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
USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110013/S005

Date of FDA Notice of Approval: February 22, 2013

Expedited: Not Applicable

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. The current supplement was submitted to expand the indication for the Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems.

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 diameter of 2.25 mm to 4.2 mm.

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 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)	140cm	
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	3.4F
Proximal Outer Diameter	2.1F	

[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 $\mu g/mm^2$. 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.

1 2.25, 2.5 and 2.75mm diameter stents are not available in lengths of 9, 15, 34 and 38 mm

2 3.0, 3.5 and 4.0mm diameter stents are not available in lengths of 8 and 14mm

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. 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]oxaazacyclohentriacontine-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.

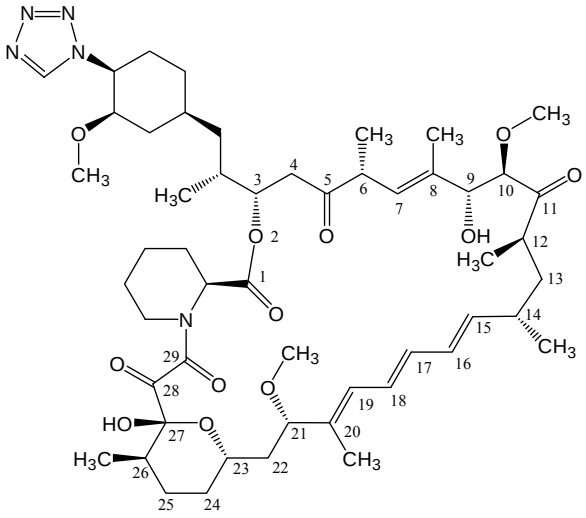


Figure 1: Chemical Structure of Zotarolimus

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

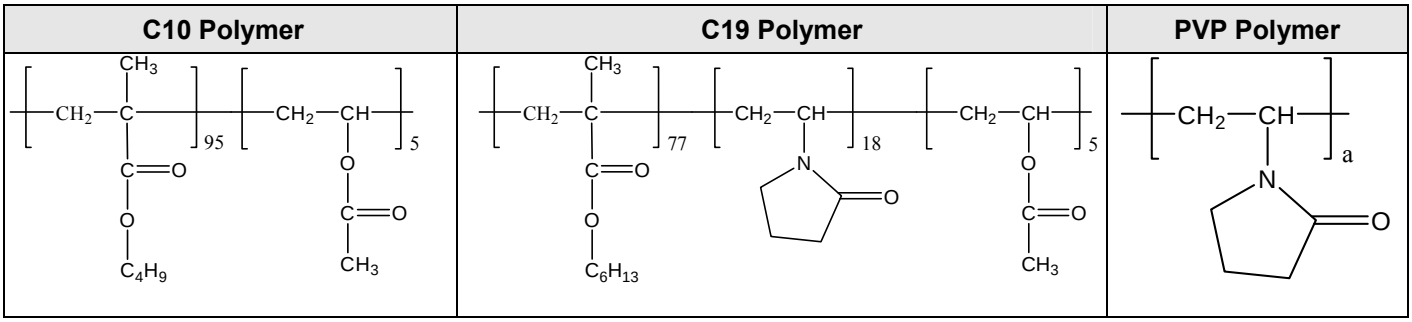


Figure 2: Chemical Structure of Biolinx Polymer Sub-units

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
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	2	153
RSINT25022W	RSINT25022UX	2.5	22	153
RSINT27522W	RSINT27522UX	2.75	22	153

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)
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 leads to inhibition of cell cycle progression from the G1 to the S phase.

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

Algeria	Costa Rica	Kazakhstan	Nigeria	Tunisia
Antigua and Barbuda	Cyprus	Kyrgyzstan	Pakistan	Uganda
Armenia	Czech Republic	Korea (South)	Paraguay	Ukraine
Aruba	Denmark	Kuwait	Peru	United Kingdom
Australia	Egypt	Laos	Philippines	United States
Austria	Estonia	Latvia	Poland	Uruguay
Bahamas	Finland	Lebanon	Portugal	Uzbekistan
Bahrain	France	Liechtenstein	Qatar	Vietnam
Bangladesh	Georgia	Lithuania	Romania	Virgin Islands
Barbados	Germany	Luxemburg	Russia	Yeman
Belarus	Ghana	Macau	Senegal	Zimbabwe
Belgium	Greece	Macedonia	Serbia	
Belize	Guyana	Malaysia	Singapore	
Bermuda	Honduras	Malta	Slovakia	
Bolivia	Hong Kong	Mauritius	Slovenia	
Bosnia-Herzegovina	Hungary	Montenegro	Spain	
Botswana	Iceland	Morocco	Sudan	
Brazil	India	Mozambique	Sweden	
Brunei	Indonesia	Myanmar	Switzerland	
Bulgaria	Ireland	Namibia	Syria	
Cambodia	Israel	Netherlands	Taiwan	
Cayman Islands	Italy	New Zealand	Thailand	
Croatia	Jamaica	Norway	Turkey	
Columbia	Japan	Nicaragua	Trinidad and Tobago	

As of October 31, 2012, approximately 580,976 Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems have been distributed outside of the U.S. This product has not been withdrawn from the market in any country for any reason.

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

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

No new preclinical studies were submitted or required for the approval of the expanded indication proposed in this PMA Supplement. Please see the original SSED for details.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The principal safety and effectiveness information for the RESOLUTE Integrity Zotarolimus-Eluting Coronary Stent Systems is derived from a series of clinical trials conducted on the Resolute Zotarolimus-Eluting Coronary Stent System (Resolute stent system). The Resolute stent system consists of the cobalt alloy bare metal stent, the zotarolimus and BioLinx stent coating, and the Sprint delivery system.

The Resolute Integrity stent mounted on the MicroTrac delivery system is similar to the Resolute stent mounted on the Sprint delivery system with regard to the stent design, the stent coating technology (drug concentration and drug to polymer ratio), and delivery system design and materials. The Resolute Integrity stent is manufactured from a single wire whereas the Resolute stent is formed from laser fused elements. The Resolute Integrity stent is mounted on the MicroTrac delivery system, which differs from the Sprint delivery system with regard to the catheter manufacturing, shaft and tip design, and stent crimping process. Given the similarities between the Resolute stent system and the Resolute Integrity stent system, and supportive bench and animal study information, the findings from the RESOLUTE clinical studies, as described below, are applicable to the Resolute Integrity stent system.

The principal safety and effectiveness information for the Resolute stent was derived from the Global RESOLUTE Clinical Trial Program, which consists of the following clinical trials - the RESOLUTE United States Clinical Trial, the RESOLUTE All-Comers Clinical Trial, the RESOLUTE International Study, the RESOLUTE First-in-Man (FIM) Clinical Trial and the RESOLUTE Japan Clinical Trial. These five studies evaluated the performance of the Resolute stent 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 in Table 4.

Table 4: Clinical Trial Comparisons

	RESOLUTE US	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan
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
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 ▪ 4.0mm 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
Lesion Criteria	▪ Single or two de novo lesions located in separate target vessels	▪ No limitation to number of lesion(s)/ vessel(s) treated or	▪ No limitation to number of lesion(s)/ vessel(s) treated or	▪ Single de novo lesion ▪ Lesion length from 14 to 27 mm	▪ Single or two de novo lesions located in separate coronary arteries

Table 4: Clinical Trial Comparisons

	RESOLUTE US	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan
	▪ 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 mm to 4.2 mm	lesion length ▪ Target vessel with RVD between 2.25 mm to 4.0 mm.	lesion length ▪ Target vessel with RVD between 2.25 mm to 4.0 mm	▪ Target vessel with RVD between 2.5 mm and 3.5 mm	▪ Lesion(s) length ≤27 mm ▪ Target vessel with RVD between 2.5 mm to 3.5 mm
Stent Sizes (Resolute)	Stent diameter: 2.25 mm – 4.0 mm Stent length: 8 mm – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 mm – 4.0 mm Stent length: 8 mm – 30 mm	Stent diameter: 2.25 mm – 4.0 mm Stent length: 8 mm – 38 mm	Stent diameter: 2.5 mm – 3.5 mm Stent length: 8 mm – 30 mm	Stent diameter: 2.5 mm – 3.5 mm Stent length: 8 mm – 30 mm
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
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
Follow-up	▪ 2.25 - 3.5 mm Main study: 30 days and 9 months: clinical; 6, 12 and 18 months, 2-5 years: telephone	▪ 30 days and 12 months: clinical ▪ 13 months (455 subject subset): angiographic	▪ 30 days, 6 months, 1-3 years: clinical or telephone	▪ 30 days: clinical ▪ (30 subject subset) and 9 months (100 subject subset): clinical and angiographic/ IVUS	▪ 30 days and 12 months: clinical ▪ 8 months: angiographic/ IVUS

Table 4: Clinical Trial Comparisons

	RESOLUTE US	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan
	▪ 4.0 mm Sub-study: 8 months: clinical and angiographic; 6, 12 and 18 months, 2-5 years: telephone ▪ 2.25 - 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; clinical visits (preferred) or patient contact 30 days (R-ASIA), 6, 12, 18 months then annually at 2, 3, 4, 5 years**	▪ 6 months and 2-5 years: telephone		▪ 6 months and 1-5 years: telephone	▪ 6, 9 and 18 months and 2-5 years: telephone
Status	12-month follow-up is complete. 551 subjects qualified for 18-month follow-up.	24-month follow-up is complete.	12-month follow-up is complete.	48-month follow-up complete.	12-month follow-up is complete.

* 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 design. The 2.25 mm Subset outcomes were compared to a performance goal.

**RESOLUTE Asia patients were consented for 5 years. At 3 years, if the event rates are demonstrated to plateau or decrease as compared to the rates in the prior years, the Steering Committee and Sponsor may consider stopping further follow-ups.

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

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

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

The 38 mm sub-study of the RESOLUTE United States Clinical Trial was performed to establish a reasonable assurance of safety and effectiveness for the proposed expanded indications under IDE G070165. Data from this clinical sub-study were the basis for the PMA Supplement approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between January 28, 2010 and March 31, 2011. The database for this PMA supplement reflected data collected through April 13, 2012 for R-US (114 patients) and April 26, 2012 for R-Asia (109 patients), for a total of 223 patients. There were 29 and 17 investigational sites in the US and in Asia, respectively.

The 38 mm Length Group includes pooled data from patients treated with a 38 mm stent from two multi-center, non-randomized studies: RESOLUTE US and RESOLUTE Asia. The primary endpoint was target lesion failure (TLF) at 12 months post-procedure, defined as cardiac death, target vessel myocardial infarction (Q wave and on-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. The RESOLUTE United States (RESOLUTE US) Clinical Trial for 38 mm lengths (including the RESOLUTE Asia 38 mm Length Sub-study) is a prospective, multicenter, non-randomized trial that evaluated the safety and effectiveness of the Resolute stent for treatment of de novo lesions in native coronary artery(ies) with reference vessel diameters (RVD) ranging from 3.0 mm to 4.2 mm and a lesion length ≤ 35 mm that is amenable to percutaneous treatment with a 38 mm length stent.

The 38 mm Length Group primary endpoint data were compared to a performance goal (PG) derived from a logistic regression model based on previous experience with the Medtronic Endeavor and the Medtronic Driver stents. The anticipated treatment difference between Driver patients and Endeavor patients (receiving clinical follow up only) was 12.6% (25.4% - 12.8%). Based on this analysis, the performance goal was set at 19%, which is 48% above the expected TLF rate for the Endeavor patients. This PG preserves 51% of the benefit vs. Driver patients. If the 12-month TLF rate of the Resolute 38 mm Length Group was shown to be significantly <19%, then the planned analysis would be considered to have met its primary objective. In other words, the assessment of TLF was tested with the following null and alternative hypotheses:

- H_0: $\pi \geq 19\%$ vs. H_1: $\pi < 19\%$, where π is the true Resolute 38 mm length stent 12-month TLF rate.

At a one-sided 0.05 level of significance, a sample size of 199 evaluable patients yields 80% power to reject the above null hypothesis in favor of the alternative, assuming the true Resolute 38 mm length stent 12-month TLF rate is 12.8%. Accounting for 10% clinical loss to follow up, a total sample size of 221 patients is needed.

All of the RESOLUTE clinical trials utilized an independent Clinical Events Committee (CEC) for adjudication of the clinical events. The definitions of clinical

events were consistent across the clinical trials and the event adjudication process was harmonized to ensure consistency and comparability of the data. All clinical trials had oversight by a Data and Safety Monitoring Board (DSMB). All trials had data monitored for verification and accuracy. Independent Angiographic Core Labs were utilized for angiographic and IVUS endpoints.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the 38 mm Length Sub-study was limited to patients who met the following inclusion criteria:

   - > 18 years old
   - Clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, and/or a positive functional study
   - Either a single target lesion, or two target lesions located in separate target vessels
   - De novo lesion(s) in native coronary artery(ies)
   - Target lesion(s) ≤35 mm for a lesion to be treated with a 38 mm length stent
   - Target lesion(s) stenosis of ≥50% and <100%
   - Target vessel(s) RVD of 3.0 to 4.2 mm for it to be treated with a 38 mm length stent
   - Target vessel(s) TIMI flow ≥2

   Patients were not permitted to enroll in the 38 mm Length Sub-study if they met any of the following exclusion criteria:

   - Serum creatinine level >2.5 mg/dl within 7 days prior to index procedure
   - Evidence of an acute MI within 72 hours of the intended study procedure: Q wave MI or any elevation of CK-MB isoenzyme above the laboratory ULN and had not returned to normal at the time of the index procedure. (Patients with evidence or suspicion of an acute MI or with an elevation of total CK greater than 2 times the ULN must have had CK-MB results reviewed prior to enrollment.)
   - Documented LVEF <30%
   - Target lesion(s) located in native vessel(s) distal to anastomosis with a bypass graft (including but not limited to a SVG or an LIMA with more than 40% DS within the graft). A target lesion distal to a graft may have been accessed through the graft.
   - Previous stenting in the target vessel(s) unless the following conditions were met:
     - It had been at least 9 months since the previous stenting, and
     - The target lesion(s) was/were at least 15 mm away from the previously placed stent
   - Target vessel(s) had/have other lesions with >40% DS based on visual estimate or on-line QCA
   - The target vessel(s) had evidence of thrombus
   - The target vessel(s) was/were excessively tortuous (two bends > 90º to reach the target lesion)

- The target lesion(s) had any of the following characteristics:
  - Lesion location was aorto-ostial, an unprotected left main lesion, or within 5 mm of the origin of the LAD or LCX
  - Involved a side branch >2.0 mm in diameter
  - Was at or distal to a >45º bend in the vessel
  - Was severely calcified
- Unprotected LM CAD (an obstruction > 50% in the LM coronary artery)

2. Follow-up Schedule

   All patients were scheduled to return for follow-up examinations at 30 days, 6 months, 9 months, 12 months, 18 months, 2 years, and annually to 5 years postoperatively. The RESOLUTE Asia patients were consented for 5 years. At 3 years, if the event rates are demonstrated to plateau or decrease as compared to the rates in the prior years, the Steering Committee and Sponsor may consider stopping further follow-ups.

   Preoperatively, evaluations of the Medical and Cardiac History, Angina Status, 12 Lead ECG, CK and CK-MB Biomarkers, QCA, and Medication Regimen were completed. Postoperatively, the objective parameters measured during the study included Angina Status, 12 Lead ECG, CK and CK-MB Biomarkers, and Medication Regimen as described in the Table below. Adverse events and complications were recorded at all visits.

Table 5: Schedule of Treatments and Assessments for the RESOLUTE 38 mm Group

	Index Hospitalization					Follow-up					
	Screening/Pre-procedure										
Event	**Screen**	**Prior to procedure within: 7 days**	**72 hours**	**Proced.**	**Post-proced.[b]**	**30 Day Clinic Visit[c]**	**6 Month Patient Contact[d]**	**9 Month Clinic Visit**	**12 Month Patient Contact[d]**	**18 Month Patient Contact[d]**	**2-5 Years Annually[a] Patient Contact[d]**
Informed Consent signed	X										
Medical and cardiac history	X										
Angina status	X				X	X	X	X	X	X	X
Pregnancy test[e]		X									
12 lead ECG		X			X Within 24 hours			X			
CK and CK-MB			X		X 6-8 hrs 12-16 hrs 20-24 hrs[f]						
QCA	X			X							
AE monitoring				X	X	X	X	X	X	X SAEs only	X SAEs only
Medication regimen	X Within 24 hours			X	X	X	X	X	X	X[h]	X[h]

a. R-Asia patients are followed through 3 years annually. Patients are consented for 5 years and additional follow up will be considered.
b. End of procedure was defined as removal of the guide catheter
c. The 30 day follow-up in R-Asia is a patient contact (phone calls, e-mail, and/or office visit)
d. Patient contact includes phone calls, e-mail, and/or office visit
e. For women of childbearing potential only
f. RESOLUTE US: If a patient was discharged prior to 20 hours, blood draw at discharge. RESOLUTE Asia: The 20-24 hour CK/CK-MB is not a protocol requirement.
g. RESOLUTE US: Baseline and final ACT required at a minimum for patients administered heparin for anticoagulation during the procedure
h. Antiplatelet/anticoagulation medications only

3. Clinical Endpoints

The Primary Safety and Effectiveness Composite Endpoint is Target Lesion Failure (TLF) at 12 months post-procedure in single lesion treated subjects. TLF was defined as Cardiac Death, Target Vessel Myocardial Infarction, or clinically-driven Target Lesion Revascularization (TLR). For dual vessel (DV) patients with 38 mm stents implanted in both vessels, one vessel/lesion was randomly selected as the target vessel/lesion and the other was treated as non-target vessel/lesion. For DV patients with one vessel implanted with a 38 mm stent and the other vessel without a 38 mm stent, the 38 mm vessel/lesion was considered as the target vessel/lesion. A clinical event that was clearly not attributed to target vessel was not included in the target vessel analysis.

With regards to safety, additional secondary endpoints include TLF, TVF, MACE, Cardiac Death or TVMI, Death or TVMI, Death (including Cardiac Death and Non-

Cardiac Death), TVMI, Clinically-driven TLR, Clinically-driven TVR, and Stent Thrombosis (Arc definite/probable, and Early versus Late).

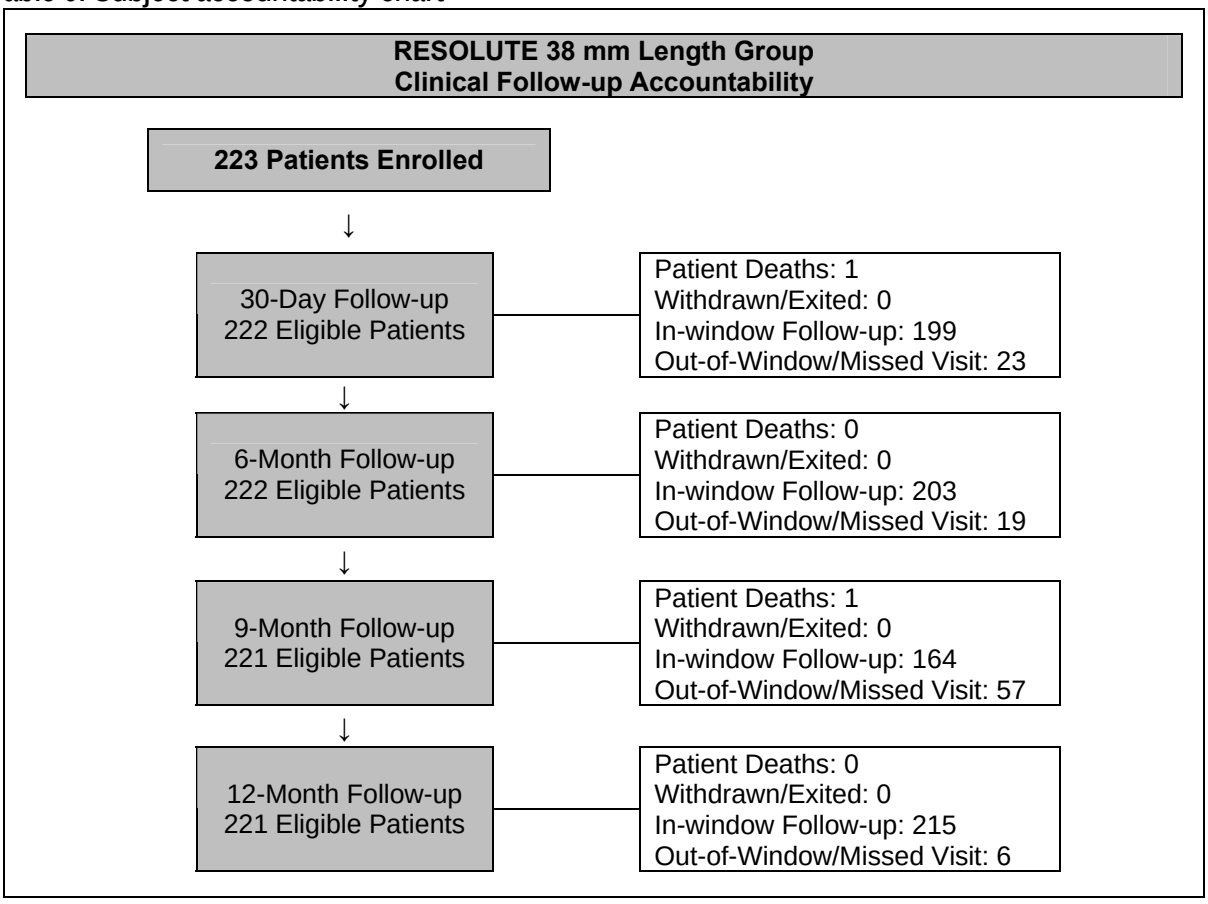
With regards to effectiveness, additional secondary endpoints include Lesion Success, Device Success, Procedure Success, and Device Specific Procedure Success.

With regard to success/failure criteria, the null hypothesis is rejected if the 12 month TLF rate for the RESOLUTE 38 mm Length Group is significantly below 19%.

B. Accountability of PMA Cohort

At the time of database lock, of 223 patients enrolled in PMA study (114 from R-US and 109 from R-Asia), 99.6% (n=222) patients are available for analysis at the completion of the study, the 12 month post-operative visit. This cohort is intent-to-treat.

Table 6: Subject accountability chart



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a Long Lesion Sub-study performed in the US. There is a higher proportion of Asian patients due to the information pooled from the Resolute-Asia study.

Table 7: Baseline Characteristics – 38 mm Length Group

Patient Characteristic	38 mm Length Group (N=223 Patients)
Age(years)	
Mean ± SD (N)	60.9±10.6 (223)
Number of Men	78.9% (176/223)
Ethnicity	
Hispanic/Latino	4.1% (9/220)
Race	
White	44.6% (99/222)
Black	3.6% (8/222)
Asia	50.9% (113/222)
Prior MI	32.4% (70/216)
Prior PCI	27.4% (61/223)
Ejection Fraction (%)	
Mean ± SD (N)	57.6±10.0 (184)
Prior CABG	7.2% (16/223)
Diabetes Mellitus	37.7% (84/223)
Insulin	10.3% (23/223)
History of Hypertension	74.9% (167/223)
History of Hyperlipidemia	58.7% (131/223)
History of Smoking	
Never	47.5% (106/223)
Former	33.6% (75/223)
Current	18.8% (42/223)
History of Stroke or TIA	5.8% (13/223)
Premature CAD in 1st Degree Relative	37.2% (71/191)
Number of diseased, native, major epicardial coronary vessels (>50% Stenosed)	
None	0.0% (0/223)
Single	46.2% (103/223)
Double	36.3% (81/223)
Triple	17.5% (39/223)
Reason for Revascularization	
Stable Angina	39.2% (76/194)
Unstable Angina	47.4% (92/194)
MI	13.4% (26/194)
CCS Class	
I	10.1% (19/189)
II	31.2% (59/189)
III	18.5% (35/189)
IV	40.2% (76/189)

Table 8. Baseline Angiographic Characteristics – 38 mm Length Group (per angio core lab)

Lesion Characteristic	38 mm Length Group (N=223 Patients, N=269 Lesions)
Vessel Location	
LAD	52.0% (116/223)
LCX	20.2% (45/223)
RCA	44.4% (99/223)
Lesion Location	
Proximal	37.6% (99/263)
Mid	43.7% (115/263)
Distal	17.1% (45/263)
Ostial	1.5% (4/263)
Length	
Discrete (<10 mm)	4.6% (12/261)
Tubular(10 - 19.9 mm)	24.5% (64/261)
Diffuse(>= 20 mm)	70.9% (185/261)
Eccentric	31.6% (83/263)
Bend	
<45 degrees	74.5% (196/263)
>=45 degrees to < 90 degrees	21.3% (56/263)
>=90 degrees	4.2% (11/263)
Thrombus	3.0% (8/263)
Tortuosity	
None	96.6% (254/263)
Moderate	3.0% (8/263)
Severe	0.4% (1/263)
Calcification	
Mild	65.0% (171/263)
Moderate	27.0% (71/263)
Severe	8.0% (21/263)
Ulcerated	4.2% (11/263)
Aneurysm	1.1% (3/263)
Intimal Flap	0.8% (2/263)
TIMI Flow	
0	2.3% (6/263)
1	3.8% (10/263)
2	6.5% (17/263)
3	87.5% (230/263)
Total Occlusion	2.3% (6/263)
Branch Vessel Disease	47.9% (126/263)
Sidebranch Stenosis	
Mean±SD (N)	30.4%±30.5% (127)
Modified ACC/AHA Lesion Class	
A	1.5% (4/263)
B1	7.2% (19/263)
B2	9.5% (25/263)
C	81.7% (215/263)

Table 9. QCA Characteristics Pre and Post Procedure – 38 mm Length Group (per angio core lab)

Lesion Characteristics	38 mm Length Group (N=223 Patients, N=269 Lesions)
Pre-Procedure	
Lesion Length (mm)	
Mean±SD (N)	25.22±8.83 (261)
Median (Q1,Q3)	26.54 (19.04,31.69)
Range (Min,Max)	(3.71,69.39)
Reference Vessel Diameter (mm)	
Mean±SD (N)	2.78±0.42 (263)
MLD (mm)	
Mean±SD (N)	0.80±0.36 (263)
% Stenosis	
Mean±SD (N)	71.33±11.61 (263)
Post-Procedure	
In-segment	
MLD (mm)	
Mean±SD (N)	2.24±0.44 (262)
% Stenosis	
Mean±SD (N)	20.82±9.94 (262)
In-stent	
MLD (mm)	
Mean±SD (N)	2.61±0.38 (261)
% Stenosis	
Mean±SD (N)	7.36±9.33 (261)

D. Safety and Effectiveness Results

1. Primary Safety and Effectiveness Endpoint

   The observed rate of 12 month target lesion failure (TLF) from the pooled RESOLUTE 38 mm Length Group when one lesion/vessel was randomly selected was 4.5% with a one-sided 95% CI of 7.5% thus, the null hypothesis was rejected as the 12 month TLF is significantly below the set Performance Goal of 19%. These analyses are based on the intent-to-treat population. The results are presented in the table below.

Table 10: Primary Endpoint Analyses – 38 mm Length Group

38 mm Length Group	Resolute (N=223)	Upper One-Sided 95% CI*	Performance Goal
Primary Analyses - all patients with randomly selected lesion/vessel			
12-month TLF			
ITT			
Available Data	4.5% (10/222)	7.5%	19.00%
Multiple Imputed Data	4.5%	6.8%	19.00%
PP			
Available Data	3.4% (7/205)	6.3%	19.00%
Multiple Imputed Data	3.4%	5.5%	19.00%
Secondary Analyses - all ITT patients with lesion/vessel selected by worst case approach **			
12-month TLF	5.4% (12/222)	8.6%	

* The one-sided 95% CI is calculated by binomial (exact) distribution for available data or by normal approximation for imputed data.

** In this analysis, the lesion/vessel with an event is selected as the TL. Note: The extended historical definition of MI is used in this table.

Adverse effects that occurred in the PMA clinical study:

Table 11: Post-Procedure Morphology – 38 mm Length Group

Lesion Characteristic	(N=223 Patients, N=269 Lesions)
No Reflow	
Transient	0.0% (0/262)
Sustained	0.0% (0/262)
Abrupt Closure	
Transient	0.4% (1/262)
Sustained	0.0% (0/262)
Post-Procedure Dissection	
None	98.9% (259/262)
Type A	0.0% (0/262)
Type B	1.1% (3/262)
Type C	0.0% (0/262)
Type D	0.0% (0/262)
Type E	0.0% (0/262)
Type F	0.0% (0/262)
Post-Procedure TIMI	
0	0.0% (0/262)
1	0.0% (0/262)
2	1.1% (3/262)
3	98.9% (259/262)
Stent Fractures	
Type I [1]	0.0% (0/262)
Type II [2]	0.0% (0/262)
Type III [3]	0.0% (0/262)
Type IV [4]	0.0% (0/262)
Type V [5]	0.0% (0/262)

[1] Stent Fracture Type I = Single strut fracture

[2] Stent Fracture Type II = Multiple single strut fractures

[3] Stent Fracture Type III = Complete transverse linear separation without stent displacement

[4] Stent Fracture Type IV = Complete transverse linear separation with stent displacement

[5] Stent Fracture Type V = Spiral dissection of stent

Table 12: ARC Defined Major Adverse Events to 360 Days – 38 mm Length Group

MAE to 360 Days - ARC Definition	(N=223 Patients)
Death	0.9% (2/222)
Cardiac Death	0.9% (2/222)
Vascular Death	0.0% (0/222)
Non Cardiovascular Death	0.0% (0/222)
All MI (Q or Non-Q wave)	19.8% (44/222)
Q Wave MI	0.9% (2/222)
Non-Q Wave MI	18.9% (42/222)
Sudden Death MI	0.0% (0/222)
TV MI (Q or Non-Q wave)	18.9% (42/222)
Q Wave MI	0.9% (2/222)
Non-Q Wave MI	18.0% (40/222)
Sudden Death MI	0.0% (0/222)
Non-TV MI (Q or Non-Q wave)	0.9% (2/222)
Q Wave MI	0.0% (0/222)
Non-Q Wave MI	0.9% (2/222)
Sudden Death MI	0.0% (0/222)
ARC Stent Thrombosis (to 360 days)	1.4% (3/222)
Definite ST	0.5% (1/222)
Probable ST	0.5% (1/222)

MAE to 360 Days - ARC Definition	(N=223 Patients)
Def + Prob ST	0.9% (2/222)
Def + Prob + Poss	1.4% (3/222)
Acute (0 to 1 day)	0.0% (0/222)
Definite ST	0.0% (0/222)
Probable ST	0.0% (0/222)
Def + Prob ST	0.0% (0/222)
Def + Prob + Poss	0.0% (0/222)
Sub-acute (2 to 30 days)	0.9% (2/222)
Definite ST	0.5% (1/222)
Probable ST	0.5% (1/222)
Def + Prob ST	0.9% (2/222)
Def + Prob + Poss	0.9% (2/222)
Early (to 30 days)	0.9% (2/222)
Definite ST	0.5% (1/222)
Probable ST	0.5% (1/222)
Def + Prob ST	0.9% (2/222)
Def + Prob + Poss	0.9% (2/222)
Late (31 days to 360 days)	0.5% (1/222)
Definite ST	0.0% (0/222)
Probable ST	0.0% (0/222)
Def + Prob ST	0.0% (0/222)
Def + Prob + Poss	0.5% (1/222)

The ARC-defined MI rates are considerably higher than the protocol-defined extended historical MI definition. The difference is due to the use of the troponin, a much more sensitive cardiac biomarker, in the ARC MI definition compared with CK and CK-MB in the extended historical MI definition.

Table 13: Stent Thrombosis (Historical Defined) to 360 Days – 38 mm Length Group

Stent Thrombosis to 360 days	(N=223 Patients)
Stent Thrombosis (Protocol)	0.9% (2/222)
Acute ST (0-1 day)	0.0% (0/222)
Sub-acute ST (>1 and <=30 days)	0.9% (2/222)
Late ST (>=31 and <=360 days)	0.0% (0/222)

It should be noted that the safety of the device 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 4.2 mm was not based on this sample alone, but rather on all the available information for the device to date. The safety data from this study were for confirmatory purposes.

2. Secondary Endpoints

The analysis of effectiveness was based on the n=222 evaluable at the 12 month time point. Key effectiveness outcomes are presented in the table below.

Table 14: Principal Safety and Effectiveness Endpoints – 38 mm Length Group

Outcomes at 12 Months	38 mm Length Group (N=223 Patients, 269 Lesions)
COMPOSITE SAFETY AND EFFECTIVENESSS	
TLF	5.4% (12/222)
TVF	6.8% (15/222)
MACE	6.3% (14/222)
EFFECTIVENESS	
Clinically-driven TVR	2.7% (6/222)
TLR	1.4% (3/222)
TLR, PCI	1.4% (3/222)
TLR, CABG	0.0% (0/223)
Non-TL TVR	1.4% (3/222)
Non-TL TVR, PCI	1.4% (3/222)
Non-TVR, CABG	0.0% (0/222)
SAFETY	
Total Death	0.9% (2/222)
Cardiac Death	0.9% (2/222)
Non Cardiac Death	0.0% (0/222)
Cardiac Death or TVMI	4.5% (10/222)
TVMI	3.6% (8/222)
Q wave MI	0.9% (2/223)
Non-Q wave MI	2.7% (6/223)
Stent Thrombosis ARC Defined	
Definite/Probable	0.9% (2/222)
Definite	0.5% (1/222)
Probable	0.5% (1/222)

N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
The definitions of the outcomes are presented as table notes to Table 8 1- Principal Adverse Events.
12-month timeframe includes follow-up window (360 days ± 30 days).
See Table 9 4 for the definition of the ARC defined Stent Thrombosis.
*In this analysis, the lesion/vessel with an event is selected as the target lesion

3. Subgroup Analyses

The 38 mm Length Sub-study data were evaluated *post hoc* for possible gender-based differences in baseline characteristics and clinical outcomes, as well as for any interaction between treatment and gender. The trial was not designed or powered to study safety or effectiveness in sex-specific subgroups, so these analyses are considered hypothesis generating.

In the 38 mm Length Sub-study population, of the 223 patients enrolled, 176 patients were male (78.9%) and 47 patients were female (21.1%). In patients

treated with the subject stent, the 12 month rate of TLF was 4.0% in males and 10.9% in females (table below). Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 15: Principal Safety and Effectiveness Endpoints by Gender – RESOLUTE 38 mm Length Group

	Male (N=176 patients)	Female (N=47pateints)	P-value*
COMPOSITE SAFETY AND EFFECTIVENESS			
TLF	4.0% (7/176)	10.9% (5/46)	0.197
TVF	5.1% (9/176)	13.0% (6/46)	0.256
MACE	5.1% (9/176)	10.9% (5/46)	0.313
EFFECTIVENESS			
Clinically Driven TVR	1.7% (3/176)	6.5% (3/46)	0.424
Clinically Driven TLR	0.6% (1/176)	4.3% (2/46)	0.275
SAFETY			
Death	0.6% (1/176)	2.2% (1/46)	0.718
Cardiac Death	0.6% (1/176)	2.2% (1/46)	0.718
Non Cardiac Death	0.0% (0/176)	0.0% (0/46)	1.000
TVMI (Extended Historical Definition)	2.8% (5/176)	6.5% (3/46)	0.266
Cardiac Death or TVMI	3.4% (6/176)	8.7% (4/46)	0.250
Stent Thrombosis ARC defined			
Definite/Probable	0.6% (1/176)	2.2% (1/46)	0.653
Definite	0.0% (0/176)	2.2% (1/46)	0.327
Probable	0.6% (1/176)	0.0% (0/46)	0.355

*P-value is adjusted to propensity score. The propensity scores were calculated with gender as dependent variable, and the following baseline variables as independent variables: age, current smoker, prior PCI, hyperlipidemia, diabetes, hypertension, prior MI, prior CABG, unstable angina or MI, LAD, B2/C lesion, moderate/severe calcification, Bend >45, TIMI 3, RVD, lesion length and %diameter stenosis.

Additional information is provided in the table below for the RESOLUTE US 38 mm Length Group in subjects with diabetes mellitus.

Table 16: RESOLUTE 38 mm Length Group: All 38 mm Subjects, Insulin-Dependent DM Subjects (IDDM), Non-Insulin Dependent DM Subjects (Non-IDDM), and Non-DM Subjects - Principal Safety and Effectiveness through 12 Months

	All Diabetic 38 mm Length Group Subjects (N=84 Patients)	38 mm Length Group IDDM (N=23 Patients)	38 mm Length Group – Non-IDDM (N=61 Patients)	38 mm Length Group – Non-DM (N=139 Patients)
COMPOSITE SAFETY AND EFFECTIVENESS				
TLF	6.0% (5/84)	4.3% (1/23)	6.6% (4/61)	5.1% (7/138)
TVF	7.1% (6/84)	4.3% (1/23)	8.2% (5/61)	6.5% (9/138)
MACE	8.3% (7/84)	4.3% (1/23)	9.8% (6/61)	5.1% (7/138)
EFFECTIVENESS				
Clinically-driven TVR	3.6% (3/84)	0.0% (0/23)	4.9% (3/61)	2.2% (3/138)

	All Diabetic 38 mm Length Group Subjects (N=84 Patients)	38 mm Length Group IDDM (N=23 Patients)	38 mm Length Group – Non-IDDM (N=61 Patients)	38 mm Length Group – Non-DM (N=139 Patients)
TLR	2.4% (2/84)	0.0% (0/23)	3.3% (2/61)	0.7% (1/138)
SAFETY				
Total Death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Cardiac Death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Non Cardiac Death	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)
Cardiac Death or TVMI	3.6% (3/84)	4.3% (1/23)	3.3% (2/61)	5.1% (7/138)
TVMI	2.4% (2/84)	4.3% (1/23)	1.6% (1/61)	4.3% (6/138)
Stent Thrombosis ARC defined				
Stent Thrombosis (ARC def/prob)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Early (<= 30 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Late (> 30 and <=360 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of the Resolute Integrity Zotarolimus- Eluting Coronary Stent System 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 clinical studies. These test results revealed the following information:

A. Effectiveness Conclusions

The observed rate of 12 month target lesion failure (TLF) from the RESOLUTE 38 mm Length Group was 4.5% with a one-sided 95% CI of 7.5%. Thus, the primary endpoint was met as the 12 month TLF rate was significantly below the Performance Goal of 19% derived from ENDEAVOR stent data.

B. Safety Conclusions

The risks of the device are based on nonclinical 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, and *in vivo* animal testing conducted demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the stents and delivery system(s) demonstrated that the performance characteristics met the product specifications and the

coating characterization testing adequately described the important attributes of the zotarolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 18 months.

The results of the RESOLUTE 38 mm Length Group clinical study showed that the principal adverse events rates for the Resolute stent were similar to those observed in the historical trials of the ENDEAVOR stent. When analyzed in conjunction with additional studies in the Global RESOLUTE Clinical Program, the clinical data available also support the safety of the Resolute stent when used in patients with diabetes mellitus. The results from the RESOLUTE clinical trials demonstrate that the Resolute product provides reasonable assurance of safety and effectiveness when used as indicated in accordance with the Directions for Use.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The Resolute stent has been shown to be beneficial for improving luminal diameter in patients with symptomatic coronary artery disease. Rates of target lesion failure (TLF) (defined as cardiac death related to the target vessel, MI related to the target vessel or target lesion revascularization) met the performance goal derived from ENDEAVOR stent data.

Additional factors to be considered in determining probable risks and benefits for the Resolute System included: Important secondary endpoints such as the rates of cardiac death, MI and stent thrombosis; the observed rates of these secondary endpoints following implantation of RESOLUTE 38 mm length stents were acceptably low.

Patient and lesion characteristics should be considered in the treatment decision regarding the treatment of stenotic coronary lesions with drug-eluting stents, bare-metal stents, medical therapy or coronary artery bypass grafting.

In conclusion, given the available information above, the data support 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 4.2 mm, the probable benefits outweigh the probable risks.

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.

XIII. CDRH DECISION

CDRH issued an approval order on February 22, 2013. The final conditions of approval cited in the approval order are described below.

1) *Resolute Integrity Post-Approval Study:* The applicant must incorporate the Resolute Integrity stent lengths 34 and 38mm (2.25 mm to 4.2 mm diameters) into the existing post-approval study required for P110013. As per investigational plan version 126 rev 1C, dated February 7, 2013 this is a prospective, open-label, multi-center post-approval study, consisting of consecutively newly enrolled US patients with a follow-up duration of at least 5 years. The primary endpoint will be a composite of cardiac death and target vessel myocardial infarction at 12 months. The secondary endpoints will be a composite of major adverse cardiac events (MACE), target lesion failure, target vessel failure, and cardiac death/target vessel MI at 5 years. Clinical secondary endpoints are to include death, MI, target lesion revascularization, target vessel revascularization, stent thrombosis, stroke, bleeding complications, and dual antiplatelet therapy compliance at 5 years. All endpoints should be evaluated separately for the following categories: (1) de novo lesion treated with stent lengths ≤ 30 mm in length (2.25 mm to 4.2 mm diameters) and (2) de novo lesion treated with stents 34 mm and 38 mm (2.25 mm to 4.2 mm diameters) as subset analyses. In addition to the original 230 patients required for enrollment in the post-approval study under P110013, the applicant will enroll 56 more patients with a minimum of 20 patients enrolled in the 34 mm cohort and a minimum of 20 patients enrolled in the 38 mm cohort.

2) *Continued Follow-up of the Premarket and OUS Cohort:* In addition to the post-approval study enrolling new US patients as outlined above, the applicant must continue follow-up of patients in the Global RESOLUTE Clinical Trial program through 5 years post-procedure, with the exception of patients enrolled in the RESOLUTE International study, which the applicant should continue to follow through 3 years post-procedure per protocol (P110013). The applicant must collect clinical outcomes as outlined in the respective investigational plans submitted in G070165, analyzing and reporting on these findings as agreed upon in the Statistical Analysis Plan version dated February 8, 2013 (email).

3) Annual testing reports will be provided that evaluate drug stability. The Resolute Integrity stent sizes (34 and 38 mm) will be incorporated into the ongoing stability protocol to bracket the additional stent sizes to be marketed.

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

XIV. 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.