)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	22.7% (17/75)
BACK PAIN	10.7% (8/75)
EXOSTOSIS	1.3% (1/75)
GROIN PAIN	2.7% (2/75)
LIMB DISCOMFORT	1.3% (1/75)
MUSCULOSKELETAL CHEST PAIN	1.3% (1/75)
MYALGIA	4.0% (3/75)
NECK PAIN	2.7% (2/75)
OSTEOARTHRITIS	1.3% (1/75)
PAIN IN EXTREMITY	2.7% (2/75)
PAIN IN JAW	1.3% (1/75)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4.0% (3/75)
BENIGN NEOPLASM OF THYROID GLAND	1.3% (1/75)
HEPATIC CANCER METASTATIC	1.3% (1/75)
LUNG NEOPLASM MALIGNANT	1.3% (1/75)
SKIN PAPILLOMA	1.3% (1/75)
NERVOUS SYSTEM DISORDERS	13.3% (10/75)
DIABETIC NEUROPATHY	1.3% (1/75)
DIZZINESS	6.7% (5/75)
HEADACHE	2.7% (2/75)
HYPOAESTHESIA	1.3% (1/75)
SCIATICA	1.3% (1/75)
SYNCOPE	1.3% (1/75)
PSYCHIATRIC DISORDERS	1.3% (1/75)
PANIC ATTACK	1.3% (1/75)
RENAL AND URINARY DISORDERS	4.0% (3/75)

Table 11: All Site Reported Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
HAEMATURIA	1.3% (1/75)
URINARY RETENTION	2.7% (2/75)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5.3% (4/75)
BENIGN PROSTATIC HYPERPLASIA	1.3% (1/75)
BREAST MASS	1.3% (1/75)
BREAST PAIN	1.3% (1/75)
PROSTATIC CALCIFICATION	1.3% (1/75)
PROSTATITIS	1.3% (1/75)
VAGINAL HAEMORRHAGE	1.3% (1/75)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	26.7% (20/75)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	2.7% (2/75)
COUGH	2.7% (2/75)
DYSPNOEA	20.0% (15/75)
DYSPNOEA EXERTIONAL	2.7% (2/75)
EPISTAXIS	1.3% (1/75)
HAEMOPTYSIS	2.7% (2/75)
PHARYNGOLARYNGEAL PAIN	1.3% (1/75)
RESPIRATORY FAILURE	1.3% (1/75)
SLEEP APNOEA SYNDROME	1.3% (1/75)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2.7% (2/75)
DERMAL CYST	1.3% (1/75)
RASH	1.3% (1/75)
SKIN IRRITATION	1.3% (1/75)
SURGICAL AND MEDICAL PROCEDURES	1.3% (1/75)
THERAPEUTIC EMBOLISATION	1.3% (1/75)
VASCULAR DISORDERS	25.3% (19/75)
HAEMATOMA	1.3% (1/75)
HYPERTENSION	9.3% (7/75)
HYPOTENSION	6.7% (5/75)
ILIAC ARTERY STENOSIS	1.3% (1/75)

Table 11: All Site Reported Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
INTERMITTENT CLAUDICATION	1.3% (1/75)
ORTHOSTATIC HYPOTENSION	1.3% (1/75)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	2.7% (2/75)
PERIPHERAL VASCULAR DISORDER	1.3% (1/75)
RAYNAUD'S PHENOMENON	1.3% (1/75)
SHOCK HAEMORRHAGIC	1.3% (1/75)

[1] Numerator (m) is the number of subjects with the specific classification, denominator (n) is the number of subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)

Table 12: All Site Reported Serious Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
Any Serious Adverse Events	36.0% (27/75)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2.7% (2/75)
ANAEMIA	2.7% (2/75)
COAGULOPATHY	1.3% (1/75)
THROMBOCYTOPENIA	1.3% (1/75)
CARDIAC DISORDERS	20.0% (15/75)
ACUTE MYOCARDIAL INFARCTION	4.0% (3/75)
ANGINA PECTORIS	2.7% (2/75)
ANGINA UNSTABLE	1.3% (1/75)
ATRIAL FLUTTER	1.3% (1/75)
BRADYCARDIA	1.3% (1/75)
CARDIAC FAILURE CONGESTIVE	1.3% (1/75)
CORONARY ARTERY DISEASE	5.3% (4/75)
CORONARY ARTERY PERFORATION	1.3% (1/75)
CORONARY ARTERY STENOSIS	1.3% (1/75)
CORONARY ARTERY THROMBOSIS	1.3% (1/75)
IN-STENT CORONARY ARTERY RESTENOSIS	2.7% (2/75)

Table 12: All Site Reported Serious Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
MYOCARDIAL INFARCTION	1.3% (1/75)
SUPRAVENTRICULAR EXTRASYSTOLES	1.3% (1/75)
SUPRAVENTRICULAR TACHYCARDIA	2.7% (2/75)
ENDOCRINE DISORDERS	1.3% (1/75)
THYROID DISORDER	1.3% (1/75)
GASTROINTESTINAL DISORDERS	2.7% (2/75)
INGUINAL HERNIA	1.3% (1/75)
RECTAL HAEMORRHAGE	1.3% (1/75)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	9.3% (7/75)
CHEST PAIN	8.0% (6/75)
PUNCTURE SITE HAEMORRHAGE	1.3% (1/75)
HEPATOBILIARY DISORDERS	1.3% (1/75)
BILE DUCT STONE	1.3% (1/75)
INFECTIONS AND INFESTATIONS	2.7% (2/75)
CELLULITIS	1.3% (1/75)
PNEUMONIA	1.3% (1/75)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5.3% (4/75)
FALL	1.3% (1/75)
IN-STENT ARTERIAL RESTENOSIS	4.0% (3/75)
INVESTIGATIONS	2.7% (2/75)
CARDIAC ENZYMES INCREASED	1.3% (1/75)
LIVER FUNCTION TEST ABNORMAL	1.3% (1/75)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2.7% (2/75)
BACK PAIN	1.3% (1/75)
OSTEOARTHRITIS	1.3% (1/75)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2.7% (2/75)
BENIGN NEOPLASM OF THYROID GLAND	1.3% (1/75)

Table 12: All Site Reported Serious Adverse Events by Type

Events	RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]
HEPATIC CANCER METASTATIC	1.3% (1/75)
LUNG NEOPLASM MALIGNANT	1.3% (1/75)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1.3% (1/75)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1.3% (1/75)
DYSPNOEA	1.3% (1/75)
HAEMOPTYSIS	1.3% (1/75)
RESPIRATORY FAILURE	1.3% (1/75)
SURGICAL AND MEDICAL PROCEDURES	1.3% (1/75)
THERAPEUTIC EMBOLISATION	1.3% (1/75)
VASCULAR DISORDERS	6.7% (5/75)
HYPOTENSION	1.3% (1/75)
ORTHOSTATIC HYPOTENSION	1.3% (1/75)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	2.7% (2/75)
SHOCK HAEMORRHAGIC	1.3% (1/75)

[1] Numerator (m) is the number of subjects with the specific classification, denominator (n) is the number of subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)

Table 13: Stent Thrombosis (ARC Definition)

Stent Thrombosis to 240 days	**RESOLUTE ONYX Core (N=75 Subjects) %(m/n)[1]**
Stent Thrombosis Related to Non Target Lesions to 240 Days	0.0% (0/75)
Early (0 to 30 Days)	0.0% (0/75)
Late (31 to 240 Days)	0.0% (0/75)
Overall Stent Thrombosis to 240 Days	
Definite ST	1.3% (1/75)
Probable ST	0.0% (0/75)
Definite + Probable ST	1.3% (1/75)
Early (0 to 30 Days)	
Definite ST	1.3% (1/75)
Probable ST	0.0% (0/75)
Definite + Probable ST	1.3% (1/75)
Late (31 to 240 Days)	
Definite ST	0.0% (0/75)
Probable ST	0.0% (0/75)
[1]ARC (Academic Research Consortium) – consensus definition for implementation in DES clinical trials created by academic, FDA and industry representatives.	
Definite + Probable ST	0.0% (0/75)
[1]Numerator (m) is the number of subjects with the specific classification, denominator (n) is the number of subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)	

2. Efficacy Results

   The analysis of efficacy was based on the 75 evaluable patients at the 8-month time point. The primary endpoint of in-stent Late Lumen Loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA) demonstrated non-inferiority ($p < 0.001$) and subsequent superiority ($p = 0.029$), when compared to the historical control in-stent late loss value from the RESOLUTE US Angio/IVUS Sub-study for the ITT population. Key outcomes for this study are presented below in **Table 15** to **Table 17**.

Table 14: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – Primary Endpoint Analysis

Primary Endpoint – In-stent Late Lumen Loss at 8 month	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions)	Historical Control Resolute (N=100 Subjects N=104 Lesions)	Difference: Resolute Onyx Core - Historical Control[1]	Upper One-sided 95% CI[2]	Non-Inferiority Margin	Non-Inferiority P value	Superiority P value[3]
Primary Analysis – with available data							
– ITT set	0.24 ± 0.05 (73)	0.36 ± 0.05 (93)	-0.14	-0.02	0.20	< 0.001	0.029
– PP set	0.24 ± 0.05 (70)	0.35 ± 0.05 (89)	-0.14	-0.01	0.20	< 0.001	0.036
Secondary Analysis – with multiple imputation							
– ITT set	0.23 ± 0.05	0.36 ± 0.05	-0.15	-0.03	0.20	< 0.001	0.023
– PP set	0.23 ± 0.05	0.35 ± 0.05	-0.15	-0.02	0.20	< 0.001	0.028

[1] The Resolute Onyx Core measure non-inferiority of 8-month in-stent late lumen loss compared to 8-month in-stent late lumen loss of the historical control
All target lesions are included in the analysis. The treatment differences have been adjusted with propensity score quintile.
[2] The CI is adjusted to propensity score, based on lesion-length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society Angina Class as the independent variables.
[3] Superiority test is performed after non-inferiority is demonstrated.

Table 15: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study– Principal Safety and Effectiveness

	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions) %(m/n)[1]
Clinical Outcomes (In-hospital)	
Target Lesion Failure (TLF)[2]	4.0% (3/75)
Target Vessel Failure (TVF)[3]	4.0% (3/75)
MACE[4]	4.0% (3/75)
Cardiac Death or Target Vessel MI (TVMI)[5]	2.7% (2/75)
Death or TVMI	2.7% (2/75)
Death	0.0% (0/75)
Cardiac Death	0.0% (0/75)

Table 15: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study– Principal Safety and Effectiveness

	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions) %(m/n)[1]
Non Cardiac Death	0.0% (0/75)
TVMI (Extended historical definition)[6]	2.7% (2/75)
Clinically Driven TLR[7]	1.3% (1/75)
Clinically Driven TVR[8]	1.3% (1/75)
Stent Thrombosis (ARC) Definite/Probable	1.3% (1/75)
Clinical Outcomes (to 6 months)	
Target Lesion Failure (TLF)[2]	5.3% (4/75)
Target Vessel Failure (TVF)[3]	8.0% (6/75)
MACE[4]	8.0% (6/75)
Cardiac Death or Target Vessel MI (TVMI)[5]	2.7% (2/75)
Death or TVMI	4.0% (3/75)
Death	1.3% (1/75)
Cardiac Death	0.0% (0/75)
Non Cardiac Death	1.3% (1/75)
TVMI (Extended historical definition)[6]	2.7% (2/75)
Clinically Driven TLR[7]	2.7% (2/75)
Clinically Driven TVR[8]	5.3% (4/75)
Stent Thrombosis (ARC) Definite/Probable	1.3% (1/75)
Clinical Outcomes (8 months)	
Target Lesion Failure (TLF)[2]	6.7% (5/75)
Target Vessel Failure (TVF)[3]	12.0% (9/75)
MACE[4]	9.3% (7/75)
Cardiac Death or Target Vessel MI (TVMI)[5]	2.7% (2/75)
Death or TVMI	4.0% (3/75)
Death	1.3% (1/75)
Cardiac Death	0.0% (0/75)
Non Cardiac Death	1.3% (1/75)
TVMI (Extended historical definition)[6]	2.7% (2/75)
Clinically Driven TLR[7]	4.0% (3/75)
Clinically Driven TVR[8]	9.3% (7/75)
Stent Thrombosis (ARC) Definite/Probable[9]	1.3% (1/75)
Early Thrombosis (<=30 days)	1.3% (1/75)

Table 15: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study– Principal Safety and Effectiveness

	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions) %(m/n)[1]
Late Thrombosis (31-240 days)	0.0% (0/75)
Angiography (8 months)	
Percent Diameter Stenosis (% DS)	
In-stent	
n	73
Mean±SD	15.70 ± 16.65
Median (1Q, 3Q)	14.86(5.33, 22.24)
Min, Max	-21.18, 82.89
In-segment	
n	73
Mean±SD	25.50 ± 14.26
Median (1Q, 3Q)	22.06(17.42, 29.64)
Min, Max	4.99, 82.89
Minimal Lumen Diameter (mm)	
In-stent	
n	73
Mean±SD	2.13 ± 0.55
Median (1Q, 3Q)	2.14(1.80, 2.45)
Min, Max	0.45, 3.69
In-segment	
n	73
Mean±SD	1.89 ± 0.49
Median (1Q, 3Q)	1.91(1.59, 2.20)
Min, Max	0.45, 3.10
Late Luminal Loss (mm)	
In-stent	
n	73
Mean±SD	0.24 ± 0.39
Median (1Q, 3Q)	0.20(0.03, 0.37)
Min, Max	-0.49, 2.06
In-segment	
n	73
Mean±SD	0.15 ± 0.38

Table 15: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study– Principal Safety and Effectiveness

	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions) %(m/n)[1]
Median (1Q, 3Q)	0.11(-0.03, 0.29)
Min, Max	-0.65, 1.88
In-Stent Binary Angiographic Restenosis (BAR) Rate	5.5% (4/73)
In-Segment Binary Angiographic Restenosis (BAR) Rate	8.2% (6/73)
IVUS (8 months)	
Incomplete stent apposition	
Persistent	10.0% (2/20)
Late	0.0% (0/20)
Neointimal hyperplastic volume (mm^3)	
n	17
Mean±SD (N)	9.88 ± 9.38
Median (Q1,Q3)	6.80(2.20, 18.10)
Min, Max	0.00, 27.20
Percent volume obstruction	
n	17
Mean±SD (N)	6.88 ± 8.00
Median (Q1,Q3)	4.52(1.48, 8.79)
Min, Max	0.00, 31.38
Effectiveness Measures	
Lesion Success[10]	100.0% (85/85)
Device Success[11]	100.0% (85/85)
Procedure Success[12]	96.0% (72/75)

Table 15: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study– Principal Safety and Effectiveness

	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions) %(m/n)[1]

Notes

8-month timeframe includes follow-up window (240 days ± 14 days).

[1] Numerator (m) is the number of Subjects with the specific classification, denominator (n) is the number of Subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)

[2]Target Lesion Failure (TLF) is defined as any Cardiac Death, Clinically Driven Target Lesion Revascularization by PCI or CABG or Target Vessel MI.

[3]Target Vessel Failure (TVF) is defined as any Cardiac Death, Clinically Driven Target Vessel Revascularization by PCI or CABG or Target Vessel MI.

[4]Major adverse cardiac events (MACE) is defined as composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or clinically driven target lesion revascularization (repeat PTCA or CABG).

[5]Cardiac death/TVMI is defined as Cardiac Death or Myocardial Infarction not clearly attributable to a non-target vessel.

[6]TVMI is composed of both Q wave and non-Q wave MI which are not clearly attributable to a non-target vessel.

[7]Target Lesion Revascularization (TLR) is defined as a clinically-driven repeat intervention of the target lesion by PCI or CABG

[8]Target Vessel Revascularization (TVR) is defined as any clinically-driven repeat intervention of the target vessel by PCI or CABG.

[9] ARC defined Stent Thrombosis.

Academic Research Consortium (ARC) stent thrombosis is defined as follows.

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases: Any unexplained death within the first 30 days following stent implantation. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause

[10]The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method.

[11]The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only.

[12]The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.

Table 16: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – ARC Defined Definite/Probable Stent Thrombosis through 8 Months

	Resolute ONYX™ (N=75 Subjects N=85 Lesions) %(m/n)[1]
Stent Thrombosis	1.3% (1/75)
Early Thrombosis (<=30 days)	1.3% (1/75)
Late Thrombosis (31-240 days)	0.0% (0/75)

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
8-month timeframe includes follow-up window (240 days ± 14days).

3. Subgroup Analyses
   The RESOLUTE ONYX Core (2.5 mm – 4.0 mm) Clinical Study did not include prespecified subgroup analyses.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of 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 89 investigators of which none were full-time or part-time employees of the sponsor and one (1) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: one (1)
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study

outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

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

Additional safety and effectiveness information for the Resolute Onyx™ stent system was derived from the Global RESOLUTE Clinical Trial Program, which consists of the following clinical trials – the RESOLUTE United States Clinical Trial (R-US), the RESOLUTE All-Comers Clinical Trial (R-AC), the RESOLUTE International Study (R-Int), the RESOLUTE First-in-Man (FIM) Clinical Trial, and the RESOLUTE Japan Clinical Trial (R-J). These five studies have evaluated the performance of the Resolute stent, Medtronic's first generation stent in the product family, in 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. Key elements of these studies are summarized below and in **Table 18**. The Resolute 38 mm Length Group was derived from subjects enrolled in the R-US and the RESOLUTE Asia study (R-Asia). In addition, the RESOLUTE INTEGRITY US Post Market Study, a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects who were treated with the Resolute Integrity Zotarolimus-Eluting Coronary Stent System, Medtronic's second generation stent in this product family, was designed to assess the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm in two groups of patients, specifically those patients receiving stents ≤ 30 mm in length, referred to as the Primary Enrollment Group (PEG) and those patients who receive extended length stents (34 mm or 38 mm) referred to as the Extended Length (XL) Sub-study. Resolute MicroTrac and Resolute Integrity were simultaneously approved under P110013. Please refer to the SSED for P110013 for more details regarding the clinical data collected for the Resolute MicroTrac and Resolute Integrity, which is summarized in Table 18.

Table 17: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program						RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	**RESOLUTE AC[1]**	**RESOLUTE Int[2]**	**RESOLUTE FIM[3]**	**RESOLUTE Japan**	**RESOLUTE Asia 38 mm Cohort**	**RESOLUTE INTEGRITY US (PEG)**	**RESOLUTE INTEGRITY US (XL Sub-study)**
Study Type	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial*	▪ Prospective ▪ Multi-center ▪ Randomized (1:1 Resolute vs. Xience V®) ▪ Two-arm, non-inferiority trial ▪ Real World subject population	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Observational study ▪ Real World subject population	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial ▪ PK Assessment	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial	▪ Prospective ▪ Multi-center ▪ Non-randomized	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Post approval	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Post approval
Number of Subjects Enrolled	Total: 1516 - 2.25–3.5 mm Main Study - 1242 subjects - 2.25 mm Cohort -150 subjects - 2.25–3.5 mm Angio/IVUS sub-study - 100 subjects - 4.0 mm Sub-study - 60 subjects - 38 mm Sub-study -114 subjects (38 mm Sub-study total patient population was 223 with 114 from RESOLUTE US and 109 from RESOLUTE Asia)	Total: 2292 (Resolute: 1140, Xience V®: 1152)	Total: 2349	Total: 139	Total: 100	Total: 109	Total:230	Total: 56

Table 17: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program						RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	**RESOLUTE AC[1]**	**RESOLUTE Int[2]**	**RESOLUTE FIM[3]**	**RESOLUTE Japan**	**RESOLUTE Asia 38 mm Cohort**	**RESOLUTE INTEGRITY US (PEG)**	**RESOLUTE INTEGRITY US (XL Sub-study)**
Lesion Criteria	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤27 mm for the Primary Enrollment Group, ≤35 mm for the 38 mm Length Group ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.0 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.0 mm	▪ Single *de novo* lesion ▪ Lesion length from 14 to 27 mm ▪ Target vessel with RVD between 2.5 and 3.5 mm	▪ Single or two *de novo* lesions located in separate coronary arteries ▪ Lesion(s) length ≤27 mm ▪ Target vessel with RVD between 2.5 to 3.5 mm	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤35 mm ▪ Target vessel with RVD between 3.0 to 4.0 mm ▪ Patients may have received treatment of up to two lesions second lesion RVD (2.25 to 4.2 mm), if the lesions were located in separate target vessels.	▪ Single target lesion or two target lesions located in separate target vessels **PEG:** ▪ Target lesion ≤27 mm ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ . Single target lesion or two target lesions located in separate target vessels **XL:** ▪ Target lesion ≤ 35 mm treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.2 mm.
Stent Sizes (Resolute)	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 38 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 38 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 34-38 mm

Table 17: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program						RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	**RESOLUTE AC[1]**	**RESOLUTE Int[2]**	**RESOLUTE FIM[3]**	**RESOLUTE Japan**	**RESOLUTE Asia 38 mm Cohort**	**RESOLUTE INTEGRITY US (PEG)**	**RESOLUTE INTEGRITY US (XL Sub-study)**
Product Used	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange AV100 Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System
Post-procedure Antiplatelet Therapy	Aspirin indefinitely and clopidogrel / ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel / ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel / ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel / ticlopidine ≥ 6 months	Aspirin indefinitely and clopidogrel / ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel / ticlopidine,for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel / ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel / ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated
Follow-up	2.25 mm - 3.5 mm Main Study: 30 days and 9 months: clinical; 6, 12 and 18 months, 2-5 years: telephone 4.0 mm Sub-study: 8 months: clinical and angiographic; 6, 12 and 18 months, 2-5 years: telephone 2.25 mm - 3.5 mm Angio/IVUS Sub-study: 8 months: clinical and angiographic/ IVUS;6, 12 and 18 months, 2-5 years: telephone 38 mm Length Sub-study: 30 days (R-US) and 9 months clinical visits (preferred) or	30 days and 12 months: clinical 13 months (455 subject subset): angiographic 6 months and 2-5 years: telephone	30 days, 6 months, 1-3 years: clinical or telephone	30 days: clinical 4 (30 subject subset) and 9 months (100 subject subset): clinical and angiographic/IVUS 6 months and 1-5 years: telephone	30 days and 12 months: clinical 8 months: angiographic/IVUS 6, 9 and 18 months and 2-5 years: telephone	30 days, 6, 9 (Clinical Visit), 12, 18 months then annually at 2 - 5 years**	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact)	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact) 3-5 years (contact)

Table 17: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program						RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	**RESOLUTE AC[1]**	**RESOLUTE Int[2]**	**RESOLUTE FIM[3]**	**RESOLUTE Japan**	**RESOLUTE Asia 38 mm Cohort**	**RESOLUTE INTEGRITY US (PEG)**	**RESOLUTE INTEGRITY US (XL Sub-study)**
	patient contact 30 days (R-Asia), 6, 12, 18 months then annually at 2, 3, 4, 5 years **							
Status	60-month follow-up is complete. 551 subjects qualified for 18-month follow-up	60-month follow-up is complete	36-month follow-up is complete	60-month follow-up complete	60-month follow-up is complete	48-month follow-up is complete	24-month follow-up is complete	Enrollment complete as of 27 October 2015

* The RESOLUTE US trial is composed of four studies. The 2.5 mm - 3.5 mm subset of the Main Study, the 2.25 mm – 3.5 mm Angio/IVUS Sub-study, the 38 mm Length Sub-study, and the 4.0mm Sub-study have historical control designs. The 2.25 mm Subset outcomes were compared to a performance goal.

[1] The term 'AC' refers to All-Comers.

[2] The term 'Int' refers to International.

[3] The term 'FIM' refers to First-In-Man.

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 Resolute Onyx is based on the results obtained from 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 clinical studies. These test results revealed the following:

A. Effectiveness Conclusions

The primary endpoint of in-stent late lumen loss at 8 months was compared to a historical control value derived from the RESOLUTE US Angio/IVUS Sub-Study with propensity score adjustment. The propensity score adjusted one-sided 95% confidence interval was -0.02 mm, which was less than the pre-specified non-inferiority margin (0.20 mm); therefore non-inferiority has been demonstrated ($p < 0.001$). After non-inferiority was demonstrated, pre-specified superiority was further evaluated; since the propensity score adjusted one-sided 95% CI was less than 0 mm, superiority was also met ($p = 0.029$).

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The biocompatibility, in vivo pharmacokinetics (data generated on the Resolute product), and in vivo performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The clinical outcomes in subjects of the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study suggest that use of the Resolute Onyx stent is associated with low adverse event rates consistent with the 9 month clinical outcomes of the RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study that evaluated a similar patient population with mandated angiographic follow up at 8 months.

The results from the RESOLUTE ONYX Core (2.25 mm - 4.0mm) Clinical Study demonstrate that the Resolute Onyx product provides reasonable assurance of safety and effectiveness when used as indicated in accordance with the Instructions for Use (IFU).

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The Resolute Onyx™ coronary stent has been shown to be beneficial for improving luminal diameter in patients with symptomatic coronary artery disease. The primary end point of in-stent Late Lumen Loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA) demonstrated not only non-inferiority ($p < 0.001$), but also superiority ($p = 0.029$) when compared to the historical control in-stent late loss value from the RESOLUTE US Angio/IVUS Sub-study.

Additional factors to be considered in determining probable risks and benefits for the Resolute Onyx™ stent system include characterization of the disease, availability of anternative 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 patient's 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 RESOLUTE ONYX Core study are in line with expectations. The study did not exclude any typical patient subgroups that would be expected to benefit from treatment. The patients treated in the RESOLUTE ONYX Core study represent a standard PCI population, and the results can be applied to the general population of patients with coronary artery disease.

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 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 diameter of 2.25 mm to 5.0 mm, the probable benefits of the Resolute Onyx™ Zotarolimus-Eluting Stent System outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent

System when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on April 28, 2017. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – Continued Follow-up of RESOLUTE ONYX Core (2.25mm-4.00mm) Clinical Study. The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The RESOLUTE ONYX Core (2.25mm-4.00mm) Clinical Study (G1401078/S001) is an open-label, single-arm, multi-center study which enrolled 75 patients and was designed to assess the safety and effectiveness of the Resolute Onyx Zotarolimus Eluting Coronary Stent System (Core Sizes) through 3 years post-index procedure. The primary endpoint is in-stent late lumen loss (LLL) at 8 months. Medtronic must collect and report clinical outcomes to FDA through 3 years post-procedure on patients enrolled in the RESOLUTE ONYX Core (2.25mm-4.00mm) Clinical Study.

2. ODE Lead PMA Post-Approval Study – RESOLUTE ONYX Post-Approval Study (PAS). The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval under G140178/S008. The RESOLUTE ONYX PAS is a single arm, non-investigational, open-label multi-center study intended to evaluate the safety and effectiveness of the Resolute Onyx Zotarolimus Eluting Coronary Stent Systems in a real world, more-comers population. The study will enroll 510 study subjects: 410 study subjects will be enrolled in the Main Study cohort (2.00-4.00mm) and 100 subjects will be enrolled in an Extra-Large (XLV) sub-study (4.50-5.00mm) cohort. The study will be conducted in up to 25 US sites (representing at least 50% of total enrollment) and up to 5 OUS sites (maximum of 50 study subjects in the Main Study cohort and 49 subjects in the in XLV sub-study cohort). The primary endpoint for all study subjects enrolled in the RESOLUTE ONYX PAS is Target Lesion Failure (TLF) at 12 months, defined as Cardiac Death, Target Vessel Myocardial Infarction or Target Lesion Revascularization. The Main Study cohort will have a performance goal (PG) of 13.2%. The XLV sub-study cohort does not have a formal hypothesis but descriptive statistics will be provided. Medtronic must collect and report clinical outcomes to FDA through 3 years post-procedure on patients enrolled in the RESOLUTE ONYX PAS.

3. The following non-clinical information will be submitted in annual drug stability reports: Long-term and accelerated stability studies will be completed on three production-scale batches of the approved finished product (according to the formal stability protocol) through the expiration dating period. All products included in these studies will be manufactured according to the US in-process inspection for coating weight tolerance. A minimum of one batch per year should be placed into the long-term stability program.

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.