

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Eluting Coronary Stent System (NIQ)
Device Trade Name: Resolute MicroTrac Zotarolimus-Eluting Coronary Stent System
Resolute Integrity Zotarolimus-Eluting Coronary Stent System

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

Date of Panel Recommendation: None

Premarket Approval Application (PMA Number): P110013

Date of FDA Notice of Approval: February 17, 2012

Expedited: Not Applicable

II. INDICATIONS FOR USE

The Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems are 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.

III. CONTRAINDICATIONS

The Resolute MicroTrac and Resolute Integrity stent systems are 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 MicroTrac Zotarolimus-Eluting Coronary Stent System and the Resolute Integrity Zotarolimus-Eluting Coronary Stent System labeling.

V. DEVICE DESCRIPTION

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

- A device component, which consists of a Driver™, Micro-Driver™ or Integrity Bare Metal Coronary Stent on the MicroTrac Delivery System. The Resolute MicroTrac utilizes the Driver™ and Micro-Driver™ Bare Metal Stent (BMS), and the Resolute Integrity utilizes the Integrity BMS. 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 MicroTrac and Resolute Integrity are described in Table 1.

Table 1: Resolute MicroTrac and Resolute Integrity Product Description

	Resolute MicroTrac RX	Resolute Integrity RX	Resolute MicroTrac OTW	Resolute Integrity OTW
Available Stent lengths (mm) ¹	8, 9, 12, 14, 15, 18, 22, 26, 30			
Available stent diameters (mm) ²	2.25, 2.5, 2.75, 3.0, 3.5, 4.0			
Stent Material	A cobalt-based alloy (MP35N)			
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 30mm) is 300µg.			
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 2.75mm diameter stents are not available in lengths of 9 and 15mm

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

A. Device Component Description

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

The Resolute MicroTrac uncoated stent is identical to the MicroDriver (2.25 mm, 2.5 mm and 2.75 mm diameters) (P030009/S2) and Driver (3.0 mm, 3.5 mm and 4.0 mm diameters) bare metal stents (P030009). The Resolute Integrity uncoated stent is identical to the Integrity bare metal stent (P030009/S039).

The Resolute MicroTrac and Resolute Integrity stents utilize the same API as the Endeavor (P060033) and Endeavor Sprint (P060033/S1) Zotarolimus-Eluting Stent (DES) Systems, but feature a different polymer coating (BioLinx). The BioLinx polymer coating is intended to provide extended elution characteristics compared to the Endeavor and Endeavor Sprint products.

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

B. Drug Component Description

The drug coating on Resolute MicroTrac and 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 same API used in the Endeavor Sprint Zotarolimus-Eluting Coronary Stent System (P060033/S001).

B1. Zotarolimus

The active pharmaceutical ingredient utilized in Resolute MicroTrac and 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.

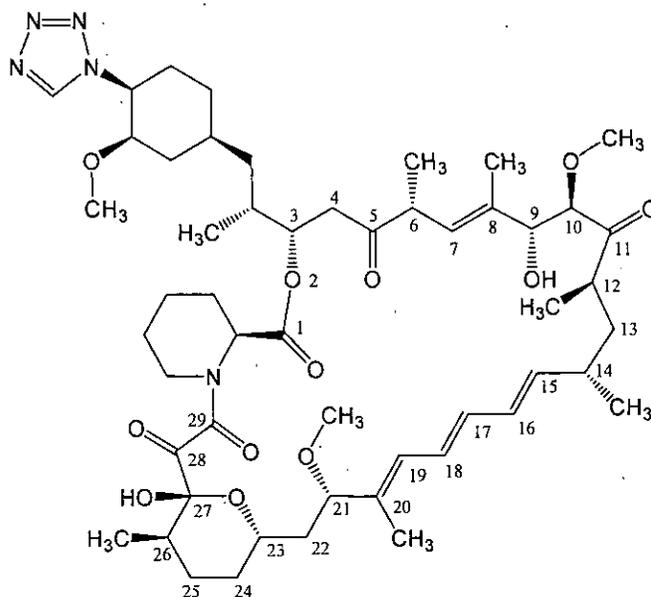


Figure 1: Chemical Structure of Zotarolimus

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 $C_{32}H_{79}N_5O_{12}$ 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 MicroTrac and 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 shown in Figure 2.

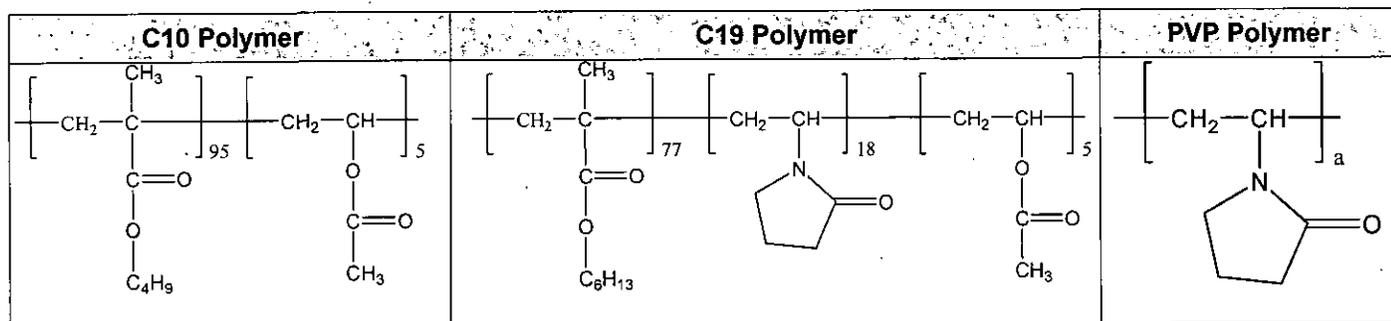


Figure 2: Chemical Structure of Biolinx Polymer Sub-units

Table 2: Product Matrix and Zotarolimus Content

Product Number Resolute MicroTrac OTW	Product Number Resolute MicroTrac RX	Product Number Resolute Integrity OTW	Product Number Resolute Integrity RX	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSMT22508W	RSMT22508UX	RSINT22508W	RSINT22508UX	2.25	8	59
RSMT25008W	RSMT25008UX	RSINT25008W	RSINT25008UX	2.5	8	59
RSMT27508W	RSMT27508UX	RSINT27508W	RSINT27508UX	2.75	8	59
RSMT30009W	RSMT30009UX	RSINT30009W	RSINT30009UX	3.0	9	90
RSMT35009W	RSMT35009UX	RSINT35009W	RSINT35009UX	3.5	9	90
RSMT40009W	RSMT40009UX	RSINT40009W	RSINT40009UX	4.0	9	90
RSMT22512W	RSMT22512UX	RSINT22512W	RSINT22512UX	2.25	12	85
RSMT25012W	RSMT25012UX	RSINT25012W	RSINT25012UX	2.5	12	85
RSMT27512W	RSMT27512UX	RSINT27512W	RSINT27512UX	2.75	12	85
RSMT30012W	RSMT30012UX	RSINT30012W	RSINT30012UX	3.0	12	120
RSMT35012W	RSMT35012UX	RSINT35012W	RSINT35012UX	3.5	12	120
RSMT40012W	RSMT40012UX	RSINT40012W	RSINT40012UX	4.0	12	120
RSMT22514W	RSMT22514UX	RSINT22514W	RSINT22514UX	2.25	14	102
RSMT25014W	RSMT25014UX	RSINT25014W	RSINT25014UX	2.5	14	102
RSMT27514W	RSMT27514UX	RSINT27514W	RSINT27514UX	2.75	14	102
RSMT30015W	RSMT30015UX	RSINT30015W	RSINT30015UX	3.0	15	150
RSMT35015W	RSMT35015UX	RSINT35015W	RSINT35015UX	3.5	15	150
RSMT40015W	RSMT40015UX	RSINT40015W	RSINT40015UX	4.0	15	150
RSMT22518W	RSMT22518UX	RSINT22518W	RSINT22518UX	2.25	18	128
RSMT25018W	RSMT25018UX	RSINT25018W	RSINT25018UX	2.5	18	128
RSMT27518W	RSMT27518UX	RSINT27518W	RSINT27518UX	2.75	18	128
RSMT30018W	RSMT30018UX	RSINT30018W	RSINT30018UX	3.0	18	180
RSMT35018W	RSMT35018UX	RSINT35018W	RSINT35018UX	3.5	18	180
RSMT40018W	RSMT40018UX	RSINT40018W	RSINT40018UX	4.0	18	180
RSMT22522W	RSMT22522UX	RSINT22522W	RSINT22522UX	2.25	2	153
RSMT25022W	RSMT25022UX	RSINT25022W	RSINT25022UX	2.5	22	153
RSMT27522W	RSMT27522UX	RSINT27522W	RSINT27522UX	2.75	22	153
RSMT30022W	RSMT30022UX	RSINT30022W	RSINT30022UX	3.0	22	220
RSMT35022W	RSMT35022UX	RSINT35022W	RSINT35022UX	3.5	22	220
RSMT40022W	RSMT40022UX	RSINT40022W	RSINT40022UX	4.0	22	220
RSMT22526W	RSMT22526UX	RSINT22526W	RSINT22526UX	2.25	26	188
RSMT25026W	RSMT25026UX	RSINT25026W	RSINT25026UX	2.5	26	188
RSMT27526W	RSMT27526UX	RSINT27526W	RSINT27526UX	2.75	26	188
RSMT30026W	RSMT30026UX	RSINT30026W	RSINT30026UX	3.0	26	260
RSMT35026W	RSMT35026UX	RSINT35026W	RSINT35026UX	3.5	26	260
RSMT40026W	RSMT40026UX	RSINT40026W	RSINT40026UX	4.0	26	260
RSMT22530W	RSMT22530UX	RSINT22530W	RSINT22530UX	2.25	30	213
RSMT25030W	RSMT25030UX	RSINT25030W	RSINT25030UX	2.5	30	213
RSMT27530W	RSMT27530UX	RSINT27530W	RSINT27530UX	2.75	30	213
RSMT30030W	RSMT30030UX	RSINT30030W	RSINT30030UX	3.0	30	300
RSMT35030W	RSMT35030UX	RSINT35030W	RSINT35030UX	3.5	30	300
RSMT40030W	RSMT40030UX	RSINT40030W	RSINT40030UX	4.0	30	300

C. Mechanism of Action

The mechanism (or mechanisms) by which Resolute MicroTrac and 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 placement of 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 MicroTrac Zotarolimus-Eluting Coronary System has not been marketed in the United States or any foreign country.

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

Table 3: Resolute Integrity Commercial Availability

Algeria	Columbia	Kazakhstan	Nicaragua	Trinidad and Tobago
Antigua and Barbuda	Cyprus	Kyrgyzstan	Nigeria	Tunisia
Armenia	Czech Republic	Korea (South)	Norway	Turkey
Aruba	Denmark	Kuwait	Pakistan	Uganda
Australia	Estonia	Laos	Paraguay	Ukraine
Austria	Finland	Latvia	Philippines	United Kingdom
Bahamas	France	Lebanon	Poland	Uruguay
Bahrain	Georgia	Liechtenstein	Portugal	Uzbekistan
Bangladesh	Germany	Lithuania	Qatar	Vietnam
Barbados	Ghana	Luxemburg	Romania	Virgin Islands
Belarus	Greece	Macau	Russia	Yemen
Belgium	Guyana	Macedonia	Senegal	Zimbabwe
Belize	Honduras	Malaysia	Serbia	
Bermuda	Hong Kong	Malta	Slovakia	
Bolivia	Hungary	Mauritius	Slovenia	
Bosnia-Herzegovina	Iceland	Montenegro	Spain	
Botswana	India	Morocco	Sudan	

Brunei	Indonesia	Mozambique	Sweden
Bulgaria	Ireland	Myanmar	Switzerland
Cambodia	Israel	Namibia	Syria
Cayman Islands	Italy	Netherlands	Taiwan
Croatia	Jamaica	New Zealand	Thailand

As of January 6, 2012, approximately 261,000 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 associated with the use of Resolute MicroTrac and 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 NONCLINICAL AND PHARMACOKINETIC STUDIES

A series of non-clinical laboratory and pharmacokinetic studies were performed on the Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Stent Systems. Studies were performed on the bare metal stent (Driver, MicroDriver or Integrity stent mounted on the stent delivery system), the coated stent alone, the polymer-only coated stent alone, the MicroTrac delivery system, and the finished combination products (i.e., Resolute MicroTrac and Resolute Integrity Coronary Stent Systems). These evaluations included biocompatibility studies, *in vivo* pharmacokinetics, *in vitro* engineering tests, coating characterization, chemistry, manufacturing, and controls (CMC) testing, animal studies, stability and shelf life, and sterilization.

A. Biocompatibility

A series of biocompatibility tests were conducted to demonstrate that the components of Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent System are non-toxic and biocompatible. The Resolute MicroTrac and Resolute Integrity stents were categorized as implant devices with permanent blood contact (>30 days). The MicroTrac Delivery System (used with both Resolute MicroTrac and Resolute Integrity stents) was categorized as an external communicating device in limited contact with circulating blood (<24 hours).

All biocompatibility testing was conducted in accordance with:

- Good Laboratory Practices Regulations (21 CFR § 58)
- Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems Document (April 18, 2010)
- ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing (2003)

With the exception of the stent-only Chromosomal Aberration testing which was conducted on Resolute stents deployed from final, sterilized clinical product mounted on the prior generation Sprint delivery system, all test articles used in the biocompatibility studies were final, sterilized Resolute Zotarolimus-Eluting Coronary Stent Systems on the MicroTrac (RX or OTW) Delivery System. When required per protocol, the stent was aseptically removed from the delivery system prior to testing.

Biocompatibility of the Resolute Integrity Zotarolimus-Eluting Coronary Stent System was demonstrated by leveraging testing previously conducted on the Integrity bare metal stent (P030009/S039) and the Resolute MicroTrac stent system. Leveraging this testing information was appropriate because the Resolute Integrity uncoated stent is identical to the Integrity bare metal stent (P030009/S039), and the Resolute Integrity stent system utilizes the same stent coating, delivery system, final packaging, and sterilization method as the Resolute MicroTrac. Two manufacturing changes were made to the MicroTrac Delivery System subsequent to the completion of the biocompatibility testing. These changes did not introduce any new materials and an appropriate justification was provided for leveraging the previously conducted biocompatibility testing.

Table 4 provides a summary of the biocompatibility testing conducted to support of Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems.

Table 4: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Cytotoxicity	MHLW Cytotoxicity, Colony Assay Method (Extraction)	Resolute Stent	Pass
		MicroTrac Rx Delivery System	
	MicroTrac OTW Delivery System		
	ISO10993-5 Direct Contact Cytotoxicity (L929 Mouse Fibroblast Cells)	Resolute Stent	Pass

Table 4: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
	ISO10993-5 Cytotoxicity (L929 MEM Elution)	MicroTrac RX Delivery System MicroTrac OTW Delivery System	Pass
Sensitization	ISO10993-10 Murine Local Lymph Node Assay	Resolute Stent	Pass
		MicroTrac RX Delivery System MicroTrac OTW Delivery System	
	ISO10993-10 ISO Maximization Sensitization	MicroTrac RX Delivery System	Pass
		MicroTrac OTW Delivery System	
Irritation/ Intracutaneous	ISO10993-10 Intracutaneous Reactivity	Resolute Stent	Pass
		MicroTrac RX Delivery System	
		MicroTrac OTW Delivery System	
Acute System Toxicity	MHLW Acute Systemic Toxicity	Resolute Stent	Pass
	ISO10993-11 Acute Systemic Toxicity	MicroTrac RX Delivery System	Pass
		MicroTrac OTW Delivery System	
Pyrogenicity	ISO10993-11 USP <151> Material Medicated Pyrogen	Resolute Stent	Pass
		MicroTrac RX Delivery System	
		MicroTrac OTW Delivery System	
Subchronic Toxicity	ISO10993-11 4 Week Systemic Toxicity	Resolute Stent	Pass
Genotoxicity	ISO10993-3 Bacterial Reverse Mutation Study	Resolute Stent	Pass
	ISO10993-3 <i>In-vivo</i> Mouse Peripheral Blood Micronucleus Study	Resolute Stent	Pass
	ISO10993-3 Chromosomal Aberration Assay	Resolute Stent	Pass
Hemocompatibility	ASTM <i>In-vitro</i> Hemolysis, Indirect Method	Resolute Stent	Pass
		MicroTrac RX Delivery System	
		MicroTrac OTW Delivery System	
	ASTM <i>In-vitro</i> Hemolysis, Direct Method	Resolute Stent	Pass
	ISO10993-4 Complement Activation C3a and SC5b-9	Resolute Stent	Pass
MicroTrac RX Delivery System MicroTrac OTW Delivery System			
ISO10993-4 <i>In-vivo</i> Thromboresistance	Resolute MicroTrac RX Delivery System (finished device)	Pass	

Table 5 summarizes studies and risk assessment that further support the safety and biocompatibility of the polymer components of the Resolute MicroTrac and Resolute Integrity stent coating.

Table 5: Summary of Additional Studies on Resolute Polymer Components

Study Category	Study Description	Conclusion
In Vitro	Assay for monocyte adhesion	The BioLinx has minimal risk of inducing an inflammatory reaction
	Assay for monocyte inflammatory activation	
	Assay for inflammation and activation of coronary vascular cells	The BioLinx polymer has minimal risk of prothrombotic potential
	Thermal stability as determined by thermogravimetric analysis (TGA)	The BioLinx polymer is biostable under physiologically and clinically relevant environments
	Hydrolytic stability as determined by BioLinx polymer characterization after PBS incubation at 37°C for 270 days	

In vivo animal testing conducted on the Resolute MicroTrac and Resolute Integrity stent systems evaluated the effects of drug and device exposure in a porcine coronary artery for up to 365 days, in lieu of ISO-10993 chronic toxicity and muscle implantation testing. These studies showed no evidence of local arterial or systemic toxicity. The resulting tissue histology in these studies did not display pathology consistent with drug or polymer-induced toxicity. The animal studies are summarized separately in Section I – Animal Studies, below.

Formal carcinogenicity and reproductive toxicity testing was not conducted on the Resolute MicroTrac or Resolute Integrity stents. The carcinogenic potential of the Resolute MicroTrac and Resolute Integrity stents is minimal based on the quantities of materials present (cobalt-chromium alloy, Parylene C primer and BioLinx polymer) and the limited period of zotarolimus release. The genotoxicity and reproductive toxicity of zotarolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*. See Section B – Studies of Drug Substance.

Based on *in vitro* analytical and stability testing results, there is no evidence to suggest that any chemical interactions occur between the BioLinx polymer and zotarolimus drug under established processing and storage conditions that would lead to the formation of covalent bonds or that would alter the structure of the drug in any way to form a new intermediate or molecular entity.

B. Studies of the Drug Substance

Medtronic Vascular provided a letter from the drug substance manufacturer, Abbott Laboratories Inc., authorizing FDA access to a Drug Master File (DMF) in support of this application. *In vivo* and *in vitro* pharmacology and toxicology studies as well as animal and human pharmacokinetic studies were conducted on zotarolimus to provide information about systemic and regional toxicity, distribution profiles, end-organ disposition, drug metabolism and potential drug-drug interactions.

The drug component of the Resolute MicroTrac and Resolute Integrity stent is identical to the active ingredient of the Endeavor Zotarolimus-Eluting Coronary Stent System. Therefore, the information provided for the studies of the drug substance for the Endeavor Zotarolimus-Eluting Coronary Stent System (P060033) is directly applicable to this PMA, and therefore is not repeated here. Details regarding the following: intravenous administration of zotarolimus, safety pharmacology, toxicology, ADME studies and drug interactions, can be found in the SSED for P060033 located at http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060033b.pdf.

C. *In Vivo* Pharmacokinetics

The pharmacokinetics information for the Resolute MicroTrac and Resolute Integrity stent systems is derived from a study conducted on the Resolute Zotarolimus-Eluting Coronary Stent System (Resolute stent system). The Resolute Integrity stent system is similar to the Resolute stent system with regard to the stent design, and the stent coating technology (dosing and drug to polymer ratio) and delivery system design and materials. Given these similarities and supportive bench and animal study information, the findings from the RESOLUTE First In Man (FIM) PK Sub-study, as described below, are applicable to both the Resolute MicroTrac and Resolute Integrity stent systems.

The pharmacokinetics (PK) of zotarolimus delivered from the Resolute Stent has been determined in subjects with coronary artery disease after stent implantation. Twenty-two subjects in the RESOLUTE-FIM Clinical Trial were enrolled in a pharmacokinetic (PK) sub-study. The RESOLUTE-FIM Clinical Trial was a prospective, multi-center, controlled trial, which took place in New Zealand and Australia. The pharmacokinetic sub-study was designed to assess the acute pharmacokinetics and safety of zotarolimus administered using the Resolute Zotarolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries.

Blood samples (5 mL) were collected at 30 days post-procedure. Selected pharmacokinetic parameters for the RESOLUTE PK sub-study analysis are provided in **Table 6**.

Table 6: Zotarolimus Pharmacokinetics in the RESOLUTE FIM Clinical Trial PK Sub-Study Patients After Implantation of Resolute Zotarolimus-Eluting Coronary Stents

PK Parameter	Units	Group I (128 µg) N = 1†	Group II ^a (180 µg) N = 11	Group III ^a (240 µg) N = 7	Group IV ^a (300 µg) N = 3
C _{max}	(ng/mL)	0.129	0.210 ±0.062	0.300 ±0.075	0.346 ±0.133
T _{max}	(h)	1.00	0.9 ±0.7	0.9 ±0.5	0.8 ±0.5
AUC _{0-last}	(ng•h/mL)	15.08	16.04 ±4.74	35.89 ±12.79	31.19 ±17.69
AUC _{0-inf} [§]	(ng•h/mL)	41.89	39.09 ±11.77	52.41 ±12.57	80.12 ±51.00
B [‡]	(1/h)	0.003	0.004 ±0.001	0.004 ±0.001	0.003 ±0.002
t _{1/2} [#]	(h)	263.4	195.5 ±74.4	167.4 ±29.7	208.3 ±144.4
CL/F [§]	(L/h)	3.06	5.23 ±2.55	4.80 ±1.11	5.14 ±3.55
V _{dβ} /F [§]	(L)	1161.2	1449.3 ±221.6	1181.2 ±336.4	1658.6 ±494.8

Notes:

C_{max} = Maximum volume of distribution

T_{max} = Time to C_{max}

AUC_{0-last} = Area under the blood concentration-time curve (AUC)

from time 0 to time of last measurable concentration

AUC_{0-inf} = AUC from time 0 to infinity (AUC_{0-inf}).

t_{1/2} = Harmonic mean half-life

CL/F = Mean apparent clearance

V_{dβ}/F = Apparent volume of distribution

^a Primary dose groups

† No SD was reported when N = 1

‡ Harmonic mean ±pseudo-standard deviation

Not a true estimate of the elimination half-life as the drug release from the stent was not complete during the course of the pharmacokinetic sampling

§ Not a true sample

The results in **Table 6** show that the pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation (including dose groups with N > 1), 180, 240 and 300 µg, following the implantation of the Resolute stents as illustrated by dose proportional increases in maximum blood concentration (C_{max}), area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration (AUC_{0-last}) and AUC from time 0 to infinity (AUC_{0-inf}). The mean apparent clearance (CL/F) and harmonic mean half-life (t_{1/2}) for the primary dose groups ranged from 4.80 to 5.23 L/h and 167.4 to 208.3 h, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 0.8 to 0.9 h after stent implantation.

The data demonstrate dose proportionality and linearity similar to that seen with increasing zotarolimus doses from the Endeavor stent (P060033) and intravenous administration. Based on available zotarolimus pharmacokinetic data, systemic safety margins at multiples of ≥78-fold has been established for the Resolute stent at 300 µg due to the extended elution of Implants in the Magnetic zotarolimus from the BioLinx polymer.

D. In Vitro Engineering Testing

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

- FDA Guidance for Industry and Staff: Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 18, 2010
- FDA Guidance for Industry and Staff: Establishing Safety and Compatibility of Passive Resonance (MR) Environment, August 2008

Testing was conducted on devices representative of Resolute MicroTrac and Resolute Integrity, except where testing could be leveraged from the Integrity (P03009/S39), Driver (P030009) and Micro-Driver (P030009/S2) Bare Metal Coronary Stent Systems. Leveraging this testing information was appropriate because the Resolute Integrity uncoated stent is identical to the Integrity bare metal stent (P030009/S039), and the Resolute MicroTrac uncoated stent is identical to the Driver and MicroDriver bare metal stent. The applicant provided an appropriate rationale where the testing was leveraged or representative devices were used for each attribute evaluated.

In addition, two manufacturing changes were made to the MicroTrac Delivery System subsequent to the completion of the *in vitro* testing. Several *in vitro* tests were repeated to support these changes, and an appropriate justification was provided for leveraging the other tests. The delivery system with the manufacturing changes implemented is referred to as “Modified MicroTrac” or “Commercial MicroTrac.”

The *in vitro* engineering studies, which support the performance of Resolute MicroTrac and Resolute Integrity, are provided in Table 7. In the table below, “Resolute stent” means the stent used in the Resolute MicroTrac system. “Pass” denotes that the test results met product specifications and/or the recommendations in the above-referenced guidance document.

Table 7: In Vitro Testing Supporting the Performance of Resolute Micro Trac and Resolute Integrity

Test	Description of Test	Test Article	Results
Stent Integrity, Dimensional and Functional Attributes			
Fretting Corrosion	This test evaluated the risk of stent failure caused by fretting corrosion of Driver, MicroDriver, Integrity, Resolute and Resolute Integrity stents deployed in an overlapped configuration in a 1.5 cm radius bend after 420 million cycles. The results met all acceptance criteria and indicated that the stents possess a high resistance to fretting corrosion.	Resolute Integrity Stent; Resolute Stent	Pass
Deployed Stent Length	This test demonstrated that the stent length is consistent with labeling when deployed at nominal pressure. Each stent was deployed to nominal pressure, and the stent length was measured. The results indicated that the length of Resolute and Resolute Integrity stents is consistent with labeling.	Resolute Integrity Stent; Resolute Stent	Pass
Foreshortening at Nominal	The 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 F2081-06. All samples met product specifications.	Resolute Integrity Stent; Resolute Stent	Pass
Foreshortening at Maximum	The test measured the change in stent length from the catheter-loaded condition to deployment at the maximum labeled diameter. Testing was conducted with consideration of the methods described in ASTM F2081-06. All samples met product specifications.	Resolute Integrity Stent; Resolute Stent	Pass
Stent Recoil	This test quantified the amount of elastic recoil for the stent and correlated this parameter to the recommended sizing procedures. The stent delivery system was inflated to nominal pressure and the stent was removed allowing for recoil to occur. The inner diameter was recorded at the distal, middle and proximal sections of the stent. Recoil was calculated by subtracting the recoiled stent inner diameter from the pre-recoil inner diameter. All samples met the acceptance criteria.	Resolute Integrity Stent; Resolute Stent	Pass
Stent ID	This test demonstrated that the stent inner diameter is consistent with labeling when deployed at nominal pressure. Each stent was deployed to nominal pressure, and the stent inner diameter was measured at the distal, middle and proximal sections of the stent. The results indicated that the inner diameter of Resolute and Resolute Integrity stents is consistent with labeling.	Resolute Integrity Stent; Resolute Stent	Pass
Stent ID Uniformity	This test demonstrated stent inner diameter uniformity when deployed at nominal pressure. Testing was conducted with consideration of the methods described in ASTM F2081. All samples met the acceptance criteria.	Resolute Integrity Stent; Resolute Stent	Pass
Stent Integrity	The test determined if the plastic deformation experienced by the stent when expanded from the compressed profile to the final maximum deployed diameter can produce crack initiation for the stent. Samples were deployed to their largest possible diameters by inflating each delivery system to maximum labeled diameter. Each stent was examined under magnification for potential cracks. All samples met the acceptance criteria with no visible cracks or notches.	Integrity Bare Metal Stent; Driver Bare Metal Stent	Pass
Stent Crossing Profile	This test verified that the stent crossing profiles of Resolute and Resolute Integrity are consistent with label claims. Testing was conducted with considerations of the methods described in ASTM F2081. All samples met product specifications.	Resolute Integrity Stent; Resolute Stent	Pass
Accelerated Durability Testing	This test evaluated the risk of stent failure caused by fretting, abrasion, and wear of Integrity and Driver bare metal stents deployed in an overlapped configuration in a 1.5cm radius bend after 420 million cycles. Stents were deployed to the largest intended diameter and tested through a simulated 10 year life. After the	Integrity Bare Metal Stent; Driver Bare Metal Stent	Pass

Table 7: In Vitro Testing Supporting the Performance of Resolute MicroTrac and Resolute Integrity

Test	Description of Test	Test Article	Results
Stent Material Analysis (Chemical Analysis)	<p>completion of the 10 year simulated durability testing, the stents were visually inspected using optical microscopy for cracks or fractures. All samples tested were free from cracks or fractures. There were no stent failures noted after 420 million cycles. Additionally stents were analyzed using SEM for fretting corrosion.</p> <p>This test confirmed that Resolute and Resolute Integrity stents are produced from material that conforms in chemical composition to ASTM F662-07. Chemical analysis was conducted on the Co-Ni-Cr-Mo alloy provided by the material supplier to confirm chemical analysis and inclusion impurity content as provided by ASTM F662 Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy for Surgical Implant Applications.</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent</p>	<p>Pass</p>
Pitting and Crevice Corrosion Potential	<p>This test evaluated the relative susceptibility to pitting/crevice corrosion of the Resolute stent compared to the Driver stent. Testing was conducted after scoring the Resolute coating down to the base metal and utilized the methods described in ASTM F746 and the experimental setup described in ASTM F2129. Results for the Resolute stent were comparable to the marketed Driver stent. This testing was also conducted on the Integrity stent.</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent Resolute Stent</p>	<p>N/A – Characterization Only</p>
Galvanic Corrosion	<p>This test evaluated whether galvanically coupling the uncoated Resolute and Resolute Integrity stents (Driver and Integrity stents) to stents constructed from 316L stainless steel may promote accelerated corrosion of either stent as measured through galvanic coupling in a physiological saline solution. The results met all acceptance criteria and indicated a high resistance to galvanic corrosion.</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent</p>	<p>N/A – Characterization Only</p>
Percent Surface Area (Stent Free Area)	<p>This test determined the percentage stent free area of the Resolute and Resolute Integrity stents. This value was calculated using stent nominal dimensional values and is based on the ratio of stent area to the area of the vessel. Metal to artery percentage ratios were calculated for all of the stent diameters recommended in the product labeling.</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent</p>	<p>N/A – Characterization Only</p>
Radial Stiffness and Radial Strength	<p>This test determined stent resistance to radial load. The stents were deployed to nominal stent diameter and placed in a radial crush tester. All samples met the acceptance criteria.</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent</p>	<p>Pass</p>
Mechanical Properties	<p>This test characterized the following properties of the annealed Co-Ni-Cr-Mo alloy bars conforming to ASTM F562. The bars were tensile tested to failure while engineering stress and strain were continuously recorded. The results were in conformance with ASTM F562</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent</p>	<p>N/A – Characterization Only</p>
Fatigue and Stress Analysis	<p>This test analyzed each stent design using a finite element analysis model to ensure that the implant conditions to which the stent would be subjected would not result in failure due to fatigue. The FEA evaluated the structural integrity of the stent when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not likely occur.</p>	<p>Integrity Bare Metal Stent; Driver Bare Metal Stent</p>	<p>Pass</p>
MRI Safety	<p>The following is included in the instructions for use: This test demonstrated that the Resolute MicroTrac and Resolute stent (up to a total length of 104 mm) and Resolute Integrity stents (up to a total length of 120 mm) are MR conditional. The stent (s) can be scanned safely under the following conditions: -Static magnetic field of 1.5 and 3 Tesla -Spatial gradient field of 1000 G/cm or less</p>	<p>Integrity Bare Metal Stent; Resolute Stent</p>	<p>Pass</p>

Table 7: In Vitro Testing Supporting the Performance of Resolute MicroTrac and Resolute Integrity

Test	Description of Test	Test Article	Results
	<p>-Maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg or less under normal operating mode only, for 15 minutes of scanning.</p> <p>1.5T</p> <p>Resolute Integrity Based on non-clinical testing and modeling, a 38 mm Resolute Integrity Stent was calculated to produce an in-vivo temperature rise of less than 2.35 °C and overlapped stents with a maximum length of 120 mm was calculated to produce an in-vivo temperature rise of less than 3.87 °C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR scanning per sequence in a 64 MHz whole body transmit coil, which corresponds to a static field of 1.5 Tesla. These calculations do not take into consideration the cooling effects of perfusion and blood flow. The maximum whole body averaged specific absorption rate (SAR) was derived by calculation.</p> <p>Resolute MicroTrac Based on non-clinical testing and modeling, a 38 mm Resolute MicroTrac stent was calculated to produce an in-vivo temperature rise of less than 1.6°C and overlapped stents with a maximum length of 104 mm was calculated to produce an in-vivo temperature rise of less than 2.0°C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR scanning in a 64 MHz whole body transmit coil, which corresponds to a static field of 1.5 Tesla. These calculations do not take into consideration the cooling effects of perfusion and blood flow. The maximum whole body averaged specific absorption rate (SAR) was derived by calculation.</p> <p>3T:</p> <p>Resolute Integrity Based on non-clinical testing and modeling, a 38 mm Resolute Integrity Stent was calculated to produce an in-vivo temperature rise of less than 3.29 °C and overlapped stents with a maximum length of 120 mm was calculated to produce an in-vivo temperature rise of less than 3.95 °C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR scanning per sequence in a 3 T GE SIGNA HDx with software version 14LXIMR release 14.0.M5A.0828.b. These calculations do not take into consideration the cooling effects of perfusion and blood flow. The maximum whole body averaged specific absorption rate (SAR) was derived by calculation.</p> <p>Resolute MicroTrac Based on non-clinical testing and modeling, a 38 mm Resolute MicroTrac stent was calculated to produce an in-vivo temperature rise of less than 1.5°C and overlapped stents with a maximum length of 104 mm was calculated to produce an in-vivo temperature rise of less than 3.0°C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR scanning in a 3.0 T Siemens TrioTIM whole body MR system using software version syngo MR B13 4VB13A. These calculations do not take into consideration the cooling effects of perfusion and blood flow. The maximum whole body averaged specific absorption rate (SAR) was derived by calculation.</p>		

Table 7: In Vitro Testing Supporting the Performance of Resolute MicroTrac and Resolute Integrity

Test	Description of Test	Test Article	Results
1.5T and 3T Radiopacity	<p>The Resolute MicroTrac or Resolute Integrity stent should not move or migrate when exposed to MR scanning immediately post-implantation. MRI at 3 Telsa and 1.5 Telsa may be performed immediately following the implantation of the stent. Non-clinical testing at field strength greater than 3 Telsa has not been performed to evaluate stent migration and heating. MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the device. Therefore, it may be necessary to optimize MR imaging parameters for the presence of the implant. The image artifact extends approximately 1cm from the device, both inside and outside the device lumen when scanned in non-clinical testing using the spin echo and gradient echo sequences specified in ASM F2119-01; the device lumen was always observed during scanning.</p> <p>This test evaluated the radiopacity of the Resolute stents prior to deployment and angiographic appearance of the stent post-deployment. Resolute and Resolute Integrity stents must have adequate radiopacity to ensure safe and effective delivery of the stents to the target vessel location.</p>	Resolute Integrity Stent; Resolute Stent	Pass
Delivery System Dimensional and Functional Attributes			
Delivery System Crossing Profile	This test verified that the crossing profile of the MicroTrac system is consistent with label claims. All samples met product specifications.	MicroTrac and Commercial MicroTrac delivery systems	Pass
Catheter Effective Length	This test measured the catheter effective length. All samples met product specifications.	MicroTrac delivery system	Pass
Distal Shaft Marker Distance	This test measured the distance of the distal shaft marker. All samples met product specifications.	MicroTrac delivery system	Pass
Delivery, Deployment and Retraction	This test assessed the ability of the delivery system to be prepared and tracked through a tortuous path and simulated vessel. This test also measured the retraction forces of the delivery system after deployment of the stent. Results indicated that the delivery system performed as intended and no damage to the stent was noted.	Resolute Integrity Stent on MicroTrac and Commercial MicroTrac delivery systems; Resolute Stent on MicroTrac delivery system	N/A – Characterization Only
Balloon Rated Burst Pressure	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 the delivery systems will not experience loss of integrity at or below the rated burst pressure.	Resolute Integrity Stent on MicroTrac and Commercial MicroTrac delivery systems; Resolute Stent on MicroTrac delivery system	Pass
Balloon Fatigue	This test demonstrated the repeatability (to 10 inflations) of successful unconstrained balloon inflation to RBP. The stent/balloon burst results show statistically that, with 95% confidence, 90% of the delivery systems will not experience balloon, shaft, or proximal/distal loss of integrity at or below the maximum recommended RBP.	Resolute Integrity Stent on MicroTrac and Commercial MicroTrac delivery systems; Resolute Stent on MicroTrac delivery system	Pass

Table 7. In Vitro Testing Supporting the Performance of Resolute MicroTrac and Resolute Integrity

Test	Description of Test	Test Article	Results
Stent Diameter vs. Balloon Pressure (Compliance)	This test quantified the stent inner diameter as a function of balloon inflation pressure. The stent sizing results verify that the stent systems meet the labeled compliance curves.	Resolute Integrity Stent on MicroTrac delivery system; Resolute Stent on MicroTrac delivery system	N/A – Characterization Only
Balloon Bond Tensile and Yield	This test demonstrated that the delivery system meets the product specifications for balloon bond tensile and yield.	MicroTrac and Commercial MicroTrac delivery systems	Pass
Catheter Bond Tensile	This test demonstrated that each delivery system meets the design requirements for catheter bond tensile. All bonds were loaded into the tensile tester and pulled to failure. All samples met the acceptance criteria.	MicroTrac and Commercial MicroTrac delivery systems	Pass
Exchange Joint Distance	This test measured the distance from the balloon bond to the exchange joint for the RX delivery system. All samples met the acceptance criteria.	MicroTrac delivery system	Pass
Balloon Inflation and Deflation Time	This test characterized the inflation time to RBP, by evaluating the time needed to manually inflate the product to RBP and the time required for the product to deflate from RBP. All samples met the product specification.	MicroTrac and Commercial MicroTrac delivery systems	Pass
Stent Securement (Distal and Proximal)	This test measured the force required to remove a stent distally and proximally from a balloon. All samples met the product specifications.	MicroTrac delivery system	Pass
Lesion Crossability and Guide Catheter Pullback	This test characterized the ability of the stent to resist shifting/dislodgement while passing through a simulated lesion. This test also 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 label claim. All samples met the acceptance criteria.	MicroTrac and Commercial MicroTrac delivery systems	Pass
Catheter Torque Testing	This test demonstrated the number of rotations the catheter can withstand prior to fracture.	MicroTrac and Commercial MicroTrac delivery systems	N/A – Characterization Only
Catheter Kink Testing	This test demonstrated the smallest radius that the catheter can conform to prior to kinking.	MicroTrac and Commercial MicroTrac delivery systems	N/A – Characterization Only

E. Coating Characterization Testing

The following methods were used to characterize and set initial specifications for Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems. The coating characterization testing conducted includes the tests summarized in Table 8.

Table 8: Coating Characterization Testing

Test	Description of Test	Test Article	Results
Particulate (Submerge and Deploy)	This test determined particulate matter after deployment of a single stent in an aqueous solution in two configurations: -to nominal (baseline) -to maximum labeled diameter (over expansion)	Resolute Integrity Stent; Resolute Stent	N/A – Characterization Only
Particulate (Bent and Overlapped)	This test determined particulate matter after two stents have been tracked through a tortuous fixture and deployed in a bent and overlapped configuration in a simulated vessel (simulated use).	Resolute Integrity Stent on MicroTrac and Commercial MicroTrac delivery systems; Resolute Stent on MicroTrac delivery system	N/A – Characterization Only
Particulate (Acute Track and Deploy)	The test used light obscuration particle count method to determine the particulate matter after a single stent has been tracked, deployed in a bent configuration and expanded to rated burst pressure (RBP), simulating clinical procedure.	Resolute Integrity Stent on MicroTrac and Commercial MicroTrac delivery systems; Resolute Stent on MicroTrac delivery system	Pass
Acute Coating Integrity	This test visually assessed the coating integrity of a single stent deployed in two configurations: -to nominal in an aqueous solution (baseline) -to maximum labeled diameter in a mock vessel after tracking through a tortuous fixture simulated use	Resolute Integrity Stent on MicroTrac delivery system; Resolute Stent on MicroTrac delivery system	N/A – Characterization Only
Chronic Coating Integrity Test	This test characterized the chronic coating integrity of overlapped Resolute stents after 420 million cycles (equivalent to ten years <i>in vivo</i>) of radial pulsation in a bent configuration. Chronic coating integrity of the Resolute stents was visually assessed by SEM imaging.	Resolute Integrity Stent; Resolute Stent	N/A – Characterization Only
Physical Structure and Chemical properties of coating components	This test described the physical and chemical properties of the Resolute Coating Components	MicroTrac delivery system	N/A – Characterization Only
Chronic Coating Fatigue particulate testing	This test determined the particulate matter of the Resolute stent after being subjected to up to 420 million cycles of heated radial fatigue post tracking and deployment in an overlapped configuration.	Resolute Integrity Stent; Resolute Stent	N/A – Characterization Only
Coating Thickness	This test characterized the coating thickness along the stent length of the Resolute stent via Scanning	Resolute Integrity Stent;	N/A –

Test	Description of Test	Test Article	Results
Testing	Electron Microscope (SEM) cross sectional imaging.	Resolute Stent	Characterization Only
Coating Adhesion Testing	This test quantitatively characterized the adhesion strength for each coating layer of the Resolute stent.	Resolute Integrity Stent; Resolute Stent	N/A – Characterization Only
Coating Stress Analysis (Finite Element Analysis)	The finite element analysis (FEA) model represented the Resolute coating experiencing the stresses and strains related to maximum diameter and cyclic loading in the straight and 1.5cm radius curvature positions.	Resolute Stent	N/A – Characterization Only
Chemical Identification Testing	This test characterized and identified particulate that had been recovered from Resolute stents that had been tracked through a clinically relevant tortuous fixture and deployed around a 1.5cm radius bend to the maximum labeled diameter in an overlapped configuration. Particulate was characterized and identified via Raman spectrometry, staining and SEM imaging	Resolute Integrity Stent on MicroTrac delivery system; Resolute Stent	N/A – Characterization Only

F. Chemistry Manufacturing and Control (CMC) Testing

Each batch of finished product undergoes CMC testing. This testing is summarized in Table 9. Where applicable, the test methods follow International Conference on Harmonization (ICH) Guidelines. All testing must meet the specifications established for finished goods release. Information to support the stability of the Resolute and Resolute Integrity stents is summarized separately in Section G, Stability and Shelf Life.

Table 9: CMC Release Testing

Test	Description of Test	Test Article
Determination of Total Drug Content (Potency and Content Uniformity)	The objective of this test is to identify and quantify zotarolimus in Resolute and Resolute Integrity stents. Tracked drug content is performed to simulate the <i>in vivo</i> tracking and deployment of the finished Resolute device.	Resolute Integrity Stent; Resolute Stent
Determination of Total Drug Related Substances	The objective of this test is to quantify related substances (degradation products) on the finished Resolute and Resolute Integrity stents.	Resolute Integrity Stent; Resolute Stent
Determination of Butylated Hydroxytoluene (BHT)	The objective of this test is to quantify the BHT content of the finished Resolute and Resolute Integrity stents.	Resolute Integrity Stent; Resolute Stent
Determination of Residual Solvents	The objective of this test is to quantify the residual solvents, used in manufacturing of finished Resolute and Resolute Integrity stents.	Resolute Integrity Stent; Resolute Stent
Elution Testing	The objective of this test is to characterize the <i>in vitro</i> elution profile of Resolute and Resolute Integrity stents.	Resolute Integrity Stent; Resolute Stent
Particulate (regulatory method)	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.	Resolute Integrity Stent on Commercial MicroTrac delivery system; Resolute Stent on Commercial MicroTrac delivery system

G. Stability and Shelf Life

Manufacturing site-specific stability studies were conducted to establish a shelf-life/expiration date for Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems. Testing in support of package integrity and functional testing of the stent systems was conducted on aged product. The testing evaluation includes drug identity, assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents, and endotoxins. Appropriate engineering tests were also performed on aged product and compared to baseline to ensure that Resolute MicroTrac and Resolute Integrity Coronary Stent Systems meet specifications throughout the shelf life. The data generated from the stability studies, coupled with the data generated from the *in vitro* shelf life studies, support an 18 month label claim and associated shelf life for both products.

H. Sterilization

Resolute MicroTrac and Resolute Integrity Coronary Stent Systems are sterilized using ethylene oxide sterilization, and have 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} . The amounts of bacterial endotoxin were verified to be within the specification limits.

I. Animal Studies

Because important arterial histopathology, histomorphometry, and tissue and stent-based pharmacokinetic data cannot be obtained from human clinical studies, a series of animal experiments using a porcine coronary artery model of stent implantation were conducted to evaluate safety, vascular compatibility, drug bioequivalence, and acute product performance. All animal studies (feasibility, safety, pharmacokinetic and acute) were conducted in accordance with § 21CFR 58 (Good Laboratory Practices), except where noted. Non-GLP studies were conducted in order to provide additional background data on non-safety related issues.

Animal testing included studies that evaluated the safety and device performance of the Resolute stent mounted on FDA-approved earlier generation catheter delivery systems (Sprint and AV100 delivery systems) and mounted on the MicroTrac delivery system. Additional studies evaluated the Resolute Integrity stent mounted on the MicroTrac delivery system.

The initial animal studies conducted on the Resolute stent mounted on the MicroTrac delivery system showed larger and more frequent myocardial ischemic lesions compared to those studies conducted on the Resolute stent mounted on earlier generation delivery catheters. To address these findings, manufacturing changes were made to the MicroTrac delivery system. An additional animal study (FS212) was conducted on the Resolute Integrity stent mounted on the modified MicroTrac delivery system (also referred to as Commercial MicroTrac). In this study, myocardial histology in animals implanted with the Resolute Integrity stent mounted on the modified MicroTrac delivery system demonstrated very few myocardial lesions, and the findings were comparable to the control articles, which consisted of FDA-approved earlier generation delivery catheters.

Animal testing also included bioequivalency studies that demonstrated bioequivalency (with respect to residual drug on the stent and drug in the treated tissue) of Resolute Integrity stents mounted on the MicroTrac delivery system and Resolute stents mounted on the MicroTrac delivery system compared to the same stent systems manufactured at an alternate site.

Summaries of the major animal studies performed to support product safety are included in Table 10.

Table 10: Summary of In Vivo Testing

Study	Stent Design	Stent Size (mm)	Type/Number of animals	Number of Stents	Follow-up duration	Major Endpoints
FS192	Test Article: Resolute Integrity RX Control: Resolute MicroTrac GLP: Yes	Diameters: 3.0 mm Length: 18 mm	Domestic Farm Swine/49	Test: 48 Control: 48	Up to 60 days	Comparison of the amount of released drug from the Resolute Integrity stent and Resolute MicroTrac stent at various time points between 0 and 60 days, through determination of residual drug content on explanted stents and drug in treated arterial tissue.
FS193	Test Article: Resolute Integrity Control: Resolute MicroTrac and Integrity Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Yucatan Mini Swine/28	Test: 28 Control: 53	90 days	Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS194	Test Article: Resolute Integrity Control: Resolute MicroTrac and Integrity Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Yucatan Mini Swine/29	Test: 29 Control: 52	28 days	Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS195	Test Article: Resolute Integrity Control: Resolute MicroTrac and Integrity Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Yucatan Mini Swine/31	Test: 26 Control: 47	5 days	Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS196	Test Article: Resolute Integrity Control: Resolute MicroTrac and Integrity Bare Metal Stent GLP: Yes	Diameters: 2.25, 2.5, 2.75 mm Lengths: 8 mm	Yucatan Mini Swine/14	Test: 14 Control: 28	28 days	Angiographic analysis Morphometric analysis Histopathology SEM analysis Radiopacity
FS197	Test Article: Resolute Integrity Control: Resolute AV100 ³ , Endeavor Sprint OTW, Resolute Sprint	Diameters: 2.25, 3.5, 4.0 mm Lengths: 8, 30, 35 mm	Domestic Farm Swine/4	Test: 56 Control: 30	Acute	Acute performance, including: System introduction, Guide Catheter and Guide Wire Compatibility, Deliverability, Trackability, Pushability, Pullback into the guide catheter (of the undeployed

³ Resolute AV100 is a predicate device, which has the identical bare metal stent and drug coating to Resolute MicroTrac but utilizes a different delivery system

Table 10: Summary of *In Vivo* Testing

Study	Stent Design	Stent Size (mm)	Type/Number of animals	Number of Stents	Follow-up duration	Major Endpoints
	RX, Endeavor Sprint RX GLP: Yes					and deployed stents), Deployment Inflation/deflation performance, Radiopacity, and Overall performance
PS255	Test Article: Resolute AV100 and Polymer-coated Stents Control: Driver Bare Metal Stent GLP: No	Diameters: 3.0, 3.5 mm Lengths: 18 mm	Domestic Farm Swine/11	Test: 20 Control: 9	28 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology
FS125	Test Article: Resolute AV100 and Polymer-coated Stents Control: Driver Bare Metal Stents GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Domestic Farm Swine/49	Test: 102 Control: 63	28 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology
FS127	Test Article: Polymer Coated Stents Control: Driver Bare Metal Stents GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 18 mm	Domestic Farm Swine/10	Test: 13 Control: 12	28 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology
FS128	Test Article: Resolute AV100 and Polymer-coated Stents Control: Driver Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Yucatan mini Swine/46	Test: 88 Control: 65	90 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM Analysis
FS129	Test Article: Resolute AV100 and Polymer-coated Stents Control: Driver Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Yucatan mini Swine/45	Test: 89 Control: 63	180 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM Analysis
FS138	Test Article: Resolute AV100 Control: Driver Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Domestic Farm Swine/18	Test: 41 Control: 27	7 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology Cellular proliferation (BrdU Analysis)
PS320	Test Article: Resolute AV100	Diameters: 3.0, 3.5 mm	Domestic Farm Swine/27	Test: 44 Control: 27	7 Days	Acute performance Angiographic analysis

Table 10: Summary of *In Vivo* Testing

Study	Stent Design	Stent Size (mm)	Type/Number of animals	Number of Stents	Follow-up duration	Major Endpoints
	Control: Driver Bare Metal Stent GLP: No	Lengths: 18 mm				Morphometric analysis Histopathology
FS149	Test Article: Resolute AV100 Control: Driver Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Lengths: 12, 18 mm	Domestic Farm Swine/18	Test: 34 Control: 26	7 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology
FS132	Test Article: Resolute AV100 Control: Polymer Coated Stents GLP: Yes	Diameter: 3.0 mm Length: 18 mm	Yucatan mini swine/30	Test: 54 Control: 4	Up to 180 Days	Zotarolimus concentration – blood Zotarolimus concentration – arterial tissue Zotarolimus concentration – myocardial tissue Zotarolimus concentration – non-target organs Stent drug content at explant
FS142	Test Article: Resolute AV100 and Polymer-coated Stents Control: Driver Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Length: 12, 18 mm	Yucatan mini swine/63	Test: 108 Control: 91	365 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS144	Test Article: Resolute AV100 and Polymer-coated Stents Control: Driver Bare Metal Stent GLP: Yes	Diameters: 2.25, 2.5 mm Length: 8 mm	Domestic Farm Swine/34	Test: 52 Control: 34	28 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS165	Test Article: Resolute Sprint Control: Resolute AV100/Driver Bare Metal Stent GLP: Yes	Diameters: 3.0, 3.5 mm Length: 18 mm	Domestic Farm Swine/16	Test: 11 Control: 26	7 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS166	Test Article: Resolute Sprint Control: Resolute AV100/Driver Bare Metal Stent	Diameters: 3.0, 3.5 mm Length: 18 mm	Domestic Farm Swine/16	Test: 12 Control: 27	28 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM analysis

Table 10: Summary of In Vivo Testing

Study	Stent Design	Stent Size (mm)	Type/Number of animals	Number of Stents	Follow-up duration	Major Endpoints
	GLP: Yes					
FS169	Test Article: Resolute Sprint Control: Resolute AV100 GLP: Yes	Diameter: 4.0 mm Length: 30 mm	Domestic Farm Swine/2	Test: 30 Control: 28	Acute	Acute performance including: System compatibility, Guide wire compatibility, Deliverability, Trackability, Pushability, Pullback into the guide catheter (of the undeployed stent), Deployment inflation/deflation performance, Radiopacity, Pullback into the guide catheter (of the deployed stent delivery system)
FS170	Test Article: Resolute Sprint and Polymer-coated Stents Control: Micro-Driver Bare Metal Stent GLP: Yes	Diameters: 2.25, 2.5 mm Length: 8 mm	Yucatan Mini Swine/21	Test: 33 Control: 21	180 Days	Acute performance Angiographic analysis Morphometric analysis Histopathology SEM analysis
FS180	Test Article: Resolute Sprint GLP: Yes	Diameter: 3.0 mm Length: 30 mm	Domestic Farm Swine/48	Test: 96	Up to 60 Days	Comparison of stent drug content at explant Comparison of cumulative drug elution rate
FS185	Test Article: Resolute MicroTrac Control: Resolute AV100 GLP: Yes	Diameters: 4.0 mm Length: 38 mm	Domestic Farm Swine/1	Test: 10 Control: 10	Acute	Acute performance including: Guide Catheter compatibility, Guide Wire compatibility, Deliverability, Trackability, Pushability, Deployment inflation/deflation performance, Radiopacity, Pullback into the guide catheter (of the deployed stent delivery system), Overall performance
FS187	Test Article: Resolute MicroTrac Control: Endeavor Sprint GLP: Yes	Diameters: 3.5 mm Length: 30 mm	Domestic Farm Swine/1	Test: 10 Control: 10	Acute	Acute performance including: Guide Catheter compatibility, Guide Wire compatibility, Deliverability, Trackability, Pushability, Deployment inflation/deflation performance, Radiopacity, Pullback into the guide catheter (of the deployed stent delivery system), Overall performance
FS190	Test Article: Resolute MicroTrac Control: Resolute Sprint	Diameters: 3.0, 3.5 mm Length:	Yucatan Mini Swine/16	Test: 14 Control: 27	28 Days	Acute performance Angiographic analysis Morphometric analysis

Table 10: Summary of In Vivo Testing

Study	Stent Design	Stent Size (mm)	Type/Number of animals	Number of Stents	Follow-up duration	Major Endpoints
	Driver Bare Metal Stents	18 mm				Histopathology SEM analysis
FS212	Test Article: Resolute Integrity Stent on the commercial MicroTrac RX Delivery System Controls: Resolute Stent on the Sprint RX Delivery System Endeavor Stent on the Sprint RX Delivery System	Diameters: 3.0, 3.5 mm Length: 18 mm	Yucatan Mini Swine/30	Test: 20 Controls: 40	28 Days	Angiographic analysis Histopathology Morphometric analysis

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X. SUMMARY OF CLINICAL STUDIES

A. Overview of Clinical Studies

The principal safety and effectiveness information for the RESOLUTE MicroTrac and 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 MicroTrac stent system features the same coated stent as the Resolute stent system, but on a different delivery system (MicroTrac).

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 MicroTrac and Resolute Integrity stent systems.

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 ≤ 27 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 11**.

The RESOLUTE United States (RESOLUTE US) Clinical Trial is a prospective, multi-center, 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 2.25 mm to 4.2 mm. The RESOLUTE US Clinical Trial is the pivotal trial of the overall Global RESOLUTE Clinical Trial Program. The RESOLUTE US trial included the following:

- The 2.25 mm to 3.5 mm Main Study: The primary endpoint was Target Lesion Failure (TLF) at 12 months post-procedure, defined as Cardiac Death, Target Vessel Myocardial Infarction (MI), or clinically driven Target Lesion Revascularization (TLR).

-
- The 2.25 mm Cohort, in which the cohort was derived from subjects treated with the 2.25mm Resolute stent in the 2.25 mm to 3.5 mm Main Study and the 2.25 to 3.5 mm Angio/IVUS sub-study. The primary endpoint was TLF at 12 months post-procedure.
 - The 2.25 mm to 3.5 mm Angio/IVUS Sub-study: The primary endpoint was in-stent late lumen loss (LL) at 8 months post-procedure as measured by quantitative coronary angiography (QCA).
 - The 4.0 mm stent Sub-study. The primary endpoint was in-segment late LL at 8 months post-procedure as measured by QCA.

The total study population of the primary enrollment group (consisting of all subjects enrolled in the four studies listed above) consisted of 1402 subjects at 116 investigational sites in the United States. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

The RESOLUTE All-Comers (RESOLUTE AC) Clinical Trial is a prospective, multi-center, two-arm randomized, non-inferiority trial that compared the Resolute stent to a control DES (the Xience V[®] stent). The eligibility criteria reflected an 'all-comers' population. A total of 2292 subjects were enrolled at 17 clinical research sites from 11 countries in Western Europe (Switzerland, Belgium, Netherlands, Denmark, France, Germany, Italy, Spain, United Kingdom, Israel, and Poland). The primary endpoint was TLF, defined as the composite of Cardiac Death, MI (not clearly attributable to a non-target vessel), or and clinically indicated TLR within 12 months post-implantation. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

The RESOLUTE International (RESOLUTE Int) study is a prospective, multi-center, non-randomized, single-arm observational study with all enrolled subjects treated according to routine practices at participating hospitals. A total of 2349 subjects were enrolled at 88 clinical research sites from 17 countries distributed over Europe, Asia, Africa and South America. The primary objective of this study was to evaluate the safety and clinical performance of the Resolute stent in an 'all-comers' patient population. The primary endpoint was the composite of Cardiac Death and MI (not clearly attributable to a non-target vessel) at 12 months post-implantation. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

The RESOLUTE FIM Clinical Trial is the first-in-human study evaluating the Resolute stent. RESOLUTE FIM is a non-randomized, prospective, multi-center, single-arm trial. The purpose of the trial was to assess the initial safety of the Resolute stent. A total of 139 subjects were enrolled at 12 investigative sites in Australia and New Zealand. The primary endpoint was in-stent late lumen loss (LL) at nine months post-implantation measured by QCA. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months. This trial had a subset of subjects undergoing pharmacokinetic (PK) assessments (see Section IX C for the pharmacokinetic profile of the Resolute stent).

The RESOLUTE Japan Clinical Trial is a prospective, multi-center, non-randomized, single-arm trial. A total of 100 subjects were enrolled at 14 investigational sites in Japan. The primary endpoint was in-stent late lumen loss (LL) at 8 months post-procedure as measured by QCA. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

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.

Table 11: Clinical Trial Comparisons

	RESOLUTE US	RESOLUTE AC[®]	RESOLUTE Int[®]	RESOLUTE FIM[®]	RESOLUTE Japan
Study Type	<ul style="list-style-type: none"> ▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial** 	<ul style="list-style-type: none"> ▪ Prospective ▪ Multi-center ▪ Randomized (1:1 Resolute vs. Xience V) ▪ Two-arm, non-inferiority trial ▪ Real World subject population 	<ul style="list-style-type: none"> ▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Observational study ▪ Real World subject population 	<ul style="list-style-type: none"> ▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial ▪ PK Assessment 	<ul style="list-style-type: none"> ▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial
Number of Subjects Enrolled	<p>Total: 1402</p> <ul style="list-style-type: none"> ▪ 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) 	<p>Total: 2292 (Resolute: 1140, Xience V: 1152)</p>	<p>Total: 2349</p>	<p>Total: 139</p>	<p>Total: 100</p>
Lesion Criteria	<ul style="list-style-type: none"> ▪ Single or two de novo lesions located in separate target vessels ▪ Lesion(s) length ≤ 27 mm ▪ Target vessel with RVD between 2.25 mm to 4.2 mm 	<ul style="list-style-type: none"> ▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 mm to 4.0 mm. 	<ul style="list-style-type: none"> ▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 mm to 4.0 mm 	<ul style="list-style-type: none"> ▪ Single de novo lesion ▪ Lesion length from 14 to 27 mm ▪ Target vessel with RVD between 2.5 mm and 3.5 mm 	<ul style="list-style-type: none"> ▪ Single or two de novo lesions located in separate coronary arteries ▪ Lesion(s) length ≤ 27 mm ▪ Target vessel with RVD between 2.5 mm to 3.5 mm
Stent Sizes (Resolute)	<p>Stent diameter: 2.25 mm – 4.0 mm</p> <p>Stent length: 8 mm – 30 mm</p>	<p>Stent diameter: 2.25 mm – 4.0 mm</p> <p>Stent length: 8 mm – 30 mm</p>	<p>Stent diameter: 2.25 mm – 4.0 mm</p> <p>Stent length: 8 mm – 38 mm</p>	<p>Stent diameter: 2.5 mm – 3.5 mm</p> <p>Stent length: 8 mm – 30 mm</p>	<p>Stent diameter: 2.5 mm – 3.5 mm</p> <p>Stent length: 8 mm – 30 mm</p>
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 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

Table 11: Clinical Trial Comparisons

	RESOLUTE US	RESOLUTE AC¹	RESOLUTE Int²	RESOLUTE FIM³	RESOLUTE Japan
Follow-up	30 days and 9 months: clinical 8 months: clinical and angiographic (4.0 mm Sub-study) 8 months: clinical and angiographic/ intravascular ultrasound (IVUS) (2.25 mm - 3.5 mm Angio/IVUS Sub-study) 6, 12 and 18 months, 2-5 years: telephone	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
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 and the 4.0mm Sub-study have historical control design. The 2.25 mm Subset outcomes were compared to a performance goal.

¹ The term 'AC' refers to All-Corners.

² The term 'Int' refers to International.

³ The term 'FIM' refers to First-In-Man

B. RESOLUTE US Trial

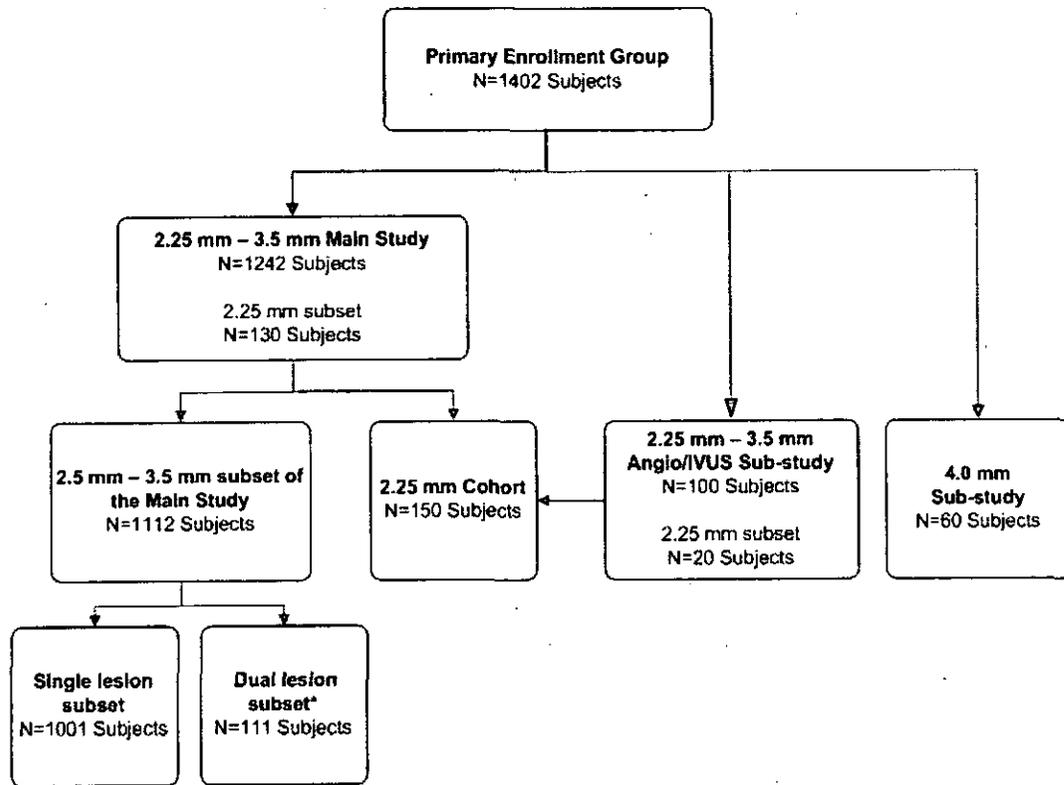
The primary objective of the RESOLUTE US trial was to assess the safety and effectiveness of the Resolute Zotarolimus-Eluting Coronary Stent System (Resolute stent) for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm.

B1. Study Design: This is a prospective, multi-center, non-randomized controlled 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 2.25 mm to 4.2 mm. The study population included subjects from 116 sites in the United States with clinical evidence of ischemic heart disease due to stenotic lesions with either one target lesion or two target lesions located in separate arteries, RVD between 2.25 mm and 4.2 mm, lesions with stenosis $\geq 50\%$ but $< 100\%$, lesion length ≤ 27 mm, and TIMI flow ≥ 2 .

The RESOLUTE US trial consists of the following:

- The 2.25 mm to 3.5 mm Main Study
- The 2.25 mm Cohort
- The 2.25 mm to 3.5 mm Angio/IVUS Sub-study
- The 4.0mm stent Sub-study

Figure 3 provides a chart of the subject study designation of the primary enrollment group. The primary enrollment group consists of the subjects in all of these studies and includes 1402 subjects.



* Three subjects had more than two lesions treated

Figure 3:– Study Designation of RESOLUTE US Primary Enrollment Group

Clinical Inclusion and Exclusion Criteria

Subject enrollment criteria common to all four studies listed above included: age >18 years old; clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, and/or a positive functional study; and no evidence of an acute MI within 72 hours of the procedure.

Follow-up Schedule

Follow-up was completed at 30 days, 6, 9 and 12 months and will be performed at 18 months, 2, 3, 4 and 5 years. All subjects enrolled in the 2.25 mm – 3.5 mm Anglo/IVUS Sub-study were consented to angiographic and IVUS follow-up at eight months post-procedure. All subjects enrolled in the 4.0 mm Sub-study were consented to angiographic follow-up at eight months post-procedure. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

Clinical Endpoints

2.5 mm – 3.5 mm Subset of the Main Study

Primary Endpoint: The primary endpoint in the 2.5 mm - 3.5 mm Subset of the Main Study was 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).

Control group and statistical analysis plan: The primary analysis was a non-inferiority comparison of the 12-month TLF rate between the single lesion subset of the Resolute stent arm and a historical control group consisting of single lesion subjects treated with Endeavor stents who were part of the clinical follow-up cohort with diameters between 2.5 mm and 3.5 mm pooled from the following studies: ENDEAVOR II, ENDEAVOR II Continued Access, ENDEAVOR IV, and ENDEAVOR US PK.

2.25 mm Cohort

Primary Endpoint: The primary endpoint in the 2.25 mm Cohort was Target Lesion Failure (TLF) at 12 months post-procedure, defined as the Cardiac Death, Target Vessel Myocardial Infarction, or clinically-driven Target Lesion Revascularization (TLR).

Control group and statistical analysis plan: The primary endpoint of 12 month TLF was compared to a performance goal set at 20% that was derived from a logistic regression of TLF rates in subjects treated with Endeavor or Driver stents pooled from the following studies: ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV. The performance goal was set at 20%, which was 55% above the expected TLF rate for a drug-eluting stent and preserved 50% of the benefit of a drug-eluting stent vs. a bare metal stent.

2.25 mm – 3.5 mm Angio/IVUS Sub-study

Primary Endpoint: The primary endpoint in the 2.25 mm to 3.5 mm Angio/IVUS Sub-study was in-stent late lumen loss (LL) at 8 months post-procedure as measured by quantitative coronary angiography (QCA).

Control group and statistical analysis plan: The primary analysis was a non-inferiority comparison of the 8-month in-stent late LL in the Resolute stent compared to a historical control population of subjects treated with an Endeavor stent in the ENDEAVOR II trial. The non-inferiority margin was set at 0.16 mm.

4.0 mm Sub-study

Primary Endpoint: The primary endpoint in the 4.0 mm Sub-study was in-segment late LL at 8 months post-procedure as measured by QCA.

Control group and statistical analysis plan: The primary analysis was a superiority comparison of the 8-month in-segment late LL in the Resolute stent compared to a historical control population of subjects treated with a Driver bare metal stent of diameters 3.5 mm or 4.0

mm in the Medtronic S8 Driver stent registry (6-month late LL) and ENDEAVOR II trial (8-month late LL).

B2. Accountability of RESOLUTE US Cohort

2.5 mm – 3.5 mm Subset of the Main Study

At the time of database lock, of 1112 patients enrolled in the RESOLUTE US 2.5 - 3.5 mm Main Study, 98.3% (1093) patients are available for analysis at the completion of the study, the 1-year post-operative visit.

2.25 mm Cohort

At the time of database lock, of 150 patients enrolled in the RESOLUTE US 2.25 mm Cohort, 97.3% (146) patients are available for analysis at the completion of the study, the 1-year post-operative visit.

2.25 mm – 3.5 mm Angio/IVUS Sub-study

At the time of database lock, of 100 patients enrolled in the RESOLUTE US 2.25 - 3.5 mm Angio/IVUS Sub-study, 98.0% (98) patients are available for analysis at the completion of the study, the 1-year post-operative visit.

4.0 mm Sub-study

At the time of database lock, of 60 patients enrolled in the RESOLUTE US 4.0 mm Study, 98.3% (59) patients are available for analysis at the completion of the study, the 1-year post-operative visit.

B3. Study Population Demographics and Baseline Parameters

2.5 mm – 3.5 mm Subset of the Main Study

There were 1112 subjects (1001 single lesion subjects and 111 dual vessel subjects) mean age of all subjects was 63.9 years with 69.2% (770/1112) being males, 20.3% (222/1095) had a prior history of MI, 32.2% (358/1112) had a prior history of PCI and 7.6% (85/1112) had a previous CABG surgery. 33.6% (374/1112) were diabetics, with 9.5% (106/1112) being insulin dependent diabetics. Past medical history of subjects indicated 87.9% (978/1112) had hyperlipidemia, 83.5% (928/1112) had hypertension, and 21.6% (240/1112) were current smokers. The mean RVD by QCA was 2.63 ± 0.42 mm, the lesion length was 13.06 ± 5.84 mm and the average percentage diameter stenosis was $70.68 \pm 11.56\%$. 75.8% (921/1215) of lesions were characterized as ACC/AHA type B2/C lesions.

2.25 mm Cohort

There were 150 subjects. The mean age of all subjects was 66.3 years with 65.3% (98/150) being males. 34.0% (49/144) had a prior history of MI, 42.0% (63/150) had a prior history of PCI and 15.3% (23/150) had a previous CABG surgery. 41.3% (62/150) were diabetics, with 10.7% (16/150) being insulin dependent diabetics. Past medical history of subjects indicated 90.0% (135/150) had hyperlipidemia, 90.7% (136/150) had hypertension, and 12.7% (19/150)

were current smokers. The mean RVD by QCA was 2.15 ± 0.40 mm, the lesion length was 12.40 ± 6.03 mm and the average percentage diameter stenosis was $72.21 \pm 10.45\%$. 67.9% (133/196) of lesions were characterized as ACC/AHA type B2/C lesions.

2.25 mm – 3.5 mm Angio/IVUS Sub-study

There were 100 subjects. The mean age of all subjects was 64.9 years with 62.0% (62/100) being males. 22.0% (22/100) had a prior history of MI, 29.0% (29/100) had a prior history of PCI and 35.0% (11/100) had a previous CABG surgery. 35.0% (35/100) were diabetics, with 9.0% (9/100) being insulin dependent diabetics. Past medical history of subjects indicated 86.0% (86/100) had hyperlipidemia, 84.0% (84/100) had hypertension, and 20.0% (20/100) were current smokers. The mean RVD by QCA was 2.48 ± 0.38 mm, the lesion length was 14.04 ± 5.87 mm and the average percentage diameter stenosis was $70.75 \pm 11.57\%$. 76.0% (79/104) of lesions were characterized as AHA type B2/C lesions.

4.0 mm Sub-study

There were 60 subjects. The mean age of all subjects was 63.7 years with 66.7% (40/60) being males. 20.0% (12/60) had a prior history of MI, 25.0% (15/60) had a prior history of PCI and 10.0% (6/60) had a previous CABG surgery. 36.7% (22/60) were diabetics, with 10.0% (6/60) being insulin dependent diabetics. Past medical history of subjects indicated 80.0% (48/60) had hyperlipidemia, 85.0% (51/60) had hypertension, and 23.3% (14/60) were current smokers. The mean RVD by QCA was 3.25 ± 0.48 mm, the lesion length was 12.83 ± 5.97 mm and the average percentage diameter stenosis was $67.70 \pm 13.09\%$. 79.1% (57/72) of lesions were characterized as ACC/AHA type B2/C lesions.

B4. Safety and Effectiveness Results

2.5 mm – 3.5 mm Subset of the Main Study

The Resolute stent single lesion cohort of the 2.5 mm – 3.5 mm subset of the Main Study met the primary 12 month TLF non-inferiority endpoint with the Resolute stent demonstrating a rate of 3.7% (36/982) in comparison to the Endeavor stent historical control rate of 6.5% (70/1076), $P_{\text{non-inferiority}} < 0.001$.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table 12:** RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - Primary Endpoint Analysis
- **Table 13:** RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - Principal Safety and Effectiveness - Single Lesion Outcome versus Historical Control (Endeavor)
- **Table 14:** RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - Principal Safety and Effectiveness - Combined Single Lesion and Dual Lesion – Treated Subjects

- **Table 15:** RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis through 12 Months
- **Table 16:** RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study Clinical Results - Single Lesion versus Dual Vessel Subjects

Table 12: RESOLUTE US 2.5 mm – 3.5 mm Subset of the Main Study - Primary Endpoint Analysis

2.5 mm – 3.5 mm Subset of the Main Study	Resolute (N = 1001)	Historical Control Endeavor (N = 1092)	Difference: Resolute – Historical Control	Upper One-sided 95% CI ¹	Non-inferiority P-value ^{1,2}
12-month TLF- Single Lesion Subjects	3.7% (36/982)	6.5% (70/1076)	-2.8%	-1.3%	<0.001

Notes

N = The total number of subjects enrolled.

TLF = Target lesion failure

Subjects are only counted once for each time period.

The numbers are % (Count/Number of Eligible Subjects) or least squares mean ± standard error.

The primary endpoint analysis for the 2.5 mm – 3.5 mm subset of the Main Study only includes subjects with a single lesion.

12-month timeframe includes follow-up window (360 days ± 30 days).

¹The CI and P-values are 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.

²One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 3.3%, to be compared at a 0.05 significance level.

Table 13: RESOLUTE US 2.5-3.5mm Subset of the Main Study - Principal Safety and Effectiveness - Single Lesion Outcome versus Historical Control (Endeavor)

Outcomes at 12 Months	Single Lesion 2.5-3.5mm Subset of Main study (N=1001 subjects)	Single Lesion Historical Control (Endeavor) (N=1092 subjects)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	3.7% (36/982)	6.5% (70/1076)
TVF	5.1% (50/982)	8.3% (89/1076)
MACE	4.3% (42/982)	7.0% (75/1076)
EFFECTIVENESS		
Clinically Driven TVR	3.7% (36/982)	6.0% (65/1076)
TLR	2.0% (20/982)	4.0% (43/1076)
TLR, PCI	1.7% (17/982)	3.7% (40/1076)
TLR, CABG	0.3% (3/982)	0.5% (5/1076)
Non-TL TVR	1.8% (18/982)	2.5% (27/1076)
Non-TL TVR, PCI	1.5% (15/982)	2.1% (23/1076)
Non-TL TVR, CABG	0.3% (3/982)	0.5% (5/1076)

SAFETY		
Total Death	0.9% (9/982)	1.3% (14/1076)
Cardiac Death	0.4% (4/982)	0.8% (9/1076)
Non-Cardiac Death	0.5% (5/982)	0.5% (5/1076)
Cardiac Death or TVMI	1.7% (17/982)	3.2% (34/1076)
TVMI	1.3% (13/982)	2.4% (26/1076)
Q wave MI	0.2% (2/982)	0.3% (3/1076)
Non-Q wave MI	1.2% (12/982)	2.1% (23/1076)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/982)	0.7% (7/1076)
Definite	0.0% (0/982)	0.5% (5/1076)
Probable	0.0% (0/982)	0.2% (2/1076)
ACUTE SUCCESS		
Procedure Success	98.6% (981/995)	97.6% (1060/1086)

Notes

N = The total number of subjects enrolled.

Numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

12-month timeframe includes follow-up window (360 days ± 30 days).

Procedure success is defined as attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.

See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 14: RESOLUTE US 2.5-3.5 mm Subset of the Main Study - Principal Safety and Effectiveness (Combined Single Lesion and Dual Lesion – Treated Subjects)

Outcomes at 12 Months	2.5 mm - 3.5 mm subset of the Main Study (N = 1112)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	3.8% (42/1093)
TVF	5.3% (58/1093)
MACE	4.6% (50/1093)
EFFECTIVENESS	
Clinically Driven TVR	3.8% (42/1093)
TLR	2.2% (24/1093)
TLR, PCI	1.9% (21/1093)
TLR, CABG	0.3% (3/1093)
Non-TL TVR	1.9% (21/1093)
Non-TL TVR, PCI	1.6% (17/1093)

Non-TL TVR, CABG	0.4% (4/1093)
SAFETY	
Total Death	0.9% (10/1093)
Cardiac Death	0.4% (4/1093)
Non-Cardiac Death	0.5% (6/1093)
Cardiac Death or TVMI	1.7% (19/1093)
TVMI	1.4% (15/1093)
Q wave MI	0.2% (2/1093)
Non-Q wave MI	1.2% (13/1093)
Stent Thrombosis ARC defined	
Definite/Probable	0.0% (0/1093)
Definite	0.0% (0/1093)
Probable	0.0% (0/1093)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 15: RESOLUTE US 2.5-3.5mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	2.5 mm - 3.5 mm subset of the Main Study (N = 1112)
Stent Thrombosis	0.0% (0/1093)
Acute (0 - 1 day)	0.0% (0/1093)
Subacute (2 - 30 days)	0.0% (0/1093)
Late (31 days - 360 days)	0.0% (0/1093)

Notes

N = The total number of subjects enrolled.
 Subjects are only counted once for each time period.
 Numbers are % (Count/Number of Eligible Subjects).
 12-month timeframe includes follow-up window (360 days ± 30 days).
 To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-360 days inclusive) or had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).
 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.

Table 16: RESOLUTE US 2.5 – 3.5 mm Subset of the Main Study Clinical Results –

Single Lesion versus Dual Lesion Subjects

Outcomes at 12 Months	Single Lesion 2.5-3.5mm Subset of Main study (N=1001 subjects)	Dual Vessel * 2.5-3.5mm Subset of Main study (N=111 subjects)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	3.7% (36/982)	5.4% (6/111)
TVF	5.1% (50/982)	7.2% (8/111)
MACE	4.3% (42/982)	7.2% (8/111)
EFFECTIVENESS		
Clinically Driven TVR	3.7% (36/982)	5.4% (6/111)
TLR	2.0% (20/982)	3.6% (4/111)
TLR, PCI	1.7% (17/982)	3.6% (4/111)
TLR, CABG	0.3% (3/982)	0.0% (0/111)
Non-TL TVR	1.8% (18/982)	2.7% (3/111)
Non-TL TVR, PCI	1.5% (15/982)	1.8% (2/111)
Non-TL TVR, CABG	0.3% (3/982)	0.9% (1/111)
SAFETY		
Total Death	0.9% (9/982)	0.9% (1/111)
Cardiac Death	0.4% (4/982)	0.0% (0/111)
Non-Cardiac Death	0.5% (5/982)	0.9% (1/111)
Cardiac Death or TVMI	1.7% (17/982)	1.8% (2/111)
TVMI	1.3% (13/982)	1.8% (2/111)
Q wave MI	0.2% (2/982)	0.9% (1/111)
Non-Q wave MI	1.2% (12/982)	1.8% (2/111)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/982)	0.0% (0/111)
Definite	0.0% (0/982)	0.0% (0/111)
Probable	0.0% (0/982)	0.0% (0/111)
ACUTE SUCCESS		
Procedure Success	98.6% (981/995)	98.2% (108/110)

Notes

* Fourteen single vessel subjects had more than one lesion. Three subjects had more than two lesions treated

N = The total number of subjects enrolled.

Numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

Procedure success is defined as attainment of < 50 % residual stenosis of the target lesion and no in-hospital MACE.

12-month timeframe includes follow-up window (360 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

2.25 mm Cohort

The Resolute stent 2.25 mm Cohort met the primary endpoint 12 month TLF rate performance goal of 20% with a rate of 4.8% (7/146) and an upper one-sided 95% CI of 8.8%. (P-value <0.001).

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table 17:** RESOLUTE US 2.25mm Cohort - Primary Endpoint Analysis
- **Table 18:** RESOLUTE US 2.25mm Cohort - Principal Safety and Effectiveness
- **Table 19:** RESOLUTE US 2.25mm Cohort - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 17: RESOLUTE US 2.25mm Cohort - Primary Endpoint Analysis

2.25 mm Subset	Resolute (N = 150)	Performance Goal	Upper One-sided 95% CI¹	P-value²
12-month TLF	4.8% (7/146)	20%	8.8%	<0.001

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

The numbers are % (Count/Number of Eligible Subjects) or least squares mean ± standard error.

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 2.25mm lesions.

12-month timeframe includes follow-up window (360 days ± 30 days).

¹ One-sided confidence interval using normal approximation.

² One sided p-value test using asymptotic test statistic, to be compared at a 0.05 significance level.

Table 18: RESOLUTE US 2.25mm Cohort – Principal Safety and Effectiveness

Outcomes at 12 Months	2.25 mm Cohort (N = 150)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	5.5% (8/146)
TVF	8.2% (12/146)
MACE	6.8% (10/146)
EFFECTIVENESS	
Clinically Driven TVR	6.8% (10/146)
TLR	4.1% (6/146)
TLR, PCI	4.1% (6/146)
TLR, CABG	0.0% (0/146)
Non-TL TVR	2.7% (4/146)
Non-TL TVR, PCI	2.7% (4/146)
Non-TL TVR, CABG	0.0% (0/146)
SAFETY	
Total Death	2.7% (4/146)
Cardiac Death	1.4% (2/146)
Non-Cardiac Death	1.4% (2/146)
Cardiac Death or TVMI	2.1% (3/146)
TVMI	0.7% (1/146)
Q wave MI	0.0% (0/146)
Non-Q wave MI	0.7% (1/146)
Stent Thrombosis ARC defined	
Definite/Probable	1.4% (2/146)
Definite	0.7% (1/146)
Probable	0.7% (1/146)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis

Table 193: RESOLUTE US 2.25mm Cohort - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	2.25 mm Subset (N = 150)
Stent Thrombosis	1.4% (2/146)
Acute (0 - 1 day)	0.0% (0/146)
Subacute (2 - 30 days)	0.7% (1/146)
Late (31 days - 360 days)	0.7% (1/146)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (Count/Number of Eligible Subjects).

12-month timeframe includes follow-up window (360 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-360 days inclusive) or had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

2.25 mm – 3.5 mm Angio/IVUS Sub-study

The 2.25 mm – 3.5 mm Angio/IVUS Sub-study met the primary non-inferiority endpoint with an 8-month in-stent late LL of 0.39 ± 0.06 mm for the Resolute stent compared to the historical control of 8-month in-stent late LL of 0.61 ± 0.03 mm for the Endeavor stent

$P_{\text{non-inferiority}} < 0.001$.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table 20:** RESOLUTE US 2.25 mm - 3.5 mm Angio/IVUS Sub-study - Primary Endpoint Analysis
- **Table 21:** RESOLUTE US 2.25 mm- 3.5 mm Angio/IVUS Sub-study - Principal Safety and Effectiveness
- **Table 22:** RESOLUTE US 2.25mm - 3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 12 Months
- **Table 23:** RESOLUTE US 2.25 mm - 3.5 mm Angio/IVUS Sub-study - Angiographic and IVUS Results

Table 20: RESOLUTE US 2.25 mm – 3.5 mm Angio/IVUS Sub-study – Primary Endpoint Analysis

2.25 mm – 3.5 mm Angio/IVUS Sub-study	Resolute (N = 100)	Historical Control Endeavor (N = 264, M=264)	Difference: Resolute - Historical Control	Upper One-sided 95% CI ¹	Non-inferiority P value ^{1,2}
8-month In-Stent Late Lumen Loss (mm)	0.39 ± 0.06 (90)	0.61 ± 0.03 (264)	-0.22	-0.11	<0.001

Notes

N = The total number of subjects enrolled.

M = The total number of lesions at baseline.

Subjects are only counted once for each time period.

The numbers are least squares mean ± standard error (number of evaluable lesions).

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual lesions.

¹ The CI and P-values are 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.

² One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16mm, to be compared at a 0.05 significance level.

Table 21: RESOLUTE US 2.25-3.5mm Angio/IVUS Sub-study – Principal Safety and Effectiveness

Outcomes at 12 Months	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	12.2% (12/98)
TVF	13.3% (13/98)
MACE	13.3% (13/98)
EFFECTIVENESS	
Clinically Driven TVR	10.2% (10/98)
TLR	8.2% (8/98)
TLR, PCI	7.1% (7/98)
TLR, CABG	1.0% (1/98)
Non-TL TVR	4.1% (4/98)
Non-TL TVR, PCI	4.1% (4/98)
Non-TL TVR, CABG	0.0% (0/98)
SAFETY	
Total Death	4.1% (4/98)
Cardiac Death	3.1% (3/98)
Non-Cardiac Death	1.0% (1/98)
Cardiac Death or TVMI	4.1% (4/98)
TVMI	1.0% (1/98)
Q wave MI	0.0% (0/98)

Outcomes at 12 Months	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)
Non-Q wave MI	1.0% (1/98)
Stent Thrombosis ARC defined	
Definite/Probable	0.0% (0/98)
Definite	0.0% (0/98)
Probable	0.0% (0/98)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 22: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 12 Months.

	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)
Stent Thrombosis	0.0% (0/98)
Acute (0 - 1 day)	0.0% (0/98)
Subacute (2 - 30 days)	0.0% (0/98)
Late (31 days - 360 days)	0.0% (0/98)

Notes

N = The total number of subjects enrolled.
 Subjects are only counted once for each time period.
 Numbers are % (Count/Number of Eligible Subjects).
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.
 To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-360 days inclusive) or had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

Table 23: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Angiographic and IVUS Results

Outcomes at 8 Months	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100, M = 104)
ANGIOGRAPHIC RESULTS	
MLD (mm), In-stent	
Post-Procedure	2.44 ± 0.39 (104)
8-Month	2.06 ± 0.66 (93)
MLD (mm), In-segment	
Post-Procedure	2.06 ± 0.39 (104)
8-Month	1.80 ± 0.58 (93)
% DS, In-stent	
Post-Procedure	4.07 ± 10.12 (104)
8-Month	16.40 ± 23.55 (93)
% DS, In-segment	
Post-Procedure	19.41 ± 8.22 (104)
8-Month	26.86 ± 19.65 (93)
Late Loss (mm)	
In-stent	0.36 ± 0.52 (93)
In-segment	0.24 ± 0.43 (93)
Binary Restenosis	
In-stent	10.8% (10/93)
In-segment	11.8% (11/93)
IVUS RESULTS	
Neointimal Volume (mm ³)	7.29 ± 9.30 (63)
% Volume Obstruction	5.34 ± 5.97 (63)
Incomplete Apposition	
Persistent	16.7% (10/60)
Late Acquired	1.7% (1/60)

Notes

N = The total number of subjects enrolled.

M = The total number of lesions at baseline.

Numbers are % (Count/Number of Evaluable Lesions) or Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

4.0 mm Sub-study

The 4.0 mm Resolute stent met the primary superiority endpoint with an 8-month in-segment late LL of 0.11 ± 0.09 mm, compared with the historical Driver stent control in-segment late LL of 0.66 ± 0.05 mm, $P_{\text{superiority}} < 0.001$.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table 24:** RESOLUTE US 4.0 mm Sub-study - Primary Endpoint Analyses,
- **Table 25:** RESOLUTE US 4.0 mm Sub-study – Principal Safety and Effectiveness,
- **Table 26:** RESOLUTE US 4.0 mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 12 Months
- **Table 27:** RESOLUTE US 4.0 mm Sub-study - Angiographic Results

Table 24: RESOLUTE US 4.0 mm Sub-study - Primary Endpoint Analyses

4.0 mm Sub-study	Resolute (N = 60, M=72)	Historical Control Driver (N = 150, M=150)	Difference: Resolute - Historical Control	Upper One-sided 95% CI¹	Superiority P-value^{1,2}
8-month in-segment late Lumen Loss (mm)	0.11 ± 0.09 (50)	0.66 ± 0.05 (150)	-0.56	-0.38	<0.001

Notes

N = The total number of subjects enrolled.

M= The total number of lesions at baseline.

Subjects are only counted once for each time period.

The numbers are least squares mean \pm standard error (number of evaluable lesions).

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 4.0mm lesions

¹ The CI and P-values are 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.

²One sided p-value by superiority test using asymptotic test statistic, to be compared at a 0.05 significance level.

Table 25: RESOLUTE US 4.0 Sub-study – Principal Safety and Effectiveness

Outcomes at 12 Months	4.0 mm Sub-Study (N = 60)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	6.8% (4/59)
TVF	6.8% (4/59)
MACE	8.5% (5/59)
EFFECTIVENESS	
Clinically Driven TVR	3.4% (2/59)
TLR	3.4% (2/59)
TLR, PCI	3.4% (2/59)
TLR, CABG	0.0% (0/59)
Non-TL TVR	1.7% (1/59)
Non-TL TVR, PCI	1.7% (1/59)
Non-TL TVR, CABG	0.0% (0/59)
SAFETY	
Total Death	1.7% (1/59)
Cardiac Death	0.0% (0/59)
Non-Cardiac Death	1.7% (1/59)
Cardiac Death or TVMI	3.4% (2/59)
TVMI	3.4% (2/59)
Q wave MI	0.0% (0/59)
Non-Q wave MI	3.4% (2/59)
Stent Thrombosis ARC defined	
Definite/Probable	0.0% (0/59)
Definite	0.0% (0/59)
Probable	0.0% (0/59)

Notes

N = The total number of subjects enrolled.

Numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

12-month timeframe includes follow-up window (360 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 26: RESOLUTE US 4.0mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	4.0 mm Sub-study (N = 60)
Stent Thrombosis	0.0% (0/59)
Acute (0 – 1 day)	0.0% (0/59)
Subacute (2 - 30 days)	0.0% (0/59)
Late (31 days – 360 days)	0.0% (0/59)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (Count/Number of Eligible Subjects).

12-month timeframe includes follow-up window (360 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-360 days inclusive) or had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

Table 27: RESOLUTE US 4.0mm Sub-study Angiographic Results

Outcomes at 8 Months	4.0 mm Sub-study (N = 60, M = 72)
ANGIOGRAPHIC RESULTS	
MLD (mm), In-stent	
Post-Procedure	3.12 ± 0.38 (72)
8-Month	2.94 ± 0.65 (60)
MLD (mm), In-segment	
Post-Procedure	2.75 ± 0.45 (72)
8-Month	2.60 ± 0.60 (60)
% DS, In-stent	
Post-Procedure	4.54 ± 9.36 (72)
8-Month	9.37 ± 19.48 (60)
% DS, In-segment	
Post-Procedure	16.62 ± 8.27 (72)
8-Month	20.22 ± 14.79 (60)
Late Loss (mm)	
In-stent	0.19 ± 0.56 (60)
In-segment	0.14 ± 0.43 (60)
Binary Restenosis	
In-stent	6.7% (4/60)
In-segment	6.7% (4/60)

Notes

N = The total number of subjects enrolled.

M = The total number of lesions at baseline.

Numbers are % (Count/Number of Evaluable Lesions) or Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

Sub-group Analysis – Gender Analysis of the RESOLUTE US Primary Enrollment Group

Table 28 shows the baseline demographic and clinical characteristics stratified by gender for subjects in the pooled RESOLUTE US analysis, 444/1402 (31.7%) subjects were female and 958/1402 (68.3%) were male. Consistent with other DES clinical studies, female patients were older and had a higher rate of diabetes and hypertension and had smaller reference vessel diameters (RVD).

Table 28: RESOLUTE US Baseline Demographic and Lesion Characteristics Male vs. Female

Patient Characteristics	Male (N=958)	Female (N=444)	p-value
Age (Years)	63.2 ± 10.5	66.2 ± 10.8	< 0.001
History of smoking/tobacco use	66.9% (641/958)	52.9% (235/444)	< 0.001
Prior PCI	34.1% (327/958)	29.5% (131/444)	0.087
Hyperlipidemia	88.5% (848/958)	86.0% (382/444)	0.190
Diabetes Mellitus	31.3% (300/958)	41.0% (182/444)	< 0.001
Insulin Dependent	7.2% (69/958)	14.9% (66/444)	< 0.001
Hypertension	82.3% (788/958)	88.3% (392/444)	0.004
Prior MI	24.6% (232/944)	15.2% (66/435)	< 0.001
Prior CABG	10.6% (102/958)	5.0% (22/444)	< 0.001
Ejection fraction - Qualitative			0.059
<30%	0.1% (1/824)	0.3% (1/385)	
30-40%	6.7% (55/824)	3.4% (13/385)	
>40%	93.2% (768/824)	96.4% (371/385)	
Lesion Class			0.019
A	5.5% (60/1083)	7.7% (37/483)	
B1	17.1% (185/1083)	22.2% (107/483)	
B2	30.8% (334/1083)	27.5% (133/483)	
C	46.5% (504/1083)	42.7% (206/483)	
Moderate/Severe Calcification	25.9% (281/1083)	29.0% (140/483)	0.217
Pre procedure RVD	2.621 ± 0.480	2.528 ± 0.435	< 0.001
Pre procedure MLD	0.754 ± 0.354	0.792 ± 0.339	0.048
Pre procedure Diameter Stenosis	71.4 ± 11.6	68.9 ± 11.2	< 0.001
Lesion Length	13.271 ± 5.892	12.603 ± 5.840	0.038

The 12 month rate of TLF was 4.4% in males and 5.3% in females (see table below). This *post hoc* analysis shows a generally similar treatment effect between genders for the primary endpoint of 12-month TLF. These data suggest that the safety and effectiveness of the Resolute stent can be generalized to males and females.

Table 29: RESOLUTE US Primary Enrollment Group - 12 Month Clinical Endpoints by Gender – Principal Safety and Effectiveness

	Male (N=958)	Female (N=444)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.4% (42/944)	5.3% (23/432)
TVF	5.6% (53/944)	7.6% (33/432)
MACE	5.4% (51/944)	5.8% (25/432)
EFFECTIVENESS		
Clinically Driven TVR	4.3% (41/944)	5.1% (22/432)
TLR	3.0% (28/944)	2.5% (11/432)
SAFETY		
Total Death	1.3% (12/944)	1.4% (6/432)
Cardiac Death	0.5% (5/944)	0.9% (4/432)
Non-Cardiac Death	0.7% (7/944)	0.5% (2/432)
TVMI	1.1% (10/944)	2.1% (9/432)
Cardiac Death or TVMI	1.6% (15/944)	3.0% (13/432)
Stent Thrombosis ARC defined		
Definite/Probable	0.2% (2/944)	0.0% (0/432)
Definite	0.1% (1/944)	0.0% (0/432)
Probable	0.1% (1/944)	0.0% (0/432)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis

See **Section G2- Gender Analysis from the RESOLUTE Pooled On-label Dataset** for the comprehensive gender analysis.

C. RESOLUTE All Comers Clinical Trial

The primary objective of the RESOLUTE All Comers (R-AC) trial was to compare the Resolute Zotarolimus-Eluting Coronary Stent System (Resolute stent) with the Abbott XIENCE V Everolimus-Eluting Coronary Stent System (Xience V stent) in a “real world” patient population with respect to Target Lesion Failure (composite of Cardiac Death, MI not clearly attributable to a non-target vessel, and clinically indicated TLR at 12 months).

The data from the RESOLUTE AC trial were used to support PMA approval of the Resolute Integrity stent. In particular, the on-label data from the RESOLUTE AC population were pooled with other on-label RESOLUTE program data to demonstrate the long term safety of the Resolute stent.

C1. Study Design: This is a prospective, multi-center, randomized, two-arm non-inferiority trial that compared the Resolute stent to the Abbott Xience V stent. A total of 2292 subjects were enrolled at 17 clinical research sites from 11 countries in Western Europe.

Clinical Inclusion and Exclusion Criteria

Patients were eligible if they had at least one coronary lesion with a diameter stenosis >50 %, in a vessel with a reference diameter between 2.25 mm and 4.0 mm. No restriction was placed on the total number of treated lesions, treated vessels, lesion length or number of stents implanted. The study was designed to enroll patients with symptomatic coronary disease including chronic stable angina, silent ischemia, and acute coronary ischemic syndromes. Subjects were stratified as being non-complex or complex (based on clinical features and coronary anatomy), with complex subjects having one or more of the following patient or lesion characteristics: Bifurcation, bypass graft, in stent restenosis, AMI < 72 hours, LVEF < 30%, unprotected left main, > 2 vessels stented, renal insufficiency or failure (serum creatinine > 2.5 mg/dL), lesion length > 27 mm, > 1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

Follow-Up Schedule

Follow-up was performed at 30 days, 6, 9, 12 and 24 months and will be performed annually out to 5 years. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 6 months and up to 12 months in those who were not at a high risk of bleeding.

Clinical Endpoints

The primary endpoint in the R-AC overall population was TLF defined as the composite of Cardiac Death, MI (not clearly attributable to a non-target vessel), or and clinically indicated TLR within 12 months post-implantation.

C2. Accountability of RESOLUTE AC Cohort

At the time of database lock, of 2292 patients enrolled in the RESOLUTE All-Comers Study, 98.1% (2249) patients are available for analysis at the completion of the study, the 2-year post-operative visit. Of the 2292 patients, 98.3% (1121/1140) Resolute and 97.9% (1128/1152) Xience were available for analysis at 2 years.

C3. Study Population Demographics and Baseline Parameters

Table 30: R-AC - Baseline Characteristics

Baseline Characteristics	Resolute (N=1140 subjects; N=1661 lesions)	Xience V (N=1152 subjects; N=1705 lesions)
Mean Age (years)	64.4	64.2
Male Enrollment	76.7% (874/1140)	77.2% (889/1152)
Hx of prior PCI	31.8% (363/1140)	32.1% (370/1152)
Hx of prior MI	28.8% (323/1122)	30.4% (341/1120)
Hx of Diabetes	23.5% (268/1140)	23.4% (270/1152)
Multi-vessel disease	58.4% (666/1140)	59.2% (682/1152)
Type B2/C lesions	77.5% (1268/1636)	74.7% (1251/1673)
Syntax Score	14.8 ± 9.3	14.6 ± 9.2
Complex*	67% (764/1140)	65.6% (756/1152)
<p>* Complex was defined as having one or more of the following patient or lesion characteristics: Bifurcation, bypass graft, in stent restenosis, AMI <72 hr, LVEF <30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine >2.5 mg/dL), lesion length >27 mm, >1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).</p> <p>The remaining baseline clinical features were well-matched between both arms.</p>		

C4. Safety and Effectiveness Results

Clinical Results: A summary of the results is presented in the following tables:

- **Table 31:** R-AC Principal Safety and Effectiveness (All subjects),
- **Table 32:** R-AC Principal Safety and Effectiveness (Complex cohort),
- **Table 33:** R-AC Principal Safety and Effectiveness (Non-Complex cohort) and
- **Table 34:** R-AC ARC Defined Definite/Probable Stent Thrombosis through 24 Months (Complex and Non-Complex)

Table 31: R-AC Principal Safety and Effectiveness (All subjects)

COMPOSITE SAFETY AND EFFECTIVENESS	All subjects			
	1 Year		2 Years	
	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 1140)	Xience V (N = 1152)
TLF	8.1% (92/1130)	8.5% (97/1138)	11.2% (126/1121)	10.7% (121/1128)
TVF	8.9% (101/1130)	9.8% (111/1138)	12.6% (141/1121)	12.2% (138/1128)
MACE	8.6% (97/1130)	9.8% (112/1138)	12.5% (140/1121)	12.9% (146/1128)
EFFECTIVENESS				
Clinically Driven TVR	4.9% (55/1130)	4.8% (55/1138)	7.3% (82/1121)	6.9% (78/1128)
TLR	3.9% (44/1130)	3.4% (39/1138)	5.7% (64/1121)	5.1% (58/1128)
TLR, PCI	3.4% (38/1130)	2.7% (31/1138)	5.0% (56/1121)	4.3% (48/1128)
TLR, CABG	0.5% (6/1130)	0.8% (9/1138)	1.1% (12/1121)	1.1% (12/1128)
Non-TL TVR	1.9% (21/1130)	2.2% (25/1138)	3.1% (35/1121)	3.2% (36/1128)
Non-TL TVR, PCI	1.5% (17/1130)	1.9% (22/1138)	2.6% (29/1121)	2.7% (30/1128)
Non-TL TVR, CABG	0.4% (4/1130)	0.4% (4/1138)	0.5% (6/1121)	0.6% (7/1128)
SAFETY				
Total Death	1.6% (18/1130)	2.7% (31/1138)	3.2% (36/1121)	4.0% (45/1128)
Cardiac Death	1.3% (15/1130)	1.7% (19/1138)	2.6% (29/1121)	2.2% (25/1128)
Non-Cardiac Death	0.3% (3/1130)	1.1% (12/1138)	0.6% (7/1121)	1.8% (20/1128)
Cardiac Death or TVMI	5.3% (60/1130)	5.5% (63/1138)	7.0% (78/1121)	6.3% (71/1128)
TVMI	4.2% (48/1130)	4.2% (48/1138)	4.7% (53/1121)	4.5% (51/1128)
Q wave MI	0.8% (9/1130)	0.4% (5/1138)	1.0% (11/1121)	0.5% (6/1128)
Non-Q wave MI	3.5% (40/1130)	3.8% (43/1138)	3.8% (43/1121)	4.0% (45/1128)
Stent Thrombosis ARC defined				
Definite/Probable	1.6% (18/1130)	0.7% (8/1138)	1.9% (21/1121)	1.0% (11/1128)
Definite	1.2% (13/1130)	0.3% (3/1138)	1.3% (15/1121)	0.5% (6/1128)
Probable	0.5% (6/1130)	0.4% (5/1138)	0.6% (7/1121)	0.4% (5/1128)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (Count/Number of Eligible Subjects).

12-month timeframe includes follow-up window (360 ± 30 days)

24-month timeframe includes follow-up window (720 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 32: R-AC Principal Safety and Effectiveness (Complex cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Complex cohort			
	1 Year		2 Years	
	Resolute (N = 764)	Xience V (N = 756)	Resolute (N = 764)	Xience V (N = 756)
TLF	8.8% (67/759)	10.1% (75/746)	12.1% (91/752)	12.6% (93/738)
TVF	9.7% (74/759)	11.4% (85/746)	13.6% (102/752)	14.2% (105/738)
MACE	9.1% (69/759)	11.8% (88/746)	13.2% (99/752)	15.3% (113/738)
EFFECTIVENESS				
Clinically Driven TVR	5.5% (42/759)	5.6% (42/746)	8.1% (61/752)	8.0% (59/738)
TLR	4.3% (33/759)	4.2% (31/746)	6.4% (48/752)	6.1% (45/738)
TLR, PCI	4.0% (30/759)	3.2% (24/746)	5.9% (44/752)	5.0% (37/738)
TLR, CABG	0.4% (3/759)	1.1% (8/746)	0.9% (7/752)	1.4% (10/738)
SAFETY				
Total Death	1.4% (11/759)	3.4% (25/746)	3.2% (24/752)	4.7% (35/738)
Cardiac Death	1.3% (10/759)	2.1% (16/746)	2.7% (20/752)	2.8% (21/738)
Non-Cardiac Death	0.1% (1/759)	1.2% (9/746)	0.3% (2/752)	0.8% (6/738)
Cardiac Death or TVMI	5.4% (41/759)	6.4% (48/746)	7.2% (54/752)	7.3% (54/738)
TVMI	4.2% (32/759)	4.7% (35/746)	13.8% (104/752)	15.7% (116/738)
Q wave MI	0.7% (5/759)	0.5% (4/746)	0.9% (7/752)	0.7% (5/738)
Non-Q wave MI	3.7% (28/759)	4.2% (31/746)	13.2% (99/752)	15.0% (111/738)
Stent Thrombosis ARC defined				
Definite/Probable	1.7% (13/759)	0.9% (7/746)	2.0% (15/752)	1.2% (9/738)
Definite	1.2% (9/759)	0.4% (3/746)	1.5% (11/752)	0.7% (5/738)
Probable	0.7% (5/759)	0.5% (4/746)	0.7% (5/752)	0.5% (4/738)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (Count/Number of Eligible Subjects).

12-month timeframe includes follow-up window (360± 30 days)

24-month timeframe includes follow-up window (720 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

Complex was defined as having one or more of the following patient or lesion characteristics: Bifurcation, bypass graft, in stent restenosis, AMI <72 hr, LVEF <30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine > 2.5 mg/dL, lesion length >27 mm, >1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

Table 33: R-AC Principal Safety and Effectiveness (Non-Complex cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Non-Complex cohort			
	1 Year		2 Years	
	Resolute (N = 376)	Xiencor V (N = 396)	Resolute (N = 376)	Xiencor V (N = 396)
TLF	6.7% (25/371)	5.6% (22/392)	9.5% (35/369)	7.2% (28/390)
TVF	7.3% (27/371)	6.6% (26/392)	10.6% (39/369)	8.5% (33/390)
MACE	7.5% (28/371)	6.1% (24/392)	11.1% (41/369)	8.5% (33/390)
EFFECTIVENESS				
Clinically Driven TVR	3.5% (13/371)	3.3% (13/392)	5.7% (21/369)	4.9% (19/390)
TLR	3.0% (11/371)	2.0% (8/392)	4.3% (16/369)	3.3% (13/390)
TLR, PCI	2.2% (8/371)	1.8% (7/392)	4.3% (16/369)	4.4% (17/390)
TLR, CABG	0.8% (3/371)	0.3% (1/392)	0.8% (3/369)	0.0% (0/390)
SAFETY				
Total Death	1.9% (7/371)	1.5% (6/392)	3.3% (12/369)	2.6% (10/390)
Cardiac Death	1.3% (5/371)	0.8% (3/392)	2.4% (9/369)	1.0% (4/390)
Non-Cardiac Death	0.5% (2/371)	0.8% (3/392)	0.8% (3/369)	1.5% (6/390)
Cardiac Death or TVMI	5.1% (19/371)	3.8% (15/392)	6.5% (24/369)	4.4% (17/390)
TVMI	4.3% (16/371)	3.3% (13/392)	4.9% (18/369)	3.6% (14/390)
Q wave MI	1.1% (4/371)	0.3% (1/392)	1.1% (4/369)	0.3% (1/390)
Non-Q wave MI	3.2% (12/371)	3.1% (12/392)	3.8% (14/369)	3.3% (13/390)
Stent Thrombosis ARC defined				
Definite/Probable	1.3% (5/371)	0.3% (1/392)	1.6% (6/369)	0.5% (2/390)
Definite	1.1% (4/371)	0.0% (0/392)	1.1% (4/369)	0.3% (1/390)
Probable	0.3% (1/371)	0.3% (1/392)	0.5% (2/369)	0.3% (1/390)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (Count/Number of Eligible Subjects).

12-month timeframe includes follow-up window (360 ± 30 days)

24-month timeframe includes follow-up window (720 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis

Complex was defined as having one or more of the following patient or lesion characteristics: Bifurcation, bypass graft, in stent restenosis, AMI <72 hr, LVEF <30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine > 2.5 mg/dL, lesion length >27 mm, >1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

Table 34: R-AC ARC Defined Definite/Probable Stent Thrombosis through 24 Months (All Subjects, and Complex and Non-Complex Subjects)

	All Subjects		Non-Complex		Complex	
	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 376)	Xience V (N = 396)	Resolute (N = 764)	Xience V (N = 756)
Cumulative Stent Thrombosis Through 1-Year	1.6% (18/1121)	0.7% (8/1128)	1.3% (5/371)	0.3% (1/392)	1.7% (13/759)	0.9% (7/746)
Cumulative Stent Thrombosis Through 2-Years	1.9% (21/1121)	1.0% (11/1128)	1.6% (6/369)	0.5% (2/390)	2.0% (15/752)	1.2% (9/738)
Acute (0 - 1 day)	0.4% (5/1121)	0.2% (2/1128)	0.3% (1/369)	0.0% (0/390)	0.5% (4/752)	0.3% (2/738)
Subacute (2 - 30 days)	0.7% (8/1121)	0.4% (4/1128)	0.3% (1/369)	0.3% (1/390)	0.9% (7/752)	0.4% (3/738)
Late (31 days - 360 days)	0.6% (7/1121)	0.2% (2/1128)	0.8% (3/369)	0.0% (0/390)	0.5% (4/752)	0.3% (2/738)
Very Late (361 days - 720 days)	0.3% (3/1121)	0.3% (3/1128)	0.3% (1/369)	0.3% (1/390)	0.3% (2/752)	0.3% (2/738)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

Numbers are % (Count/Number of Eligible Subjects).

12-month timeframe includes follow-up window (360± 30 days)

24-month timeframe includes follow-up window (720 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

Complex was defined as having one or more of the following patient or lesion characteristics: Bifurcation, bypass graft, in stent restenosis, AMI <72 hr, LVEF <30%, unprotected left main, >2 vessels stented, renal insufficiency or failure (serum creatinine > 2.5 mg/dL), lesion length >27 mm, >1 lesion per vessel, lesion with thrombus or total occlusion (pre procedure TIMI = 0).

D. RESOLUTE International Clinical Trial

The primary objective of the RESOLUTE International (R-Int) trial was to evaluate the safety and overall clinical performance of the Resolute Zotarolimus-Eluting Coronary Stent System (the Resolute stent) in an ‘all-comers’ patient population requiring stent implantation by assessing the rates of cardiac death and myocardial infarction at 12 months.

D1. Study Design: This is a prospective, multi-center, non-randomized observational study. A total of 2349 subjects were enrolled at 88 clinical research sites from 17 countries in Europe, Asia, Africa and South America where the Resolute stent is commercially available.

Clinical Inclusion and Exclusion Criteria

This study was designed to treat all enrolled subjects according to routine hospital practice. No restriction was placed on the total number of treated lesions, treated vessels, lesion length or number of stents implanted. The study enrolled patients with symptomatic coronary disease (including chronic stable angina, silent ischemia, and acute coronary ischemic syndromes). Enrolled subjects were permitted to have complex clinical or anatomic features as described in **Section C4 – Safety and Effectiveness Results of the RESOLUTE All Comers Clinical Trial.**

Follow-Up Schedule

Follow-up was performed at 30 days, 6 and 12 months and will be performed annually out to 3 years. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

Clinical Endpoints

The primary clinical endpoint of the R-Int trial was the composite of Cardiac Death and MI (not clearly attributable to a non-target vessel) at 12 months post-implantation.

D2. Accountability of RESOLUTE-Int Cohort

At the time of database lock, of 2349 patients enrolled in the RESOLUTE International Study, 97.9% (2299) patients are available for analysis at the completion of the study, the 1-year post-operative visit.

D3. Study Population Demographics and Baseline Parameters

The baseline demographics and clinical characteristics show a mean age of 63.5 years with a male enrollment of 77.8% (1828/2349). Of the subjects enrolled in this study, 29.6% (696/2349) of subjects had a prior percutaneous coronary revascularization and 8.4% (197/2349) had previous CABG surgery. In total, 30.5% (716/2349) of the subjects had a history of diabetes mellitus with 9.0% (211/2349) being insulin dependent. Past medical history of subjects indicated 63.9% (1501/2349) had hyperlipidemia, 68.0% (1598/2349) had hypertension, and 24.2% (569/2349) were current smokers. The mean RVD was 2.94 ± 0.46 mm, the lesion length was 18.75 ± 10.77 mm and the average percentage diameter stenosis was $84.50 \pm 12.12\%$. The ACC/AHA lesion classification was reported by sites as type B2/C for 57.1% (1798/3147) of the lesions.

D4. Safety and Effectiveness Results

Results: These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table 35:** RESOLUTE International Principal Safety and Effectiveness
- **Table 36:** RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 35: RESOLUTE International - Principal Safety and Effectiveness

Outcomes at 12 Months	(N = 2349)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	7.0% (162/2299)
TVF	7.7% (177/2299)
MACE	8.2% (188/2299)
EFFECTIVENESS	
Clinically Driven TVR	4.2% (97/2299)
TLR	3.4% (79/2299)
TLR, PCI	3.1% (72/2299)
TLR, CABG	0.3% (8/2299)
Non-TL TVR	1.1% (26/2299)
Non-TL TVR, PCI	1.1% (26/2299)
Non-TL TVR, CABG	0.0% (0/2299)
SAFETY	
Total Death	2.4% (56/2299)
Cardiac Death	1.4% (33/2299)
Non-Cardiac Death	1.0% (23/2299)
Cardiac Death or MI	4.3% (98/2299)
TVMI	3.1% (71/2299)
Q wave MI	0.5% (12/2299)
Non-Q wave MI	2.6% (59/2299)
Stent Thrombosis ARC defined	
Definite/Probable	0.9% (20/2299)
Definite	0.7% (15/2299)
Probable	0.3% (6/2299)

Notes

N = The total number of subjects enrolled.

Numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

12-month timeframe includes follow-up window (360 days ± 30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 36: RESOLUTE International ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

	Resolute (N = 2349)
Stent Thrombosis	0.9% (20/2299)
Acute (0 - 1 day)	0.1% (3/2299)
Subacute (2 - 30 days)	0.6% (14/2299)
Late (31 – 360 days)	0.1% (3/2299)

Notes

N = The total number of subjects enrolled.

Numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

12-month time frame includes follow-up window (360 days ±30 days).

See Table 15 for the definition of the ARC defined Stent Thrombosis.

E. RESOLUTE FIM Clinical Trial

The primary objective of the RESOLUTE FIM trial was to evaluate the safety, effectiveness, and pharmacokinetics (PK) of the Resolute Zotarolimus-Eluting Coronary Stent (Resolute stent) for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) between 2.5 mm and 3.5 mm in diameter.

E1. Study Design: The RESOLUTE FIM Clinical Trial, the first-in-human study for the Resolute stent, is a non-randomized, prospective, multi-center, single-arm trial. A total of 139 subjects were enrolled at 12 investigative sites in Australia and New Zealand.

Clinical Inclusion and Exclusion Criteria

The RESOLUTE FIM included patients who presented with symptomatic ischemic heart disease due to a *de novo* stenotic lesion contained within a native coronary artery with a reference vessel diameter between 2.5 mm and 3.5 mm and a lesion length between 14 mm and 27 mm amenable to percutaneous treatment with a single stent.

Follow-Up Schedule

Follow-up was performed at 30 days, 4, 9, 12 months and annually at 2, 3 and 4 years. Follow-up will be performed at 5 years. Thirty subjects were consented to have an angiographic and IVUS follow-up at 4 months post-procedure while an additional 100 subjects were consented to have the same type of follow-up at 9 months post-procedure. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 6 months.

Clinical Endpoints

The primary endpoint was in-stent late lumen loss (LL) at 9 months post-procedure as measured by QCA. The primary analysis was a non-inferiority comparison of the 9-month in-stent late LL in the Resolute stent compared to a historical control population of subjects treated with an Endeavor stent in the ENDEAVOR II trial. The non-inferiority margin was set at 0.16 mm.

E2. Accountability of RESOLUTE FIM Cohort

At the time of database lock, of 139 patients enrolled in the RESOLUTE FIM Study, 99.3% (138) patients are available for analysis at the completion of the study, the 4-year post-operative visit.

E3. Study Population Demographics and Baseline Parameters

The mean age was 60.7 years, with 76.3% (106/139) men, 17.3% (24/139) diabetics, 18.7% (26/139) with a history of prior percutaneous coronary revascularization, 46.4% (64/138) with a history of prior MI and 2.9% (4/139) with a history of prior CABG. Past medical history of subjects indicated 94.2% (131/139) had hyperlipidemia and 66.9% (93/139) had hypertension. The mean RVD was 2.81 ± 0.40 mm, the lesion length was 15.61 ± 6.13 mm and the average percentage diameter stenosis was $70.30 \pm 11.37\%$. The ACC/AHA lesion classification was reported by sites as type B2/C for 81.4% (114/140) of the lesions.

E4. Safety and Effectiveness Results

The Resolute stent met the primary non-inferiority endpoint with a 9 months in-stent late LL of 0.22 ± 0.27 mm, compared with the historical Endeavor stent control 8-month in-stent late LL of 0.62 ± 0.45 mm, $p_{\text{non-inferiority}} < 0.001$.

These analyses are based on the intent-to-treat population. PK results are presented in **Section IX.C** for the Pharmacokinetics of the Resolute stent. The results are presented in the following tables:

- **Table 37:** RESOLUTE FIM – Primary Endpoint Analysis
- **Table 38:** RESOLUTE FIM – Principal Safety and Effectiveness
- **Table 39:** RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis through 48 Months and
- **Table 40:** RESOLUTE FIM - Angiographic and IVUS Results

Table 37: RESOLUTE FIM Primary Endpoint Result

Primary Endpoint ¹	RESOLUTE (N = 139, M = 140)	ENDEAVOR II Endeavor (N = 256, M = 256)	Difference [95% CI] ²	Non-Inferiority P-value ³
9-month In-stent Late Lumen Loss (mm)	0.22 ± 0.27 (96)	0.62 ± 0.45 (256)	-0.39 [-0.49, -0.30]	<0.001

Notes

N is The total number of subjects enrolled.

M is the total number of lesions at baseline.

Numbers are Mean \pm SD (number of evaluable lesions).

Subjects are only counted once for each time period.

¹ Angiographic Follow-Up for RESOLUTE was at 9 Months and for Endeavor stent from the ENDEAVOR II trial was at 8 Months.

² Confidence interval calculated using normal approximation.

³ One sided p-value by non-inferiority test using t test with non-inferiority margin of 0.16 mm, to be compared at a 0.05 significance level.

Table 38: RESOLUTE FIM Principal Safety and Effectiveness

	Outcomes at 9 Months (N = 139)	Outcomes at 12 Months (N = 139)	Outcomes at 48 Months (N = 139)
COMPOSITE SAFETY AND EFFECTIVENESS			
TVF	6.5% (9/139)	7.2% (10/139)	10.1% (14/138)
MACE	7.2% (10/139)	8.6% (12/139)	13.8% (19/138)
EFFECTIVENESS			
Clinically Driven TVR	0.0% (0/139)	0.7% (1/139)	3.6% (5/138)
TLR	0.0% (0/139)	0.7% (1/139)	2.2% (3/138)
TLR, PCI	0.0% (0/139)	0.7% (1/139)	2.2% (3/138)
TLR, CABG	0.0% (0/139)	0.0% (0/139)	0.0% (0/138)
Non-TL TVR	0.0% (0/139)	0.0% (0/139)	1.4% (2/138)
Non-TL TVR, PCI	0.0% (0/139)	0.0% (0/139)	1.4% (2/138)
Non-TL TVR, CABG	0.0% (0/139)	0.0% (0/139)	0.0% (0/138)
SAFETY			
Total Death	1.4% (2/139)	2.2% (3/139)	5.8% (8/138)
Cardiac Death	0.7% (1/139)	0.7% (1/139)	0.7% (1/138)
Non-Cardiac Death	0.7% (1/139)	1.4% (2/139)	5.1% (7/138)
Cardiac Death or MI	6.5% (9/139)	6.5% (9/139)	6.5% (9/138)
MI	5.8% (8/139)	5.8% (8/139)	5.8% (8/138)
Q wave MI	0.0% (0/139)	0.0% (0/139)	0.0% (0/138)
Non-Q wave MI	5.8% (8/139)	5.8% (8/139)	5.8% (8/138)
Stent Thrombosis ARC defined			
Definite/Probable	0.0% (0/139)	0.0% (0/139)	0.0% (0/138)
Definite	0.0% (0/139)	0.0% (0/139)	0.0% (0/138)
Probable	0.0% (0/139)	0.0% (0/139)	0.0% (0/138)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 9-month timeframe includes follow-up window (270 days ± 14 days).
 12-month timeframe includes follow-up window (360 days ± 30 days).
 48-month timeframe includes follow-up window (1440 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 39: RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis through 48 Months

	Resolute (N = 139)
Stent Thrombosis	0.0% (0/138)
Acute (0 - 1 day)	0.0% (0/138)
Subacute (2 - 30 days)	0.0% (0/138)
Late (31 - 360 days)	0.0% (0/138)
Very late (361 - 1440 days)	0.0% (0/138)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 48-month time frame includes follow-up window (1440 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis

Table 40: RESOLUTE FIM Angiographic and IVUS Results

	Outcomes at 4 Months (N = 30, M = 30)	Outcomes at 9 Months (N = 100, M = 101)
ANGIOGRAPHIC RESULTS		
MLD (mm), In-stent		
Post-Procedure	2.76 ± 0.39 (140)	2.76±0.39 (140)
Follow Up	2.68±0.39 (30)	2.51±0.48 (96)
MLD (mm), In-segment		
Post-Procedure	2.36 ± 0.43 (140)	2.36±0.43 (140)
Follow Up	2.38±0.40 (30)	2.21±0.45 (96)
% DS, In-stent		
Post-Procedure	3.36±8.54 (140)	3.36±8.54 (140)
Follow Up	7.18±7.86 (30)	10.13±12.63 (96)
% DS, In-segment		
Post-Procedure	17.80±8.24 (140)	17.80±8.24 (140)
Follow Up	17.74±7.57 (30)	21.08±10.62 (96)
Late Loss (mm)		
In-stent	0.12±0.26 (30)	0.22±0.27 (96)
In-segment	0.05±0.20 (30)	0.12±0.27 (96)
Binary Restenosis		
In-stent	0.0% (0/30)	1.0% (1/96)
In-segment	0.0% (0/30)	2.1% (2/96)

	Outcomes at 4 Months (N = 30, M = 30)	Outcomes at 9 Months (N = 100, M = 101)
IVUS RESULTS		
Neointimal Volume (mm ³)	3.72±4.21 (24)	6.55±7.83 (88)
% Volume Obstruction	2.23±2.43 (24)	3.73±4.05 (88)
Incomplete Apposition		
Persistent	6.7% (2/30)	17.0% (15/88)
Late Acquired	3.3% (1/30)	6.8% (6/88)

Notes

139 subjects with 140 lesions underwent angiographic follow-up at baseline.

N = The total number of subjects enrolled.

M = The total number of lesions at baseline.

Numbers are % (Count/Number of Eligible Subjects) or Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

F. RESOLUTE Japan (R-J) Clinical Trial

The primary objective of the RESOLUTE Japan trial was to verify the safety and effectiveness of the Resolute Zotarolimus-Eluting Coronary Stent (Resolute Stent) in a Japanese population for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5 mm to 3.5 mm and lesion lengths ≤27 mm.

F1. Study Design: This is a non-randomized, prospective, multi-center, single-arm trial. A total of 100 subjects were enrolled at 14 investigational sites in Japan.

Clinical Inclusion and Exclusion Criteria

Resolute Japan trial included patients with ischemic heart disease due to stenotic lesions of native coronary arteries with reference vessel diameters between 2.5 and 3.5 mm and lesion lengths ≤ 27 mm that were amenable to percutaneous treatment with stenting. Up to two lesions in two separate target vessels could be treated under this protocol.

Follow-Up Schedule

Follow-up was performed at 30 days, 6, 9, and 12 months and will be performed annually out to 5 years. All subjects were scheduled to have angiographic and IVUS follow-up at eight months post-procedure. Following the index procedure, subjects were to be treated with aspirin indefinitely and clopidogrel/ticlopidine for a minimum of six months and up to 12 months in subjects who were not at a high risk of bleeding.

Clinical Endpoints

The primary endpoint was in-stent late LL at 8 months post-procedure as measured by QCA. The primary analysis was a non-inferiority comparison of the 8-month in-stent late LL in the Resolute stent compared to a historical control population of subjects treated with a Taxus stent in the ENDEAVOR IV trial. The non-inferiority margin was set at 0.20 mm. If the non-inferiority endpoint was met, a superiority test would be performed.

F2. Accountability of RESOLUTE Japan Cohort

At the time of database lock, of 100 patients enrolled in the RESOLUTE Japan Study, 100% (100) patients are available for analysis at the completion of the study, the 1-year post-operative visit.

F3. Study Population Demographics and Baseline Parameters

Baseline demographics and clinical characteristics shows a mean age of 67.7 years with 77.0% (77/100) of subjects enrolled being males. Of the subjects enrolled 45.0% (45/100) had diabetes mellitus, 22.0% (22/100) were current smokers, 25.0% (25/100) had prior myocardial infarction (MI), 42.0% (42/100) had prior PCI, 81.0% (81/100) had hypertension and 78.0% (78/100) reported hyperlipidemia. Baseline lesion characteristics include 42.6% (46/108) LAD lesions, a mean lesion length of 15.52 ± 5.37 mm, 52.8% (57/108) ACC/AHA type B2/C lesions and 18.5% (20/108) lesions involving a bifurcation. The mean RVD was 2.85 ± 0.44 mm and the percentage diameter stenosis was 69.17 ± 7.80 %.

F4. Safety and Effectiveness Results

The Resolute stent in-stent late LL at 8 months was 0.13 ± 0.22 mm, which met the primary non-inferiority endpoint (and demonstrated superiority) compared with the historical Taxus stent 8-month in-stent late LL of 0.42 ± 0.50 mm.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

Table 41: RESOLUTE Japan - Primary Endpoint Analysis

Table 42: RESOLUTE Japan - Principal Safety and Effectiveness

Table 43: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 44: RESOLUTE Japan - Angiographic and IVUS Results

Table 41: RESOLUTE Japan - Primary Endpoint Result

Primary Endpoint	Resolute (N = 100, M=108)	ENDEAVOR IV Taxus (N = 164, M=164)	Difference 95%CI ¹	Non-Inferiority P-value ²	Superiority P-value ³
8-month In-stent Late Lumen Loss (mm)	0.13 ±0.22 (99)	0.42 ±0.5 (135)	-0.29[-0.41 , -0.16]	<0.001	<0.001

Notes

N = The total number of subjects enrolled.

M = The number of lesions at baseline.

Numbers are Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

Confidence interval and p values are adjusted using propensity score method.

¹ Confidence interval calculated using normal approximation.

² One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.20 mm to be compared at a 0.05 significance level.

³ Two-sided p-value by superiority test using asymptotic test statistic, to be compared at a 0.05 significance level.

Table 42: RESOLUTE Japan – Principal Safety and Effectiveness

Outcomes at 12 Months	(N = 100)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	4.0% (4/100)
TVF	5.0% (5/100)
MACE	5.0% (5/100)
EFFECTIVENESS	
Clinically Driven TVR	1.0% (1/100)
TLR	0.0% (0/100)
TLR, PCI	0.0% (0/100)
TLR, CABG	0.0% (0/100)
Non-TL TVR	1.0% (1/100)
Non-TL TVR, PCI	1.0% (1/100)
Non-TL TVR, CABG	0.0% (0/100)
SAFETY	
Total Death	1.0% (1/100)
Cardiac Death	0.0% (0/100)
Non-Cardiac Death	1.0% (1/100)
Cardiac Death or MI	4.0% (4/100)
TVMI	4.0% (4/100)
Q wave MI	0.0% (0/100)

Outcomes at 12 Months	(N = 100)
Non-Q wave MI	4.0% (4/100)
Stent Thrombosis ARC defined	
Definite/Probable	0.0% (0/100)
Definite	0.0% (0/100)
Probable	0.0% (0/100)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 43: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

	Resolute (N = 100)
Stent Thrombosis	0.0% (0/100)
Acute (0 - 1 day)	0.0% (0/100)
Subacute (2 - 30 days)	0.0% (0/100)
Late (31 - 360 days)	0.0% (0/100)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 44: RESOLUTE Japan - Angiographic and IVUS Results

Outcomes at 8 Months	(N = 100, M = 108)
ANGIOGRAPHIC RESULTS	
MLD (mm), In-stent	
Post-Procedure	2.79 ± 0.40 (108)
8-Month	2.66 ± 0.46 (107)
MLD (mm), In-segment	
Post-Procedure	2.45 ± 0.43 (108)
8-Month	2.35 ± 0.47 (107)
% DS, In-stent	
Post-Procedure	3.28 ± 7.19 (108)
8-Month	6.52 ± 9.20 (107)
% DS, In-segment	
Post-Procedure	15.23 ± 7.39 (108)
8-Month	17.71 ± 8.72 (107)
Late Loss (mm)	
In-stent	0.12 ± 0.22 (107)
In-segment	0.10 ± 0.25 (107)
Binary Restenosis	
In-stent	0.0% (0/107)
In-segment	0.0% (0/107)
IVUS RESULTS	
Neointimal Volume (mm ³)	3.10 ± 4.46 (98)
% Volume Obstruction	2.10 ± 2.66 (98)
Incomplete Apposition	
Persistent	4.9% (5/102)
Late Acquired	2.9% (3/102)

Notes

N = The total number of subjects enrolled.

M = The number of lesions at baseline.

Numbers are % (Count/Number of Evaluable Lesions) or Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

G. Pooled Results of the Global RESOLUTE Clinical Trial Program (RESOLUTE FIM, RESOLUTE US, RESOLUTE AC, RESOLUTE Int, RESOLUTE Japan)

In order to better estimate the incidence of low-frequency events or outcomes in various specific patient subgroups, a subject-level pooled analysis was conducted. **Table 45** below provides the total number of subjects included in the analyses.

Table 45: Subjects Included in the analyses by clinical study

	All Subjects	On-label
RESOLUTE (FIM)	139	139
RESOLUTE All-Corers – Resolute	1140	376
RESOLUTE International	2349	764
RESOLUTE US	1402	1402
RESOLUTE Japan	100	100
Pooled Resolute Dataset	5130	2781

The on-label subgroup includes all enrolled subjects except those that had a total occlusion, target lesions involving a bifurcation lesion, target lesions involving a Saphenous Vein Graft lesion (SVG), an In-Stent Restenosis target lesion (ISR), a subject having an Acute Myocardial Infarction (AMI) (≤ 72 hrs), subjects with a demonstrated Left-Ventricular Ejection Fraction (LVEF) less than 30%, target lesions located in an unprotected Left Main Artery, subjects with ≥ 3 treated vessels, subjects with a serum creatinine > 2.5 mg/dL, a lesion length > 27 mm, two or more lesions treated per vessel, and target lesions with the presence of a thrombus.

It is acknowledged that the results of retrospective pooled analyses have limitations. Definitive proof of the presence or absence of any differences between sub-groups requires prospectively powered assessments in clinical trials. The results are presented in the following tables:

- **Table 46:** Resolute Pooled Analysis – Principal Safety and Effectiveness
- **Table 47:** Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 46: Resolute Pooled Analysis – Principal Safety and Effectiveness

	All Subjects (N = 5130)	On-label (N = 2781)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	6.6% (333/5044)	5.4% (149/2734)
TVF	7.5% (379/5044)	6.6% (180/2734)
MACE	7.5% (378/5044)	6.3% (171/2734)
EFFECTIVENESS		
Clinically Driven TVR	4.3% (217/5044)	3.7% (101/2734)
TLR	3.2% (163/5044)	2.5% (67/2734)
SAFETY		
Total Death	1.9% (96/5044)	1.6% (43/2734)
Cardiac Death	1.1% (58/5044)	0.9% (25/2734)
Non-Cardiac Death	0.8% (38/5044)	0.7% (18/2734)
TVMI	3.0% (150/5044)	2.5% (67/2734)
Cardiac Death or TVMI	3.9% (199/5044)	3.3% (90/2734)
Stent Thrombosis ARC defined		
Definite/Probable	0.8% (40/5044)	0.3% (9/2734)
Definite	0.6% (29/5044)	0.2% (6/2734)
Probable	0.3% (13/5044)	0.1% (3/2734)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month time frame includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 47: Resolute Pooled Analysis – ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	All Subjects (N = 5130)	On-label (N = 2781)
Stent Thrombosis	0.8% (40/5044)	0.3% (9/2734)
Early (0 - 30 days)	0.2% (11/5044)	0.1% (4/2734)
Late (31 days – 360 days)	0.8% (40/5044)	0.3% (9/2734)

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month time frame includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis

G1. Subgroup Analysis - Subjects with Diabetes Mellitus in the Resolute Pooled Analysis

Subjects with diabetes mellitus (DM) comprise an important patient subgroup that is at increased risk for cardiovascular morbidity and mortality^{4,5}. A Global Statistical Analysis Plan (GSAP) was created with a pre-specified hypothesis to evaluate the safety and effectiveness of the Resolute stent to treat stenotic lesions in diabetic subjects with coronary artery disease. This section provides an overview of this plan and the results supporting the indication of the Resolute stent to treat coronary artery disease in subjects with diabetes mellitus.

The primary objective of this analysis was to assess the safety and effectiveness of the Resolute Zotarolimus-Eluting Coronary Stent System (Resolute stent) for the treatment of de novo lesions in native coronary arteries in patients with DM with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm.

Population: The study population for the GSAP was selected by combining subjects with DM from the Global RESOLUTE Clinical Trial Program. The study population selected for this analysis met pre-defined general and angiographic inclusion and exclusion criteria. Analysis populations consisted of consecutively enrolled eligible diabetic subjects in the trials noted below.

The following Global RESOLUTE Clinical Trials contributed subjects to the DM cohort.

- RESOLUTE FIM
- RESOLUTE All-Comers
- RESOLUTE International
- RESOLUTE United States, and
- RESOLUTE Japan

⁴ American Heart Association. Heart Disease and Stroke Statistics - 2008 Update. www.americanheart.org/statistics [Online publication]. Accessed 12 November 2008, 2008.

⁵ Fang J, Alderman MH. Impact of the increasing burden of diabetes on acute myocardial infarction in New York City: 1990-2000. *Diabetes*. 2006;55(3):768-773.

In total there were 878 subjects included in the Resolute DM cohort. RESOLUTE US provided the highest percentage of subjects at 54.9% (482/878) while RESOLUTE Int contributed 27.6% (242/878), RESOLUTE AC 9.7% (85/878), RESOLUTE Japan 5.1% (45/878), and RESOLUTE 2.7% (24/878).

Design: The Resolute stent performance for treatment of lesions in patients with DM was compared with a performance goal (PG) derived from a meta-analysis of published studies of coronary DES use in DM subjects and from data from the ENDEAVOR pooled studies.

Inclusion of study subjects in this analysis were required to have DM defined by either a history of DM or use of medications to treat DM (i.e., oral hypoglycemics or insulin) at time of enrollment. The Resolute DM subjects, and those included in the meta-analysis were also required to have clinical characteristics of an on-label population consistent with the enrollment criteria of the RESOLUTE US Clinical Trial. That is, subjects with following clinical or lesion characteristics were excluded: total lesion length per vessel > 27mm, > 2 lesions per vessel, unprotected left main lesions, bifurcation lesions, total occlusions, bypass grafts, acute MI within 72 hours of the index procedure, thrombus-containing lesions, left ventricular ejection fraction <30%, or renal impairment (serum creatinine > 2.5 mg/dL).

The Resolute DM TVF rate at 12-month follow-up was compared to a performance goal to demonstrate the safety and effectiveness of the Resolute stent in diabetic subjects. The objective of the primary endpoint analysis in the RESOLUTE DM cohort was to assess whether the true primary endpoint rate of 12-month Target Vessel Failure (TVF) for the Resolute stent met the PG established as 14.5% (which is a 31% increase over the expected rate of 11.08% for DES use in DM subjects derived from the meta-analysis). The hypothesis for this analysis accounted for the differences in the protocols of the individual studies in the published literature, the ENDEAVOR pooled studies, and the Global RESOLUTE Clinical Trial Program. Specifically, in calculating the meta-analytic PG for DM subjects, adjustments were made to the for 12-month TVF rate based on protocol-required follow-up angiography and protocol-required post-PCI cardiac biomarker measurements.

Demographics: The mean age of subjects was 65.2 years and 66.4% (583/878) were male. Of the subjects included in this analysis, 28.5% (250/878) of the subjects were insulin dependent diabetics. 24.9% (216/867) of the subjects had a prior MI and 28.9% (254/878) were undergoing revascularization for unstable angina.

Primary Endpoint: The primary endpoint was Target Vessel Failure (TVF) at 12 months following the intervention. The TVF composite endpoint includes Cardiac Death, MI that cannot be attributed to vessel(s) other than the target vessel, and clinically driven Target Vessel Revascularization (TVR).

Results: The analysis met the primary endpoint's performance goal of 14.5%, as the TVF rate of the DM Cohort was 7.84% at 12 months with an upper bound of the 95% CI of 9.51%.

These analyses are based on the intent-to-treat population. The results are presented in the following tables:

- **Table 48:** RESOLUTE Diabetes Mellitus Cohort - Primary Endpoint Analysis
- **Table 49:** RESOLUTE Diabetes Mellitus (DM and non-DM) Cohort – Principal Safety and Effectiveness

- **Table 50: RESOLUTE Diabetes Mellitus Cohort - ARC Defined Definite/Probable Stent Thrombosis Events through 12 Months**

Table 48: Resolute Diabetes Mellitus Cohort – Primary Endpoint Analysis

Primary Endpoint	RESOLUTE DM (N = 878)	Upper Bound of 95%CI ¹	Performance Goal	P-value ²
12-month TVF	7.84% (68/867)	9.51%	14.5%	<0.001

Notes

N is the total number of subjects.

Numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual lesions.

12-month time frame includes follow-up window (360 days ±30 days).

¹ One sided confidence interval using exact method.

² One sided p-value using asymptotic test statistic to be compared at a 0.05 significance level.

Table 49: RESOLUTE Diabetes Mellitus (DM) Cohort: All DM 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 DM Subjects (N = 878)	IDDM (N = 250)	Non IDDM (N = 628)	Non DM (N = 1903)
COMPOSITE SAFETY AND EFFECTIVENESS				
TLF	6.6% (57/867)	10.6% (26/246)	5.0% (31/621)	4.9% (92/1867)
TVF	8.1% (70/867)	11.8% (29/246)	6.6% (41/621)	5.9% (110/1867)
MACE	7.5% (65/867)	11.8% (29/246)	5.8% (36/621)	5.7% (106/1867)
EFFECTIVENESS				
Clinically Driven TVR	5.1% (44/867)	6.5% (16/246)	4.5% (28/621)	3.1% (57/1867)
TLR	3.3% (29/867)	5.3% (13/246)	2.6% (16/621)	2.0% (38/1867)
TLR, CABG	0.2% (2/867)	0.8% (2/246)	0.0% (0/621)	0.3% (6/1867)
TLR, PCI	3.1% (27/867)	4.5% (11/246)	2.6% (16/621)	1.7% (32/1867)
Non-TL TVR	2.2% (19/867)	1.6% (4/246)	2.4% (15/621)	1.3% (24/1867)
Non-TL TVR, CABG	0.1% (1/867)	0.0% (0/246)	0.2% (1/621)	0.2% (4/1867)
Non-TL TVR, PCI	2.1% (18/867)	1.6% (4/246)	2.3% (14/621)	1.1% (20/1867)
SAFETY				
Total Death	2.8% (24/867)	4.1% (10/246)	2.3% (14/621)	1.0% (19/1867)
Cardiac Death	2.0% (17/867)	2.8% (7/246)	1.6% (10/621)	0.4% (8/1867)
Non-Cardiac Death	0.8% (7/867)	1.2% (3/246)	0.6% (4/621)	0.6% (11/1867)
Cardiac Death or TVMI	3.6% (31/867)	6.1% (15/246)	2.6% (16/621)	3.2% (59/1867)
TVMI	1.8% (16/867)	4.1% (10/246)	1.0% (6/621)	2.7% (51/1867)

Q wave MI	0.3% (3/867)	0.8% (2/246)	0.2% (1/621)	0.3% (5/1867)
Non-Q wave MI	1.5% (13/867)	3.3% (8/246)	0.8% (5/621)	2.5% (46/1867)
Stent Thrombosis ARC defined				
Definite/Probable	0.3% (3/867)	0.8% (2/246)	0.2% (1/621)	0.3% (6/1867)
Definite	0.2% (2/867)	0.4% (1/246)	0.2% (1/621)	0.2% (4/1867)
Probable	0.1% (1/867)	0.4% (1/246)	0.0% (0/621)	0.1% (2/1867)

Notes

N = The total number of subjects.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

Table 50: RESOLUTE Diabetes Mellitus Cohort – ARC Defined Definite/Probable Stent Thrombosis Events through 12 Months

	Resolute (N = 878)
Stent Thrombosis	0.3% (3/867)
Acute (0 – 1 day)	0.1% (1/867)
Subacute (2 - 30 days)	0.1% (1/867)
Late (31 – 360 days)	0.1% (1/867)

Notes

N is the total number of subjects.
 Numbers are % (Count/Number of Eligible Subjects).
 12-month time frame includes follow-up window (360 days ±30 days).
 Subjects are only counted once for each time period.
 See Table 15 for the definition of the ARC defined Stent Thrombosis.

G2. Gender Analysis from the RESOLUTE Pooled On-label Dataset

In the United States, an estimated 17,600,000 adults age 20 and older (9.1% of men and 7.0% of women) suffer from coronary artery disease (CAD).⁶ However, it is estimated that only 36% of annual PCIs are performed in women. In PCI clinical trials, women represent only 25-35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in clinical studies may be partly attributable to gender differences in presenting symptoms and pathophysiology⁷, which may lead to under-diagnosis and under-referral of female patients with CAD. Once diagnosed and treated, poorer revascularization outcomes have been reported in women (compared with men) due to smaller

⁶ Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update. A Report From the American Heart Association. *Circulation*. 2010;121(7):e46-e215.

⁷ Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women’s Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006; 47(3):S4-S20.

coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease compared with men.

Table 51 describes the baseline and demographic characteristics by gender for subjects in the pooled on label analysis, 783/2781 (28.2%) subjects were female and 1998/2781 (71.8%) were male. Female patients at baseline were older and had a higher rate of diabetes, hypertension, and smaller reference vessel diameters (RVD).

Table 51: Baseline Characteristics of Male vs. Female for Pooled On Label Resolute Patients

Patient Characteristics	Male (N=1998)	Female (N=783)	p-value
Age (Years)	62.9 ± 10.5	67.0 ± 10.6	< 0.001
History of smoking/tobacco use	64.1% (1281/1998)	45.6% (357/783)	< 0.001
Prior PCI	32.3% (646/1998)	28.1% (220/783)	0.032
Hypertlipidemia	78.6% (1570/1998)	80.8% (633/783)	0.194
Diabetes Mellitus	29.2% (583/1998)	37.7% (295/783)	< 0.001
Insulin Dependent	7.1% (141/1998)	13.9% (109/783)	< 0.001
Hypertension	75.1% (1501/1998)	84.3% (660/783)	< 0.001
Prior MI	28.1% (556/1979)	18.3% (141/771)	< 0.001
Prior CABG	9.4% (188/1998)	5.6% (44/783)	0.001
Ejection fraction			0.114
<30%	0.1% (1/1465)	0.2% (1/592)	
30-40%	6.9% (101/1465)	4.6% (27/592)	
>40%	93.0% (1363/1465)	95.3% (564/592)	
Lesion Class			0.118
A	7.7% (172/2222)	9.5% (81/856)	
B1	25.8% (573/2222)	27.6% (236/856)	
B2	32.0% (711/2222)	29.8% (255/856)	
C	34.5% (766/2222)	33.2% (284/856)	
Moderate/Severe Calcification	28.2% (626/2219)	30.4% (260/854)	0.230
Pre procedure RVD	2.738 ± 0.494	2.629 ± 0.471	< 0.001
Pre procedure MLD	0.733 ± 0.401	0.770 ± 0.383	0.021
Pre procedure Diameter Stenosis	73.0 ± 13.8	70.5 ± 13.5	< 0.001
Lesion Length	13.848 ± 5.824	12.935 ± 5.749	< 0.001

The pooled Resolute stent on-label use data were evaluated retrospectively for gender-based clinical outcomes. Table 52 shows a post-hoc analysis of the principle safety and effectiveness outcomes through 12 months in subjects treated with Resolute stents for on-label

indications stratified by gender. In general, event rates were low for both gender groups. Although event rates were numerically higher in women (except for non-cardiac death), the results suggest that the safety and effectiveness profile of the Resolute stent is generalizable to both males and females.

Table 52: Resolute Pooled on-label Gender (male vs. female) – Principal Safety and Effectiveness Through 12 Months

	Male (N=1998)	Female (N=783)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.9% (96/1970)	6.9% (53/764)
TVF	5.8% (114/1970)	8.6% (66/764)
MACE	5.8% (115/1970)	7.3% (56/764)
EFFECTIVENESS		
Clinically Driven TVR	3.3% (65/1970)	4.7% (36/764)
TLR	2.3% (45/1970)	2.9% (22/764)
SAFETY		
Total Death	1.5% (29/1970)	1.8% (14/764)
Cardiac Death	0.7% (14/1970)	1.4% (11/764)
Non-Cardiac Death	0.8% (15/1970)	0.4% (3/764)
TVMI	2.1% (41/1970)	3.4% (26/764)
Cardiac Death or TVMI	2.7% (54/1970)	4.7% (36/764)
Stent Thrombosis ARC defined		
Definite/Probable	0.3% (5/1970)	0.5% (4/764)
Definite	0.2% (4/1970)	0.3% (2/764)
Probable	0.1% (1/1970)	0.3% (2/764)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis

The RESOLUTE clinical trials were not designed or powered to study safety or effectiveness of the Resolute or Resolute Integrity stent in gender-specific subgroups, so these post-hoc analyses are considered hypothesis-generating.

G3. Subset Analyses from the Resolute Pooled Dataset – Further Subset Outcomes

In order to provide the totality of data on the Resolute stent, the clinical outcomes in key patient and lesion subsets are provided. The RESOLUTE All-Comers Clinical Trial and the RESOLUTE International Study enrolled an ‘all-comers’ patient population representing an expanded use of the Resolute stent beyond those enrolled in the pivotal RESOLUTE US trial. In the RESOLUTE All-Comers and RESOLUTE International trials, 33% of enrolled subjects fit the on-label criteria, whereas the remaining 67% had complex subject/lesion characteristics. Clinical outcomes at 12 months in key patient subsets from the pooled Resolute trials are provided in the Table 53 below.

It is acknowledged that the results of such retrospective pooled analyses have limitations. Definitive proof of the presence or absence of any differences between subsets requires prospectively powered assessments in clinical trials.

Table 53: Resolute Pooled Analysis – Subset Outcomes Through 12 Months

	On-label: Single lesion (N = 2466)	Age ≥65 yrs (N = 2547)	Male (N = 3843)	Female (N = 1287)	B2/C Lesions (N = 3636)	RVD ≤2.5 mm (N = 1956)	Lesion Length ≥2.5 mm (N = 509)
COMPOSITE SAFETY AND EFFECTIVENESS							
TLF	5.3% (128/2428)	7.0% (177/2515)	6.3% (239/3780)	7.4% (94/1264)	6.7% (239/3577)	7.3% (141/1928)	7.9% (39/495)
TVF	6.4% (155/2428)	8.0% (202/2515)	7.1% (270/3780)	8.6% (109/1264)	7.6% (272/3577)	8.5% (164/1928)	8.5% (42/495)
MACE	6.1% (147/2428)	8.4% (211/2515)	7.3% (277/3780)	8.0% (101/1264)	7.6% (271/3577)	8.1% (157/1928)	9.3% (46/495)
EFFECTIVENESS							
Clinically Driven TVR	3.6% (88/2428)	4.3% (108/2515)	4.3% (162/3780)	4.4% (55/1264)	4.4% (157/3577)	5.0% (96/1928)	5.7% (28/495)
TLR	2.4% (58/2428)	3.1% (79/2515)	3.3% (124/3780)	3.1% (39/1264)	3.3% (118/3577)	3.7% (71/1928)	5.1% (25/495)
SAFETY							
Total Death	1.6% (39/2428)	3.1% (78/2515)	1.9% (70/3780)	2.1% (26/1264)	1.7% (62/3577)	1.7% (32/1928)	3.2% (16/495)
Cardiac Death	0.9% (22/2428)	1.9% (48/2515)	1.0% (39/3780)	1.5% (19/1264)	1.0% (36/3577)	1.0% (20/1928)	1.8% (9/495)
Non-Cardiac Death	0.7% (17/2428)	1.2% (30/2515)	0.8% (31/3780)	0.6% (7/1264)	0.7% (26/3577)	0.6% (12/1928)	1.4% (7/495)
TVMI	2.3% (57/2428)	2.9% (74/2515)	2.8% (105/3780)	3.6% (45/1264)	3.2% (115/3577)	3.5% (67/1928)	1.8% (9/495)
Cardiac Death or TVMI	3.2% (77/2428)	4.5% (113/2515)	3.6% (137/3780)	4.9% (62/1264)	4.0% (144/3577)	4.4% (84/1928)	3.4% (17/495)
Stent Thrombosis ARC defined							
Definite/Probable	0.3% (7/2428)	0.8% (19/2515)	0.8% (31/3780)	0.7% (9/1264)	0.9% (31/3577)	0.7% (14/1928)	1.0% (5/495)
Definite	0.2% (5/2428)	0.5% (12/2515)	0.6% (24/3780)	0.4% (5/1264)	0.7% (25/3577)	0.5% (10/1928)	0.6% (3/495)
Probable	0.1% (2/2428)	0.3% (8/2515)	0.2% (9/3780)	0.3% (4/1264)	0.2% (8/3577)	0.3% (6/1928)	0.4% (2/495)

Table 53: Resolute Pooled Analysis – Subset Outcomes Through 12 Months

	Multiple Stents (N =1788)	Overlapping Stents (N =644)	Saphenous Vein Graft (N =64)	Multi-Vessel Stenting (N=770)	BMS In-Stent Restenosis (N=199)
COMPOSITE SAFETY AND EFFECTIVENESS					
TLF	7.8% (137/1758)	7.8% (49/632)	17.2% (11/64)	8.2% (62/756)	11.1% (22/198)
TVF	8.6% (152/1758)	8.7% (55/632)	17.2% (11/64)	8.9% (67/756)	12.1% (24/198)
MACE	8.8% (155/1758)	9.3% (59/632)	17.2% (11/64)	9.0% (68/756)	12.1% (24/198)
EFFECTIVENESS					
Clinically Driven TVR	5.1% (89/1758)	5.4% (34/632)	10.9% (7/64)	5.0% (38/756)	9.1% (18/198)
TLR	4.1% (72/1758)	4.4% (28/632)	7.8% (5/64)	4.4% (33/756)	8.1% (16/198)
SAFETY					
Total Death	2.0% (36/1758)	3.0% (19/632)	3.1% (2/64)	1.9% (14/756)	3.0% (6/198)
Cardiac Death	1.3% (22/1758)	1.4% (9/632)	3.1% (2/64)	1.3% (10/756)	2.0% (4/198)
Non-Cardiac Death	0.8% (14/1758)	1.6% (10/632)	0.0% (0/64)	0.5% (4/756)	1.0% (2/198)
TVMI	3.5% (62/1758)	3.3% (21/632)	7.8% (5/64)	3.3% (25/756)	3.0% (6/198)
Cardiac Death or TVMI	4.5% (79/1758)	4.4% (28/632)	9.4% (6/64)	4.5% (34/756)	4.0% (8/198)
Stent Thrombosis ARC defined					
Definite/Probable	1.1% (20/1758)	1.1% (7/632)	1.6% (1/64)	1.2% (9/756)	2.5% (5/198)
Definite	0.9% (15/1758)	0.6% (4/632)	0.0% (0/64)	0.7% (5/756)	1.5% (3/198)
Probable	0.4% (7/1758)	0.6% (4/632)	1.6% (1/64)	0.7% (5/756)	1.0% (2/198)

Table 53: Resolute Pooled Analysis – Subset Outcomes Through 12 Months

	Bifurcation (N = 702)	Total Occlusion ¹ (N = 505)	Unprotected Left Main (N = 57)	Renal Insufficiency ² (N = 135)	AMI <72 hours (N = 799)
COMPOSITE SAFETY AND EFFECTIVENESS					
TLF	10.3% (71/690)	6.2% (31/497)	16.1% (9/56)	12.0% (16/133)	7.5% (59/788)
TVF	11.4% (79/690)	6.6% (33/497)	16.1% (9/56)	12.8% (17/133)	8.1% (64/788)
MACE	11.3% (78/690)	6.6% (33/497)	17.9% (10/56)	16.5% (22/133)	8.2% (65/788)
EFFECTIVENESS					
Clinically Driven TVR	6.1% (42/690)	4.2% (21/497)	7.1% (4/56)	4.5% (6/133)	5.6% (44/788)
TLR	4.8% (33/690)	3.6% (18/497)	7.1% (4/56)	3.0% (4/133)	4.7% (37/788)
SAFETY					
Total Death	2.3% (16/690)	1.2% (6/497)	7.1% (4/56)	10.5% (14/133)	2.2% (17/788)
Cardiac Death	1.6% (11/690)	1.0% (5/497)	5.4% (3/56)	6.8% (9/133)	1.5% (12/788)
Non-Cardiac Death	0.7% (5/690)	0.2% (1/497)	1.8% (1/56)	3.8% (5/133)	0.6% (5/788)
TVMl	5.9% (41/690)	2.4% (12/497)	7.1% (4/56)	5.3% (7/133)	2.4% (19/788)
Cardiac Death or TVMl	7.1% (49/690)	3.4% (17/497)	10.7% (6/56)	9.8% (13/133)	3.8% (30/788)
Stent Thrombosis ARC defined					
Definite/Probable	2.0% (14/690)	2.0% (10/497)	3.6% (2/56)	2.3% (3/133)	2.2% (17/788)
Definite	1.6% (11/690)	1.0% (5/497)	1.8% (1/56)	0.8% (1/133)	1.5% (12/788)
Probable	0.6% (4/690)	1.0% (5/497)	1.8% (1/56)	1.5% (2/133)	0.8% (6/788)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 12-month time frame includes follow-up window (360 days ± 30 days).
 See Table 15 for the definition of the ARC defined Stent Thrombosis
¹Total Occlusion is defined as pre procedure TIMI = 0.
²Renal Insufficiency is defined as serum creatinine > 2.5 mg/dL.

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 THE PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems are 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. SAFETY CONCLUSIONS

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-US 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, the clinical data available also support the safety of the Resolute stent when used in patients with Diabetes Mellitus. The clinical testing conducted demonstrated that the Resolute MicroTrac and Resolute Integrity provide a reasonable assurance of safety and effectiveness when used as indicated in accordance with the Directions for Use.

B. EFFECTIVENESS CONCLUSIONS

RESOLUTE US

2.5 mm – 3.5 mm Subset of the Main Study

The results of this analysis showed that the Resolute stent single lesion cohort of the 2.5 mm – 3.5 mm subset of the Main Study met the primary 12 month TLF non-inferiority endpoint with the Resolute stent demonstrating a rate of 3.7% (36/982) in comparison to the Endeavor stent historical control rate of 6.5% (70/1076), $P_{\text{non-inferiority}} < 0.001$. The composite endpoint of TLF contains both safety and effectiveness components.

2.25 mm Cohort

The Resolute stent 2.25 mm Cohort met the primary endpoint 12 month TLF rate performance goal of 20% with a rate of 4.8% (7/146) and an upper one-sided 95% CI of 8.8% (P-value <0.001).

2.25 mm – 3.5 mm Angio/IVUS Sub-study

The 2.25 mm – 3.5 mm Angio/IVUS Sub-study met the primary non-inferiority endpoint with an 8-month in-stent late LL of 0.39 ± 0.06 mm for the Resolute stent compared to the historical control of 8-month in-stent late LL of 0.61 ± 0.03 mm for the Endeavor stent $P_{\text{non-inferiority}} < 0.001$.

4.0 mm Sub-study

The 4.0 mm Resolute stent met the primary superiority endpoint with an 8-month in-segment late LL of 0.11 ± 0.09 mm, compared with the historical Driver stent control in-segment late LL of 0.66 ± 0.05 mm, $P_{\text{superiority}} < 0.001$.

Subjects with Diabetes Mellitus

The analysis met the primary endpoint 12-month TVF rate performance goal of 14.5%, with a rate of 7.84% at 12 months with an upper bound of the 95% CI of 9.51%.

C. OVERALL CONCLUSIONS

The clinical testing conducted demonstrated that the Resolute MicroTrac and Resolute Integrity Zotarolimus-Eluting Coronary Stent Systems provide a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIII. CDRH DECISION

CDRH issued an approval order on February 17, 2012. The final conditions of approval cited in the approval order are described below.

1. *Resolute Integrity Post-Approval Study*: The study must be conducted as per approved protocol IP126, Rev 1A, dated February 8, 2012 (P110013/A024). The study will consist of a prospective, multi-center, non-randomized, single-arm, open-label study of newly enrolled US patients treated with the Resolute Integrity Zotarolimus-Eluting Coronary Stent System.

The primary study objective is to assess the safety and effectiveness of the Resolute Integrity stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.2 mm. The primary endpoint for this trial is the composite of cardiac death and target vessel myocardial infarction (MI) at 12 months post-procedure.

The secondary endpoints assessed at hospital discharge, 30 days, 6 months, 12 months and 24 months post-procedure will include a composite of major adverse cardiac events (MACE), target lesion failure, target vessel failure, cardiac death, and target vessel MI. Clinical secondary endpoints are to include death, MI, target lesion revascularization, target vessel revascularization, stent thrombosis, stroke, and dual antiplatelet therapy compliance.

The study population will consist of adult patients with *de novo* lesions in native coronary arteries treated with the device per labeling followed up to 2 years post-procedure.

A total of 230 patients must be enrolled to ensure that at least 200 patients will be evaluable at 12 months (95% confidence interval = 0.5%, 5.0%). This assumes that the 12-month risk of the composite cardiac death and target vessel myocardial infarction endpoint is 2.0% (as observed in the Resolute-US pre-approval trial) and a lost to follow up rate of 10% per year.

2. *Continued Follow-up of the Premarket and OUS Cohort:* In addition to the post-approval study enrolling new US patients as outlined above, you 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 you should continue to follow through 3 years post-procedure. You 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 (P110013/A010).
3. The issue of the optimal duration of dual antiplatelet therapy following PCI with drug-eluting stents (DES) remains a critical question that is currently being studied in the DAPT trial. FDA acknowledges that you are participating in this trial to address a condition of approval for the Endeavor Zotarolimus Eluting Coronary Stent System (P060033). As the duration of dual antiplatelet therapy is also relevant for the Resolute MicroTrac and Resolute Integrity Zotarolimus Eluting Coronary Stent Systems, you must fulfill your commitment to the condition of PMA approval for P060033. When appropriate or as requested by FDA, you should submit PMA supplements to the Resolute MicroTrac and Resolute Integrity PMA (P110013) requesting approval to update your IFU to include the data collected in the DAPT trial. If you do not fulfill the condition of approval for P060033, you must conduct or participate in a separate clinical trial that will develop data to study the duration of dual antiplatelet therapy following implantation of the Resolute MicroTrac and Resolute Integrity Zotarolimus Eluting Coronary Stent Systems and subsequently

submit PMA supplements to this PMA requesting approval to include these data in an update to the IFU.

You have agreed to provide the following data as part of a future supplement or report (as defined below):

4. Within 16 months of PMA approval, you should submit a PMA supplement that includes a report of your post-approval study evaluating the suitability of implementing an elution specification criterion of mean $\pm 10\%$. The report should include the summary and discussion of the entire elution data collected from the currently available batches and all additional batches manufactured within the first year after the product's approval. The study's objective should be to target an elution acceptance criterion of mean $\pm 10\%$ for the 1, 6, 24, and 48 hours timepoints and greater than 80% for the 72 hours timepoint, with data collected based on L1/L2/L3, as appropriate. If the results from this analysis indicate that the $\pm 10\%$ acceptance criteria cannot be implemented when the same elution specifications are used for all stents independently of their design, an analysis of the applicability of a $\pm 10\%$ elution acceptance criteria by stent design should be performed. Based on the results of this study, you must either revise elution specification criterion to mean $\pm 10\%$, or provide a scientifically valid explanation for why the revised elution specification cannot be implemented.
5. Within 12 months of PMA approval, you should submit a PMA supplement requesting approval to tighten the in-process coating weight specifications.
6. Within 12 months of PMA approval, you should submit a PMA supplement with details of your investigation into the process losses observed during manufacturing. The supplement should include a detailed explanation of the cause of all process losses, and of your investigations to mitigate these losses. This supplement should also request approval to change the current overage to 3% or less, or demonstrate that the identified losses are unavoidable in order to maintain an overage higher than 3%. A progress report on your efforts to address this issue should be submitted within 6 months of PMA approval.
7. As soon as the data are available, but no later than 18 months following PMA approval, you should submit a nonclinical postapproval report with the results of particulate testing on real-time aged samples of the Resolute MicroTrac and Resolute Integrity on the modified MicroTrac delivery system to confirm the specifications and shelf life established based on results from testing of accelerated aged samples. If the results from testing of real-time aged samples do not confirm the prior results, you should submit a PMA supplement requesting to modify the shelf life accordingly, to establish tighter release specifications for particulates, or both.

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 product labeling

Hazard to Health from Use of the Product: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling

Post-approval Requirements and Restrictions: See Approval Order