



Medtronic

**Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System
Rapid Exchange Delivery System**

INSTRUCTIONS FOR USE

CAUTION – Federal (USA) law restricts this device for sale by or on the order of a physician.

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THE COMPONENTS OF THE RESOLUTE INTEGRITY ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM ARE STERILE.

1 RESOLUTE INTEGRITY™ ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM

The Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System (Resolute Integrity System) is a device/drug combination product comprised of the following device components: The Integrity Coronary Stent and MicroTrac delivery systems and a drug component (a formulation of zotarolimus in a polymer coating). The characteristics of the Resolute Integrity System are described in Table 1-1.

Table 1-1: Device Component Description and Nominal Dimensions

Component	Resolute Integrity Zotarolimus-Eluting Coronary Stent System Rapid Exchange Delivery System	
	Small Vessel	Medium/Large Vessel
Available Stent Diameters (mm):	2.25, 2.5, 2.75	3.0, 3.5, 4.0
Available Stent Lengths Unexpanded (mm):	8, 12, 14, 18, 22, 26, 30	9, 12, 15, 18, 22, 26, 30, 34, 38
Stent Material & Geometry:	A cobalt-based alloy conforming to ASTM F562 and ISO 5832-6:1997 with 1.0 mm length elements, 7.5 alternating crowns and 0.0035" strut thickness; the stent utilizes a single helix fusion pattern. The coronary stent is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are provided in multiple lengths and diameters.	A cobalt-based alloy conforming to ASTM F562 and ISO 5832-6:1997 with 0.9 mm length elements, 9.5 alternating crowns and 0.0035" strut thickness; utilizes a helical u-joint fusion pattern. The coronary stent is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are provided in multiple lengths and diameters.
Drug Component:	A coating of polymers loaded with zotarolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.6 µg/mm ² which results in a maximum nominal drug content of 380 µg on the largest stent (4.0 x 38 mm).	
Delivery System Working Length:	140 cm	
Delivery System Luer Adapter Ports:	Single access port to the inflation lumen. A guidewire exit port is located approximately 25 cm from the tip. Designed for guidewire less than or equal to 0.36 mm (0.014 inch).	
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 (912 kPa) Rated Burst Pressure: 16 ATM (1621 kPa) for 2.25-3.5mm diameters 15 ATM (1520 kPa) for 4.0 mm diameter	
Minimum Guide Catheter Inner Diameter:	≥ 5 F (1.42 mm, 0.056 inch)	
Catheter Shaft Outer Diameter:	Proximal OD: 2.1 F (0.69 mm, 0.027 inch) Distal Section OD: 2.7 F (0.91 mm, 0.036 inch)	

1.1 Device Component Description

The Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System (Resolute Integrity System) consists of a balloon-expandable intracoronary drug-eluting stent pre-mounted on the MicroTrac Rapid Exchange (RX) stent delivery system. The Resolute Integrity Stent is manufactured from a cobalt alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are available in multiple lengths and diameters. The delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014 inch (0.36mm) guidewires. The MicroTrac RX delivery system (Figure 1-1) has an effective length of 140 cm.

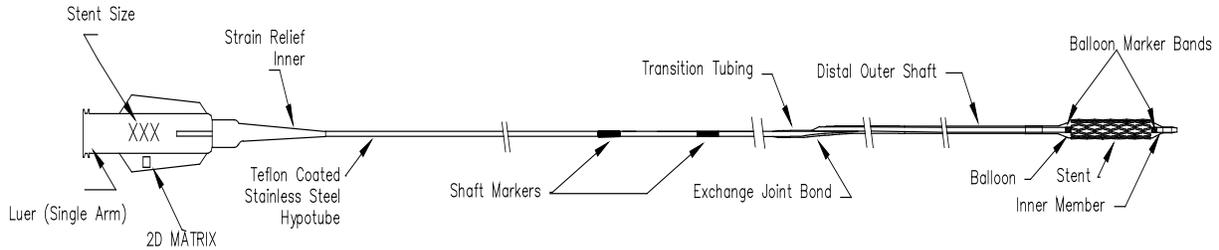


Figure 1-1: MicroTrac RX Delivery System (with Stent)

The stent is crimped on various size delivery catheter balloons, which are sized from 2.25 to 4.0 mm. The Resolute Integrity available stent sizes are listed in Table 1-2.

Table 1-2: Resolute Integrity Stent Sizes

Diameter (mm)	Stent Length (mm)										
	8	9	12	14	15	18	22	26	30	34	38
2.25	✓	---	✓	✓	---	✓	✓	✓	✓	---	---
2.5	✓	---	✓	✓	---	✓	✓	✓	✓	---	---
2.75	✓	---	✓	✓	---	✓	✓	✓	✓	---	---
3.0	---	✓	✓	---	✓	✓	✓	✓	✓	✓	✓
3.5	---	✓	✓	---	✓	✓	✓	✓	✓	✓	✓
4.0	---	✓	✓	---	✓	✓	✓	✓	✓	✓	✓

Note: "—" indicates sizes not offered; "✓" indicates sizes offered.

1.2 Drug Component Description

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

1.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the Resolute Integrity System 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-tetrazol-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 1-2:

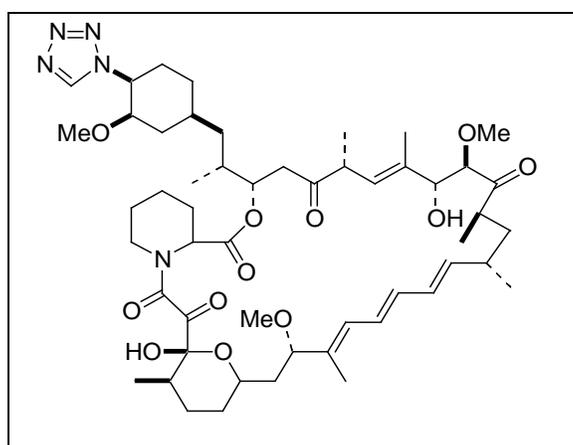


Figure 1-2: Zotarolimus Chemical Structure

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

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

1.2.2 Polymer System Description

The Resolute Integrity stent is comprised of a bare metal stent with a Parylene C primer coat and a coating that consists of a blend of the drug zotarolimus and the BioLinx polymer system. BioLinx is a blend of the Medtronic proprietary components C10 and C19, and PVP (polyvinyl pyrrolidone). The structural formula of the BioLinx polymer subunits are shown in Figure 1-3:

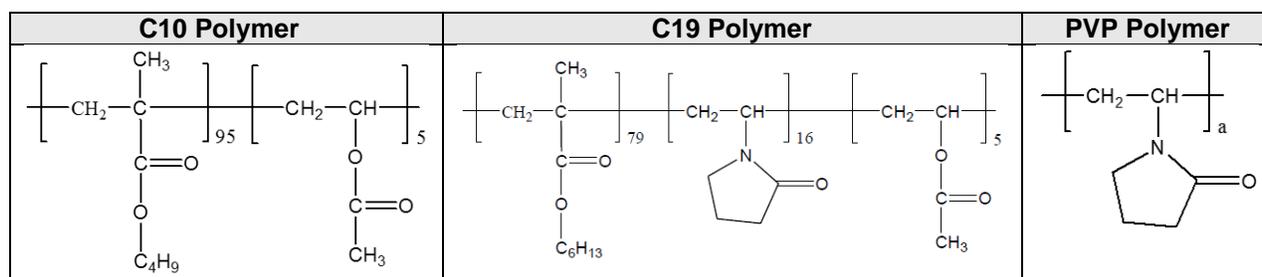


Figure 1-3: Chemical Structure of the BioLinx Polymer Subunits

1.2.3

Product Matrix and Zotarolimus Content

**Table 1-3: Resolute Integrity Zotarolimus-Eluting Coronary Stent System
Product Matrix and Nominal Zotarolimus Doses**

Product Number RX	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSINT22508UX	2.25	8	59
RSINT25008UX	2.5	8	59
RSINT27508UX	2.75	8	59
RSINT30009UX	3.0	9	90
RSINT35009UX	3.5	9	90
RSINT40009UX	4.0	9	90
RSINT22512UX	2.25	12	85
RSINT25012UX	2.5	12	85
RSINT27512UX	2.75	12	85
RSINT30012UX	3.0	12	120
RSINT35012UX	3.5	12	120
RSINT40012UX	4.0	12	120
RSINT22514UX	2.25	14	102
RSINT25014UX	2.5	14	102
RSINT27514UX	2.75	14	102
RSINT30015UX	3.0	15	150
RSINT35015UX	3.5	15	150
RSINT40015UX	4.0	15	150
RSINT22518UX	2.25	18	128
RSINT25018UX	2.5	18	128
RSINT27518UX	2.75	18	128
RSINT30018UX	3.0	18	180
RSINT35018UX	3.5	18	180
RSINT40018UX	4.0	18	180
RSINT22522UX	2.25	22	153
RSINT25022UX	2.5	22	153
RSINT27522UX	2.75	22	153
RSINT30022UX	3.0	22	220
RSINT35022UX	3.5	22	220
RSINT40022UX	4.0	22	220
RSINT22526UX	2.25	26	188
RSINT25026UX	2.5	26	188
RSINT27526UX	2.75	26	188
RSINT30026UX	3.0	26	260
RSINT35026UX	3.5	26	260
RSINT40026UX	4.0	26	260
RSINT22530UX	2.25	30	213
RSINT25030UX	2.5	30	213

**Table 1-3: Resolute Integrity Zotarolimus-Eluting Coronary Stent System
Product Matrix and Nominal Zotarolimus Doses**

Product Number RX	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSINT27530UX	2.75	30	213
RSINT30030UX	3.0	30	300
RSINT35030UX	3.5	30	300
RSINT40030UX	4.0	30	300
RSINT30034UX	3.0	34	340
RSINT35034UX	3.5	34	340
RSINT40034UX	4.0	34	340
RSINT30038UX	3.0	38	380
RSINT35038UX	3.5	38	380
RSINT40038UX	4.0	38	380

2 INDICATIONS

The Resolute Integrity Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length \leq 35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 4.2 mm. In addition, the Resolute Integrity Zotarolimus-Eluting Coronary Stent System is indicated for treatment of *de novo* chronic total occlusions.

3 CONTRAINDICATIONS

The Resolute Integrity System is contraindicated for use in:

- Patients with known hypersensitivity or allergies to aspirin, heparin, bivalirudin, clopidogrel, prasugrel, ticagrelor, ticlopidine, drugs such as zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with a known hypersensitivity to the BioLinx polymer or its individual components (see details in **Section 1.2.2 – Polymer System Description**).

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.

4 WARNINGS

- Please ensure that the inner package has not been opened or damaged as this would indicate the sterile barrier has been breached.
- The use of this product carries the same risks associated with coronary artery stent implantation procedures which include subacute and late vessel thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

5 PRECAUTIONS

- Only physicians who have received adequate training should perform implantation of the stent.
- Subsequent stent restenosis or occlusion may require repeat catheter-based treatments (including balloon dilatation) of the arterial segment containing the stent. The long-term outcome following repeat catheter-based treatments of previously implanted stents is not well characterized.
- The risks and benefits of stent implantation should be assessed for patients with a history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents such as alcohol.

- When drug eluting stents (DES) are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the RESOLUTE pivotal clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death. Data from the RESOLUTE clinical trials have been prospectively evaluated and adjudicated using the definition developed by the Academic Research Consortium (ARC) (see **Section 9.8 Pooled Results of the Global RESOLUTE Clinical Trial Program (RESOLUTE FIM, RESOLUTE US, RESOLUTE AC, RESOLUTE International, RESOLUTE Japan)** for more information).

5.1 Pre- and Post-Procedure Antiplatelet Regimen

In the Medtronic RESOLUTE US Clinical Trial, RESOLUTE AC Clinical Trial, RESOLUTE International Study, RESOLUTE First-In-Man (FIM) Clinical Trial and RESOLUTE Japan Clinical Trial, the protocol specified administration of clopidogrel or ticlopidine prior to the procedure and for a period of at least 6 months post-procedure and up to 12 months in patients who were not at high risk of bleeding. Aspirin was administered prior to the procedure concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. In the Medtronic RESOLUTE US Primary Enrollment Group, 95.9%, 93.8% and 46.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE AC Clinical Trial, 93.1%, 84.2% and 11.0% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE International Study, 95.9%, 91.1% and 34.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 36 months, respectively. In the RESOLUTE FIM Clinical Trial, 79.1%, 58.1% and 39.4% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE Japan Clinical Trial, 99.0%, 94.9% and 62.5% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE 38 mm Length Group, 92.8%, 91.4% and 61.5% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. See **Section 9 - CLINICAL STUDIES** for more information.

5.1.1 Oral Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) using a combination treatment of aspirin with a P2Y₁₂ platelet inhibitor after percutaneous coronary intervention (PCI), reduces the risk of stent thrombosis and ischemic cardiac events, but may increase the risk of bleeding complications. The optimal duration of DAPT, specifically a P2Y₁₂ platelet inhibitor in addition to aspirin, following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. It is very important that the patient is compliant with the post-procedural antiplatelet recommendations.

Per 2016 ACC/AHA guidelines,¹ a daily aspirin dose of 81 mg is recommended indefinitely after PCI. A P2Y₁₂ platelet inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS).

In pivotal trials of current generation DES, subjects were prescribed DAPT for at least 6 months post-procedure, and most patients who were not at high risk of bleeding used DAPT for at least 12 months.

Consistent with the 2016 ACC/AHA guidelines,¹ and the DAPT Study,² longer duration of DAPT may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at

¹ Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016; doi:10.1016/j.jacc.2016.03.513. For full text, please refer to the following website: <http://content.onlinejacc.org/article.aspx?doi=10.1016/j.jacc.2016.03.513>

² Mauri L, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. *N Engl J Med.* 2014;371:2155–66.

high bleeding risk. In patients who are at a high risk of bleeding or who develop significant bleeding during DAPT treatment, these guidelines suggest that a shorter DAPT duration may be reasonable. However, definitive evidence supporting the safety of short DAPT duration has not been established in prospective clinical studies.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of ischemic and bleeding risks, and patient preference.

Premature discontinuation or interruption of prescribed antiplatelet medication could result in an increased risk of stent thrombosis, MI or death.

Prior to PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient whether a DES and its associated recommended DAPT regimen is the appropriate PCI choice.

Following PCI, if elective noncardiac surgery requiring suspension of antiplatelet therapy is considered, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption of antiplatelet therapy.

Patients who require premature DAPT discontinuation should be carefully monitored for cardiac events. At the discretion of the patient's treating physician(s), the antiplatelet therapy should be restarted as soon as possible.

5.2 Use of Multiple Stents

The long-term effects of zotarolimus are currently unknown. The extent of the patient's exposure to zotarolimus drug and the stent and polymer coating is directly related to the number of stents and total stent length implanted.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the Resolute Integrity stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

When using two wires, care should be taken when introducing, torquing and removing one or both guidewires to avoid entanglement. In this situation, it is recommended that one guidewire be completely withdrawn from the patient before removing any additional equipment.

5.3 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with Resolute Integrity stent implantation have not been established.

5.4 Brachytherapy

The safety and effectiveness of the Resolute Integrity stent in target lesions treated with prior brachytherapy, or the use of brachytherapy to treat in-stent restenosis of a Resolute Integrity stent, have not been established.

5.5 Use in Special Populations

Information on use of the Resolute Integrity stent in certain special patient populations is derived from clinical studies of the Resolute stent system, which uses the same drug (zotarolimus) – see **Section 7 - OVERVIEW OF CLINICAL TRIALS** for a description of the other features of the Resolute Stent System compared to the Resolute Integrity Stent System.

5.5.1 Pregnancy

Pregnancy Category C. See **Section 6.6 Pregnancy** under **Drug Information**. There are no well-controlled studies in pregnant women or men intending to father children. The Resolute Integrity stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus. Effective contraception should be initiated before implanting a Resolute Integrity stent and for 1 year after implantation.

5.5.2 Lactation

It is not known whether zotarolimus is excreted in human milk. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant a Resolute Integrity stent, taking into account the importance of the stent to the mother. **See Section 6.7 – Lactation** under **Drug Information**.

5.5.3 Gender

Clinical studies of the Resolute stent did not suggest any significant differences in safety and effectiveness for male and female patients. See **Section 9.9.1 – Gender Analysis from the RESOLUTE Pooled On-label Dataset**.

5.5.4 Ethnicity

Clinical studies of the Resolute stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

5.5.5 Pediatric Use

The safety and effectiveness of the Resolute Integrity stent in patients below the age of 18 years have not been established.

5.5.6 Geriatric Use

Clinical studies of the Resolute stent did not have an upper age limit. Among the 1242 patients treated with the Resolute stent in the Resolute US Main Study that included 2.25-3.5 mm stents, 617 patients were age 65 or older and 88 patients were age 80 or older. A post hoc analysis of patients treated with the Resolute stent showed no significant differences between subjects under age 65 vs. age 65 and older in the rates of cardiac death, target vessel MI, target lesion revascularization, ARC definite or probable stent thrombosis, or target lesion failure at 12 months. The rate of all-cause death at 12 months was 0.3% in patients under age 65 vs. 1.8% in patients age 65 or older.

5.5.7 Lesion/Vessel Characteristics

The safety and effectiveness of the Resolute Integrity stent have not been established in the cerebral, carotid, or peripheral vasculature or in the following coronary disease patient populations:

- Patients with coronary artery reference vessel diameters < 2.25 mm or > 4.2 mm.
- Patients with coronary artery lesions longer than 35 mm or requiring more than one Resolute Integrity stent.
- Patients with evidence of an acute MI within 72 hours of intended stent implantation.
- Patients with vessel thrombus at the lesion site.
- Patients with lesions located in a saphenous vein graft, in the left main coronary artery, ostial lesions, or bifurcation lesions.

- Patients with diffuse disease or poor flow distal to identified lesions.
- Patients with tortuous vessels in the region of the target vessel or proximal to the lesion.
- Patients with in-stent restenosis.
- Patients with moderate or severe lesion calcification at the target lesion.
- Patients with occluded target lesions including chronic total occlusions.
- Patients with 3 vessel disease.
- Patients with a left ventricular ejection fraction of < 30%.
- Patients with a serum creatinine of > 2.5 mg/dl.
- Patients with longer than 24 months of follow-up.

5.6 Drug Interactions

The effect of potential drug interactions on the safety or effectiveness of the Resolute Integrity stent has not been investigated. While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP12) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by CYP3A4, a human cytochrome P450 enzyme. When administered concomitantly with 200 mg ketoconazole bid, a strong inhibitor of CYP3A4, zotarolimus produces less than a 2-fold increase in AUC_{0-inf} with no effect on C_{max} . Therefore, consideration should be given to the potential for drug interactions when deciding to place a Resolute Integrity stent in a patient who is taking drugs that are known substrates or inhibitors of the cytochrome P450 isoenzyme CYP3A4. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

Formal drug interaction studies have not been conducted with the Resolute Integrity stent.

5.7 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated the Resolute Integrity Stent up to a total length of 120 mm is MR Conditional. It 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
- 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.

1.5 T

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 were 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.

3 T

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 were 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 14\LX\MR 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.

1.5 T and 3 T

The Resolute Integrity Stent should not move or migrate when exposed to MR scanning immediately post-implantation. MRI at 3 Tesla and 1.5 Tesla may be performed immediately following the implantation of the stent. Non-clinical testing at field strength greater than 3 Tesla 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 stent. The image artifact extends approximately 1 cm 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 ASTM F2119-01; the device lumen was always observed during scanning. This testing was completed using a GE SIGNA HDx with software version 14\LX\MR release 14.0.M5A.0828.b.

5.8 Stent Handling Precautions

- For single use only. The Resolute Integrity System is provided sterile. Do not resterilize or reuse this product. Note the “Use By” date on the product label. Do not use if package or product has been opened or damaged.
- Only the contents of the pouch should be considered sterile. The outside surface of the pouch is not sterile.
- Do not remove the contents of the pouch until the device will be used immediately.
- Do not remove the stent from the delivery balloon; removal may damage the stent and polymer coating and/or lead to stent embolization. The Resolute Integrity System is intended to perform as a system. The stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the rotating hemostatic valve and guide catheter hub.
- Do not try to straighten a kinked shaft or hypotube. Straightening a kinked metal shaft may result in breakage of the shaft.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.
- The Resolute Integrity System must not be exposed to any direct handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug elution.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.
- The Resolute Integrity stent delivery system should not be used in conjunction with any other stents or for post-dilatation.

5.9 Stent Placement Precautions

- The vessel must be pre-dilated with an appropriate sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 13.5 – Delivery Procedure**. Failure to do so may increase the risk of placement difficulty and procedural complications.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in **Section 13 – DIRECTIONS FOR USE**.
- Guide catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device Component Description** in Table 1-1).
- After preparation of the stent delivery system, do not induce negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon or delivery difficulties.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- In small or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel (see **Section 5 - PRECAUTIONS–Stent/System Removal Precautions**).
- Placement of the stent has the potential to compromise side branch patency.
- Do not attempt to pull an unexpanded stent back through the guide catheter, as dislodgement of the stent from the balloon may occur. Remove as a single unit per instructions in **Section 5 - PRECAUTIONS –Stent/System Removal Precautions**.
- Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon.

- Stent retrieval methods (e.g., use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.
- Administration of appropriate anticoagulant, antiplatelet and coronary vasodilator therapy is critical to successful stent implantation.

5.10 Stent/System Removal Precautions

If removal of a stent system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the stent delivery system and cautiously withdraw the stent delivery system into the guide catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guide catheter, the stent delivery system and the guide catheter should be removed as a single unit. This must be done under direct visualization with fluoroscopy.

When removing the stent delivery system and guide catheter as a single unit:

- Do not retract the stent delivery system into the guide catheter. Maintain guidewire placement across the lesion and carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is aligned with the distal tip of the guide catheter.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guide catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the stent delivery system into the guide catheter and the subsequent removal of the stent delivery system and the guide catheter from the arterial sheath.

Failure to follow these steps and/or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent and/or stent delivery system components such as the balloon.

5.11 Post-Procedure

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, an optical coherence tomography (OCT) catheter, a coronary guidewire or a balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Post-dilatation: All efforts should be made to assure that the stent is not under dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. **Do not use the stent delivery balloon for post-dilatation.**
- If patient requires MR imaging, refer to **Section 5.7 – Magnetic Resonance Imaging (MRI)** above.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – Section 5.1 - Pre- and Post-Procedure Antiplatelet Regimen**). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding), should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, antiplatelet therapy should be restarted as soon as possible.

6 DRUG INFORMATION

6.1 Mechanisms of Action

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 results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control.

6.2 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the demethyl and hydroxylated metabolites of the parent drug. Further metabolism can lead to the formation of hydroxyl-demethyl and dihydroxyl-demethyl metabolites. Enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities; however, the IC₅₀ values (3 µM and above) are many fold higher than the systemic concentrations expected following implantation of a drug-eluting stent. The anticipated zotarolimus blood levels in

stented patients are expected to be less than 0.004 μM , suggesting that clinically significant drug-drug interactions are unlikely.

6.3 Pharmacokinetics of the Resolute Stent

The pharmacokinetics information for the Resolute Integrity stent system is derived from a study conducted on the Resolute stent system. The Resolute Integrity stent system is similar to the Resolute stent system with regards to the stent design, 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 pharmacokinetics information from the RESOLUTE FIM PK Sub-study, as described below, is applicable to the Resolute Integrity stent system.

The pharmacokinetics (PK) of zotarolimus delivered from the Resolute Stent has been determined in patients with coronary artery disease after stent implantation in the Medtronic RESOLUTE FIM Clinical Trial. The dose of zotarolimus was calculated per stent unit surface area and the key pharmacokinetic parameters determined from these patients are provided in Table 6-1.

Table 6-1: Zotarolimus Pharmacokinetics in the Medtronic 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 \pm 0.062	0.300 \pm 0.075	0.346 \pm 0.133
T_{max}	(h)	1.00	0.9 \pm 0.7	0.9 \pm 0.5	0.8 \pm 0.5
$\text{AUC}_{0\text{-last}}$	(ng•h/mL)	15.08	16.04 \pm 4.74	35.89 \pm 12.79	31.19 \pm 17.69
$\text{AUC}_{0\text{-inf}}^{\$}$	(ng•h/mL)	41.89	39.09 \pm 11.77	52.41 \pm 12.57	80.12 \pm 51.00
$\beta^{\$}$	(1/h)	0.003	0.004 \pm 0.001	0.004 \pm 0.001	0.003 \pm 0.002
$t_{1/2}^{\#}$	(h)	263.4	195.5 \pm 74.4	167.4 \pm 29.7	208.3 \pm 144.4
$\text{CL}/\text{F}^{\$}$	(L/h)	3.06	5.23 \pm 2.55	4.80 \pm 1.11	5.14 \pm 3.55
$\text{Vd}_\beta/\text{F}^{\$}$	(L)	1161.2	1449.3 \pm 221.6	1181.2 \pm 336.4	1658.6 \pm 494.8

Notes

C_{max}	Maximum observed blood concentration	a	Primary dose groups
T_{max}	Time to C_{max}	†	No SD was reported when N = 1
$\text{AUC}_{0\text{-last}}$	Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration	‡	Harmonic mean \pm pseudo-standard deviation
$\text{AUC}_{0\text{-inf}}$	AUC from time 0 to infinity ($\text{AUC}_{0\text{-inf}}$).	#	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
$t_{1/2}$	Harmonic mean half-life		
CL/F	Mean apparent clearance		
Vd_β/F	Apparent volume of distribution	\\$	Not a true sample

The results in Table 6-1 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 ($\text{AUC}_{0\text{-last}}$) and AUC from time 0 to infinity ($\text{AUC}_{0\text{-inf}}$). 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 and intravenous administration. Based on available zotarolimus pharmacokinetic data, systemic safety margins of \geq 78-fold have been established for the Resolute stent at 380 μg due to the extended elution of zotarolimus from the BioLinX polymer.

6.4 Pharmacokinetics following Multi-dose Intravenous Administration of Zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. Table 6-2 provides a summary of the pharmacokinetic analysis.

Table 6-2: Pharmacokinetic Parameters (Mean ± Standard Deviation) in Patients Following Multi-dose Intravenous Administration of Zotarolimus

PK Parameters	Units	200 µg QD N = 15		400 µg QD N= 16		800 µg QD N=16	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C _{max}	(ng/mL)	11.41 ± 1.38 [‡]	11.93 ± 1.25	21.99 ± 3.79	23.31 ± 3.15	37.72 ± 7.00	41.79 ± 6.68
T _{max}	(h)	1.05 ± 0.04 [‡]	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
AUC ₀₋₂₄	(ng•h/mL)	34.19 ± 4.39 [‡]	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
t _{1/2} [§]	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL ^b	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

Notes

^{*}N = 16;

[‡] Harmonic mean ± pseudo-standard deviation

^b Clearance data is calculated using compartmental methods.

All other data presented in Table 6-2 is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400 and 800 µg, zotarolimus was generally well tolerated by the subjects. No clinically significant abnormalities in physical examinations, vital signs or laboratory measurements were observed during the study.

6.5 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.5.1 Mutagenesis

Zotarolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the human peripheral lymphocyte chromosomal aberration assay, or the *in vivo* mouse micronucleus assay.

6.5.2 Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of zotarolimus. The carcinogenic potential of the Resolute stent is expected to be minimal based on the types and quantities of materials present.

6.5.3 Reproductive Toxicology

No effect on fertility or early embryonic development in female rats was observed following the IV administration of zotarolimus at dosages up to 100 µg/kg/day (approximately 19 times the cumulative blood exposure provided by Resolute stents coated with 300 µg zotarolimus).

For male rats, there was no effect on the fertility rate at IV dosages up to 30 µg/kg/day (approximately 21 times the cumulative blood exposure provided by Resolute stents coated with 300 µg zotarolimus). Reduced sperm counts and motility, and failure in sperm release were observed in male rats following the IV administration of zotarolimus for 28 days at dosages of > 30 µg/kg/day. Testicular germ cell degeneration and histological lesions were observed in rats following IV dosages of 30 µg/kg/day and above.

6.6 Pregnancy

Pregnancy Category C: There are no well-controlled studies in pregnant women, lactating women, or men intending to father children for this product.

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day resulted in embryoletality. Fetal ossification delays were also observed at this dosage, but no major fetal malformations or minor fetal anomalies were observed in this study. A 60 µg/kg/day dose in rats results in approximately 47 times the maximum blood level and about 11 times the cumulative blood exposure in patients receiving Resolute Integrity stents coated with 300 µg zotarolimus total dose.

No embryo-fetal effects were observed in pregnant rabbits administered zotarolimus in a developmental toxicity study at intravenous dosages up to 100 µg/kg/day. This dose in rabbits results in approximately 215 times the maximum blood level and about 37 times the cumulative blood exposure in patients receiving Resolute Integrity stents coated with 300 µg zotarolimus total dose.

Effective contraception should be initiated before implanting a Resolute Integrity stent and continued for one year post-stent implantation. The Resolute Integrity stent should be used in pregnant women only if potential benefits justify potential risks.

6.7 Lactation

It is not known whether zotarolimus is excreted in human milk. The potential adverse reactions in nursing infants from zotarolimus have not been determined. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

7 OVERVIEW OF CLINICAL TRIALS

Clinical Trials in support of Pre-market Approval:

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

The principal safety and effectiveness information for the Resolute stent was derived from the Global RESOLUTE Clinical Trial Program, which consists of the following clinical trials – the RESOLUTE United States Clinical Trial(R-US), the RESOLUTE All-Comers Clinical Trial(R-AC), the RESOLUTE International Study(R-Int), the RESOLUTE First-in-Man (FIM) Clinical Trial, and the RESOLUTE Japan Clinical Trial(R-J). These five studies have evaluated the performance of the Resolute stent in improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 4.2 mm. Key elements of these studies are summarized below and in Table 7-1. The Resolute 38 mm Length Group was derived from subjects enrolled in the R-US and the RESOLUTE Asia study (R-Asia) (For 38 mm Length Group data see Table 7-1).

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 analysis, in which the cohort was derived from subjects treated with the 2.25 mm 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 6 months and up to 12 months in subjects who were not at a high risk of bleeding.

- The 38 mm Length Group: In addition to the primary enrollment group, the 38 mm Length Group is made up of 38 mm subjects from RESOLUTE US 38 mm Length Sub-study pooled with subjects from the RESOLUTE Asia (R-Asia) 38 mm cohort (see description of the R Asia study below). 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 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' patient 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 clinically indicated TLR within 12 months post-implantation. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 6 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 6 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 6 months. This trial had a subset of subjects undergoing pharmacokinetic (PK) assessments (see **Section 6.3** for the **Pharmacokinetic 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 6 months and up to 12 months in subjects who were not at a high risk of bleeding.

The RESOLUTE Asia (R Asia) study is a prospective, multi-center, non-randomized study. The primary objective of this study was to document the safety and effectiveness of the Endeavor Resolute Zotarolimus-Eluting Coronary Stent system in a patient population with long lesion(s). The Primary endpoint for the 38 mm cohort was target lesion failure (TLF) at 12 months post-procedure, defined as a composite of cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. The RESOLUTE Asia trial was designed to be included in the pooled dataset for the RESOLUTE 38 mm Length Group (38 mm subjects from RESOLUTE US and RESOLUTE Asia). A total of 109 subjects were enrolled in the 38 mm cohort across 17 clinical research sites from six (6) countries throughout Asia.

All 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.

Post-market Approval Study:

The RESOLUTE INTEGRITY US Post Market Study is a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects that are treated with the commercially available Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System. The objective of this study is to assess the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm in two groups of patients, specifically those patients receiving stents \leq 30 mm in length, referred to as the Primary Enrollment Group (PEG) and those patients who receive extended length stents (34 mm or 38 mm) referred to as the Extended Length (XL) Sub-study. The primary endpoint for this study is composite rate of cardiac death and target vessel myocardial infarction (MI) at 12 months.

Table 7-1 summarizes the clinical trial designs for the Global RESOLUTE Clinical Trial Program and Post-market Approval Study.

Table 7-1: Clinical Trial Comparisons

	Pre-market Approval Studies; Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	Post-market Approval Study	
	RESOLUTE US [*]	RESOLUTE AC ¹	RESOLUTE Int ²	RESOLUTE FIM ³	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG) ⁴	RESOLUTE INTEGRITY US (XL Sub-study) ⁵
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 	<ul style="list-style-type: none"> ■ Prospective ■ Multi-center ■ Non-randomized 	<ul style="list-style-type: none"> ■ Prospective ■ Multi-center ■ Non-randomized Post approval 	<ul style="list-style-type: none"> ■ Prospective ■ Multi-center ■ Non-randomized Post approval
Number of Subjects Enrolled	Total: 1516 - 2.25–3.5 mm Main Study - 1242 subjects - 2.25 mm Cohort -150 subjects - 2.25–3.5 mm Angio/IVUS sub-study - 100 subjects - 4.0 mm Sub-study - 60 subjects - 38 mm Sub-study -114 subjects (38 mm Sub-study total patient population was 223 with 114 from RESOLUTE US and 109 from RESOLUTE Asia)	Total: 2292 (Resolute: 1140, Xience V: 1152)	Total: 2349	Total: 139	Total: 100	Total: 109	Total:230	Total: 56
Lesion Criteria	<ul style="list-style-type: none"> ■ Single or two <i>de novo</i> lesions located in separate target vessels ■ Lesion(s) length ≤27 mm for the Primary Enrollment Group, ≤35 mm for the 38 mm Length Group ■ Target vessel with RVD between 2.25 to 4.2 mm 	<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 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 to 4.0 mm 	<ul style="list-style-type: none"> ■ Single <i>de novo</i> lesion ■ Lesion length from 14 to 27 mm ■ Target vessel with RVD between 2.5 and 3.5 mm 	<ul style="list-style-type: none"> ■ Single or two <i>de novo</i> lesions located in separate coronary arteries ■ Lesion(s) length ≤27 mm ■ Target vessel with RVD between 2.5 to 3.5 mm 	<ul style="list-style-type: none"> ■ Single or two <i>de novo</i> lesions located in separate target vessels ■ Lesion(s) length ≤35 mm ■ Target vessel with RVD between 3.0 to 4.0 mm ■ Patients may have received treatment of up to two lesions second lesion RVD (2.25 to 4.2 mm), if the lesions were located in separate target vessels. 	<ul style="list-style-type: none"> ■ Single target lesion or two target lesions located in separate target vessels PEG: <ul style="list-style-type: none"> ■ Target lesion ≤27 mm Target vessel with RVD between 2.25 to 4.2 mm 	<ul style="list-style-type: none"> ■ Single target lesion or two target lesions located in separate target vessels XL: <ul style="list-style-type: none"> ■ Target lesion ≤ 35 mm treated or lesion length Target vessel with RVD between 2.25 to 4.2 mm.
Stent Sizes (Resolute)	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 38 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 38 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 34-38 mm
Product Used	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange AV100 Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System
Post-procedure Antiplatelet Therapy	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine ≥ 6 months	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine, for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated

Table 7-1: Clinical Trial Comparisons

	Pre-market Approval Studies; Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	Post-market Approval Study	
	RESOLUTE US*	RESOLUTE AC ¹	RESOLUTE Int ²	RESOLUTE FIM ³	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG) ⁴	RESOLUTE INTEGRITY US (XL Sub-study) ⁵
Follow-up	2.25 mm - 3.5 mm Main Study: 30 days and 9 months: clinical; 6, 12 and 18 months, 2-5 years: telephone 4.0 mm Sub-study: 8 months: clinical and angiographic; 6, 12 and 18 months, 2-5 years: telephone 2.25 mm - 3.5 mm Angio/IVUS Sub-study: 8 months: clinical and angiographic/ IVUS; 6, 12 and 18 months, 2-5 years: telephone 38 mm Length Sub-study: 30 days (R-US) and 9 months clinical visits (preferred) or patient contact 30 days (R-Asia), 6, 12, 18 months then annually at 2, 3, 4, 5 years	30 days and 12 months: clinical 13 months (455 subject subset): angiographic 6 months and 2-5 years: telephone	30 days, 6 months, 1-3 years: clinical or telephone	30 days: clinical 4 (30 subject subset) and 9 months (100 subject subset): clinical and angiographic/IVUS 6 months and 1-5 years: telephone	30 days and 12 months: clinical 8 months: angiographic/IVUS 6, 9 and 18 months and 2-5 years: telephone	30 days, 6, 9 (Clinical Visit), 12, 18 months then annually at 2 - 5 years	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact)	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact) 3-5 years (contact)
Status	60-month follow-up is complete. 551 subjects qualified for 18-month follow-up	60-month follow-up is complete	36-month follow-up is complete	60-month follow-up complete	60-month follow-up is complete	60-month follow-up is complete	24-month follow-up is complete	12-month follow-up is complete

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

¹ The term 'AC' refers to All-Comers.

² The term 'Int' refers to International.

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

⁴ The term 'PEG' refers to Primary Enrollment Group.

⁵ The term 'XL' refers to Extended Length.

8 ADVERSE EVENTS

8.1 Observed Adverse Events

Observed adverse event experience with the Resolute stent is derived from the following five clinical trials: the RESOLUTE US, RESOLUTE AC, RESOLUTE Int, RESOLUTE FIM and RESOLUTE Japan. In addition, the adverse event experience from the Resolute Integrity US Primary Enrollment Group (PEG) Post-market Approval Study and the Extended Length (XL) Sub-study have been included.

See **Section 9 - CLINICAL STUDIES** for a more complete description of the trial designs and results.

The Global RESOLUTE Clinical Trial Program has evaluated the performance of the Resolute stent in subjects, including those with diabetes mellitus, with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. The Resolute Integrity US Post-market Approval Study assessed the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries. Principal adverse events are shown in Table 8-1 below.

Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US ¹	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
	Resolute (N = 1402)	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)	Resolute Integrity (PEG) (N = 230)	RESOLUTE INTEGRITY US (XL Sub-study) (N=56)
In-Hospital									
TLF ²	1.3% (18/1402)	3.7% (42/1140)	4.5% (52/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
TVF ³	1.3% (18/1402)	3.8% (43/1140)	4.7% (54/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
MACE ⁴	1.3% (18/1402)	3.8% (43/1140)	4.9% (56/1152)	2.7% (63/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
Total Death	0.0% (0/1402)	0.1% (1/1140)	0.8% (9/1152)	0.3% (7/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Cardiac Death	0.0% (0/1402)	0.1% (1/1140)	0.6% (7/1152)	0.3% (6/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Cardiac Death	0.0% (0/1402)	0.0% (0/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
TVMI ⁵	1.1% (16/1402)	3.1% (35/1140)	3.6% (42/1152)	2.2% (51/2349)	4.3% (6/139)	2.0% (2/100)	3.1% (7/223)	1.7% (4/230)	1.8% (1/56)
Q wave MI	0.1% (1/1402)	0.3% (3/1140)	0.4% (5/1152)	0.3% (8/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Q Wave MI	1.1% (15/1402)	2.8% (32/1140)	3.2% (37/1152)	1.8% (43/2349)	4.3% (6/139)	2.0% (2/100)	2.7% (6/223)	1.7% (4/230)	1.8% (1/56)
Cardiac Death or TVMI ⁶	1.1% (16/1402)	3.2% (36/1140)	4.0% (46/1152)	2.4% (56/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
Clinically Driven TVR ⁷	0.1% (2/1402)	0.9% (10/1140)	0.9% (10/1152)	0.4% (10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
TLR ⁸	0.1% (2/1402)	0.7% (8/1140)	0.7% (8/1152)	0.4% (10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
Non-TL TVR	0.0% (0/1402)	0.4% (4/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
ARC Def/Prob ST ⁹	0.0% (0/1402)	0.6% (7/1140)	0.3% (4/1152)	0.4% (9/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	1.8% (1/56)
30 Days									
MACE	1.4% (20/1399)	4.4% (50/1133)	5.2% (60/1146)	3.3% (78/2345)	4.3% (6/139)	3.0% (3/100)	4.5% (10/223)	3.0% (7/230)	3.6% (2/56)
12 Months									
TLF	4.7% (65/1390)	8.1% (92/1132)	8.5% (97/1142)	7.1% (165/2337)	7.2% (10/139)	4.0% (4/100)	5.4% (12/222)	4.9% (11/226)	7.4% (4/54)
TVF	6.2% (86/1390)	8.9% (101/1132)	9.7% (111/1142)	7.7% (180/2337)	7.2% (10/139)	5.0% (5/100)	6.8% (15/222)	7.1% (16/226)	7.4% (4/54)
MACE	5.5% (77/1390)	8.6% (97/1132)	9.8% (112/1142)	8.3% (193/2337)	8.6% (12/139)	5.0% (5/100)	6.3% (14/222)	5.8% (13/226)	9.3% (5/54)
Total Death	1.4% (19/1390)	1.6% (18/1132)	2.7% (31/1142)	2.4% (57/2337)	2.2% (3/139)	1.0% (1/100)	0.9% (2/222)	1.8% (4/226)	1.9% (1/54)
Cardiac Death	0.7% (9/1390)	1.3% (15/1132)	1.7% (19/1142)	1.5% (34/2337)	0.7% (1/139)	0.0% (0/100)	0.9% (2/222)	1.3% (3/226)	1.9% (1/54)
Non-Cardiac Death	0.6% (9/1390)	0.3% (3/1132)	1.1% (12/1142)	1.0% (23/2337)	1.4% (2/139)	1.0% (1/100)	0.0% (0/222)	0.4% (1/226)	0.0% (0/54)
TVMI	1.3% (18/1390)	4.2% (48/1132)	4.2% (48/1142)	3.0% (71/2337)	5.8% (8/139)	4.0% (4/100)	3.6% (8/222)	2.2% (5/226)	5.6% (3/54)
Q wave MI	0.1% (2/1390)	0.8% (9/1132)	0.4% (5/1142)	0.5% (12/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.0% (0/226)	1.9% (1/54)
Non-Q Wave MI	1.2% (16/1390)	3.5% (40/1132)	3.8% (43/1142)	2.5% (59/2337)	5.8% (8/139)	4.0% (4/100)	2.7% (6/222)	2.2% (5/226)	3.7% (2/54)
Cardiac Death or TVMI	2.0% (28/1390)	5.3% (60/1132)	5.5% (63/1142)	4.2% (99/2337)	6.5% (9/139)	4.0% (4/100)	4.5% (10/222)	3.5% (8/226)	7.4% (4/54)
Clinically Driven TVR	4.6% (64/1390)	4.9% (55/1132)	4.8% (55/1142)	4.2% (99/2337)	0.7% (1/139)	1.0% (1/100)	2.7% (6/222)	4.4% (10/226)	1.9% (1/54)
TLR	2.9% (40/1390)	3.9% (44/1132)	3.4% (39/1142)	3.5% (81/2337)	0.7% (1/139)	0.0% (0/100)	1.4% (3/222)	2.2% (5/226)	1.9% (1/54)
Non-TL TVR	2.2% (30/1390)	1.9% (21/1132)	2.2% (25/1142)	1.2% (27/2337)	0.0% (0/139)	1.0% (1/100)	1.4% (3/222)	2.2% (5/226)	0.0% (0/54)
ARC Def/Prob ST ⁹	0.1% (2/1390)	1.6% (18/1132)	0.7% (8/1142)	0.9% (20/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.9% (2/226)	1.9% (1/54)
Latest Follow-up	60 Months	60 Months		36 Months	60 Months	60 Months	60 Months	24 Months	
TLF	12.3% (164/1329)	17.0% (191/1123)	16.2% (183/1133)	11.4% (261/2284)	11.0% (15/136)	6.1% (6/98)	13.8% (30/217)	9.1% (20/219)	
TVF	17.5% (233/1329)	20.0% (225/1123)	19.1% (216/1133)	12.9% (294/2284)	13.2% (18/136)	10.2% (10/98)	17.1% (37/217)	12.3% (27/219)	
MACE	18.0% (239/1329)	21.9% (246/1123)	21.6% (245/1133)	14.4% (329/2284)	16.2% (22/136)	14.3% (14/98)	17.5% (38/217)	11.0% (24/219)	
Total Death	9.6% (127/1329)	11.0% (123/1123)	10.8% (122/1133)	6.1% (139/2284)	6.6% (9/136)	7.1% (7/98)	6.5% (14/217)	2.7% (6/219)	
Cardiac Death	4.1% (55/1329)	6.5% (73/1123)	5.7% (65/1133)	3.6% (82/2284)	1.5% (2/136)	1.0% (1/98)	4.1% (9/217)	1.8% (4/219)	
Non-Cardiac Death	5.4% (72/1329)	4.5% (50/1123)	5.0% (57/1133)	2.5% (57/2284)	5.1% (7/136)	6.1% (6/98)	2.3% (5/217)	0.9% (2/219)	
TVMI	3.2% (43/1329)	5.7% (64/1123)	5.7% (65/1133)	3.9% (89/2284)	6.6% (9/136)	4.1% (4/98)	6.0% (13/217)	4.1% (9/219)	
Q wave MI	0.4% (5/1329)	1.3% (15/1123)	0.8% (9/1133)	0.9% (20/2284)	0.0% (0/136)	0.0% (0/98)	0.9% (2/217)	0.9% (2/219)	
Non-Q Wave MI	2.9% (38/1329)	4.6% (52/1123)	4.9% (56/1133)	3.0% (69/2284)	6.6% (9/136)	4.1% (4/98)	5.1% (11/217)	3.2% (7/219)	
Cardiac Death or TVMI	6.7% (89/1329)	11.5% (129/1123)	10.6% (120/1133)	7.0% (161/2284)	8.1% (11/136)	5.1% (5/98)	8.8% (19/217)	5.9% (13/219)	
Clinically Driven TVR	12.5% (166/1329)	11.4% (128/1123)	10.9% (123/1133)	7.4% (168/2284)	5.1% (7/136)	5.1% (5/98)	9.7% (21/217)	8.2% (18/219)	
TLR	6.5% (86/1329)	7.8% (88/1123)	7.1% (81/1133)	5.7% (130/2284)	2.9% (4/136)	1.0% (1/98)	6.0% (13/217)	5.0% (11/219)	
Non-TL TVR	8.1% (107/1329)	6.1% (68/1123)	6.1% (69/1133)	2.6% (59/2284)	2.2% (3/136)	4.1% (4/98)	3.7% (8/217)	4.1% (9/219)	
ARC Def/Prob ST	0.5% (7/1329)	2.4% (27/1123)	1.7% (19/1133)	1.1% (26/2284)	0.0% (0/136)	0.0% (0/98)	1.4% (3/217)	1.8% (4/219)	

Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US ¹	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
	Resolute (N = 1402)	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)	Resolute Integrity (PEG) (N= 230)	RESOLUTE INTEGRITY US (XL Sub-study) (N=56)

Notes

N = The total number of subjects enrolled.

The numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

NA = Not applicable; variable and/or time point not calculated

In-hospital is defined as hospitalization less than or equal to the discharge date

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

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

36-month timeframe includes follow-up window (1080 days ± 30 days).

60-month timeframe includes follow-up window (1800 days ± 30 days).

¹ Primary Enrollment Group consisted of 1402 subjects, including 1242 subjects in the 2.25 mm - 3.5 mm Main Study, 100 subjects in the 2.25 mm - 3.5 mm Angio/IVUS Sub-study and 60 subjects in the 4.0 mm Sub-study. The Primary Enrollment Group does not include the 38 mm Length Sub-study.

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

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

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

⁵TVMI is composed of both Q wave and non-Q wave MI which are not clearly attributable to a non-target vessel.

Q wave MI defined when any occurrence of chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data, or new pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data, the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.

Non-Q Wave MI is defined as elevated CK ≥ 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves.

[Note: Periprocedural MIs (events <48 hours post-PCI) that did not fulfill the criteria for Q-wave MI are included in Non-Q Wave MI category. Periprocedural MIs did not require clinical symptoms or ECG evidence of myocardial ischemia, and in the absence of CK measurements, were based on an elevated CKMB > 3 X the upper laboratory normal, an elevated troponin > 3 X the upper laboratory normal, or CEC adjudication of the clinical scenario.]

⁶Cardiac death/TVMI is defined as Cardiac Death or Myocardial Infarction not clearly attributable to a non-target vessel.

⁷Target Vessel Revascularization (TVR) is defined as any clinically-driven repeat intervention of the target vessel by PCI or CABG.

⁸Target Lesion Revascularization (TLR) is defined as a clinically-driven repeat intervention of the target lesion by PCI or CABG

⁹See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

8.2 Potential Adverse Events

8.2.1 Potential Adverse Events Related to Zotarolimus

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The 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

8.2.2 Potential Adverse Events Related to BioLinx polymer

Although the type of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings, the potential for these risks are currently unknown as the coating has limited previous use in humans. These risks may include but are not limited to the following:

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

8.2.3 Potential Risks Associated with Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks (in alphabetical order) may include but are not limited to the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias, including ventricular fibrillation
- Balloon rupture
- Bleeding
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Incomplete stent apposition
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis
- Peripheral ischemia / peripheral nerve injury
- Renal Failure

- Restenosis of the stented artery
- Shock / pulmonary edema
- Stable or Unstable angina
- Stent deformation, collapse, or fracture
- Stent migration or embolization
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute, subacute or late)

9 CLINICAL STUDIES

9.1 Results of the RESOLUTE US Trial

Primary Objective: 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.

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 (≤ 35 for the 38 mm Length Group), 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 analysis,
- The 2.25 mm to 3.5 mm Angio/IVUS Sub-study,
- The 4.0 mm stent Sub-study.
- The 38 mm Length Group³

Figure 9-1 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.

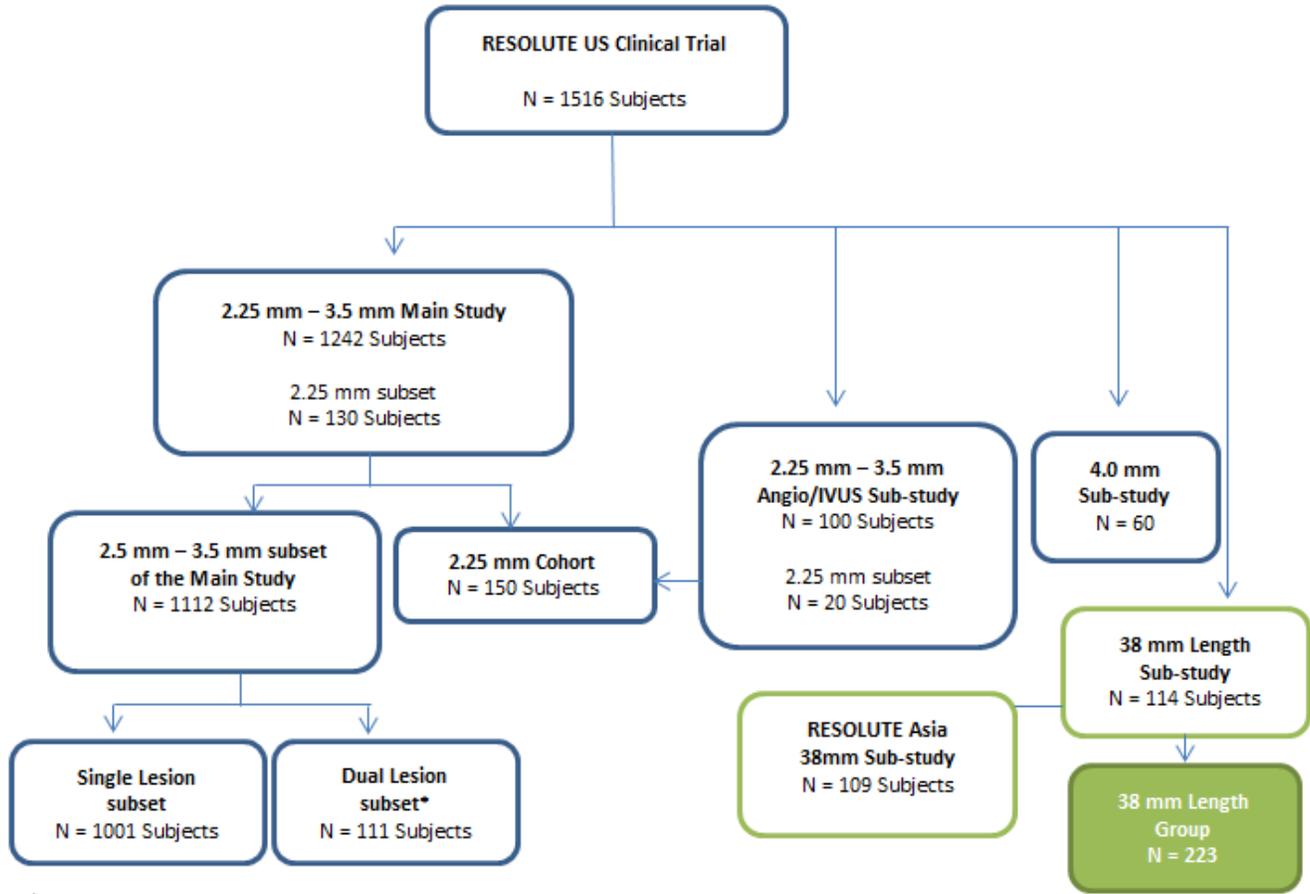
Subject enrollment criteria common to all four studies listed above included: age >18 years old; clinical evidence of ischemic heart disease, stable or unstable angina, silent ischemia, and/or a positive functional study; and no evidence of an acute MI within 72 hours of the procedure.

Follow-up 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 Angio/IVUS Sub-study were consented to angiographic and IVUS follow-up at 8 months post-procedure. All subjects enrolled in the 4.0 mm Sub-study were consented to angiographic follow-up at 8 months post-procedure. 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 subjects who were not at a high risk of bleeding.

The 12 month and 5 year follow-up rates for the primary enrollment group were 97.3% (1364/1402) and 92.2% (1293/1402) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

³ The 38 mm data was analyzed separately from the R-US Primary Enrollment Group.



*Three subjects had more than two lesions treated

Figure 9-1: Study Designation of RESOLUTE US Clinical Trial

2.5 mm – 3.5 mm Subset of the Main Study

Demographics and clinical characteristics: There were 1112 subjects (1001 single lesion subjects and 111 dual vessel subjects). The 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 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% of lesions (921/1215) were characterized as ACC/AHA type B2/C.

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. TLF was defined as the 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.

Results: 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 3.6% (36/994) 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 9-1: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - Primary Endpoint Analysis
- Table 9-2: 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 9-3: 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 9-4: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months
- Table 9-5: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study Clinical Results – Single versus Dual Lesion Subjects

Table 9-1: 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	3.6% (36/994)	6.5% (70/1076)	-2.9%	-1.4%	< 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 \pm standard error.

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

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

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 3.3%, to be compared at a 0.05 significance level.

Table 9-2: RESOLUTE US 2.5-3.5 mm Subset of the Main Study - Principal Safety and Effectiveness - Single Lesion Outcome versus Historical Control (Endeavor)

Outcomes at 12 Months	Single Lesion 2.5-3.5 mm Subset of Main study (N=1001 subjects)	Single Lesion Historical Control (Endeavor) (N=1092 subjects)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	3.6% (36/994)	6.5% (70/1076)
TVF	5.0% (50/994)	8.3% (89/1076)
MACE	4.3% (43/994)	7.0% (75/1076)
EFFECTIVENESS		
Clinically Driven TVR	3.7% (37/994)	6.0% (65/1076)
TLR	2.1% (21/994)	4.0% (43/1076)
TLR, PCI	1.8% (18/994)	3.7% (40/1076)
TLR, CABG	0.3% (3/994)	0.5% (5/1076)
Non-TL TVR	1.8% (18/994)	2.5% (27/1076)
Non-TL TVR, PCI	1.5% (15/994)	2.1% (23/1076)
Non-TL TVR, CABG	0.3% (3/994)	0.5% (5/1076)
SAFETY		
Total Death	1.0% (10/994)	1.3% (14/1076)
Cardiac Death	0.5% (5/994)	0.8% (9/1076)
Non-Cardiac Death	0.5% (5/994)	0.5% (5/1076)
Cardiac Death or TVMI	1.7% (17/994)	3.2% (34/1076)
TVMI	1.2% (12/994)	2.4% (26/1076)
Q wave MI	0.2% (2/994)	0.3% (3/1076)
Non-Q wave MI	1.0% (10/994)	2.1% (23/1076)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/994)	0.7% (7/1076)
Definite	0.0% (0/994)	0.5% (5/1076)
Probable	0.0% (0/994)	0.2% (2/1076)
ACUTE SUCCESS		
Procedure Success	98.7% (982/995)	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.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

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

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-3: RESOLUTE US 2.5-3.5 mm Subset of the Main Study - Principal Safety and Effectiveness - Combined Single Lesion and Dual Lesion – Treated Subjects Through 60 Months

2.5 mm – 3.5 mm subset of the Main Study (N = 1112)	Outcomes at 12 Months	Outcomes at 60 Months
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	3.8% (42/1105)	10.9% (115/1051)
TVF	5.2% (58/1105)	16.1% (169/1051)
MACE	4.6% (51/1105)	16.7% (175/1051)
EFFECTIVENESS		
Clinically Driven TVR	3.9% (43/1105)	11.4% (120/1051)
TLR	2.3% (25/1105)	5.7% (60/1051)
TLR, PCI	2.0% (22/1105)	5.0% (53/1051)
TLR, CABG	0.3% (3/1105)	0.7% (7/1051)
Non-TL TVR	1.9% (21/1105)	7.3% (77/1051)
Non-TL TVR, PCI	1.5% (17/1105)	6.4% (67/1051)
Non-TL TVR, CABG	0.4% (4/1105)	1.0% (10/1051)
SAFETY		
Total Death	1.0% (11/1105)	8.8% (92/1051)
Cardiac Death	0.5% (5/1105)	3.4% (36/1051)
Non-Cardiac Death	0.5% (6/1105)	5.3% (56/1051)
Cardiac Death or TVMI	1.7% (19/1105)	6.0% (63/1051)
TVMI	1.3% (14/1105)	3.2% (34/1051)
Q wave MI	0.2% (2/1105)	0.4% (4/1051)
Non-Q wave MI	1.1% (12/1105)	2.9% (30/1051)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/1105)	0.5% (5/1051)
Definite	0.0% (0/1105)	0.3% (3/1051)
Probable	0.0% (0/1105)	0.2% (2/1051)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-4: RESOLUTE US 2.5-3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	2.5 mm - 3.5 mm subset of the Main Study (N = 1112)
Stent Thrombosis	0.5% (5/1051)
Acute (0 - 1 day)	0.0% (0/1051)
Subacute (2 - 30 days)	0.0% (0/1051)
Late (31 - 360 days)	0.0% (0/1051)
Very Late (361 - 1800 days)	0.5% (5/1051)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

60-month timeframe includes follow-up window (1800 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 9-5: RESOLUTE US 2.5 - 3.5 mm Subset of the Main Study Clinical Results – Single versus Dual Lesion Subjects

	Single Lesion 2.5 - 3.5 mm Subset of Main study (N = 1001 subjects)	Dual Lesion* 2.5 - 3.5 mm Subset of Main study (N = 111 subjects)	Single Lesion 2.5 - 3.5 mm Subset of Main study (N = 1001 subjects)	Dual Lesion* 2.5 - 3.5 mm Subset of Main study (N = 111 subjects)
	Outcomes at 12 Months		Outcomes at 60 Months	
COMPOSITE SAFETY AND EFFECTIVENESS				
TLF	3.6% (36/994)	5.4% (6/111)	10.3% (98/947)	16.3% (17/104)
TVF	5.0% (50/994)	7.2% (8/111)	15.7% (149/947)	19.2% (20/104)
MACE	4.3% (43/994)	7.2% (8/111)	16.3% (154/947)	20.2% (21/104)
EFFECTIVENESS				
Clinically Driven TVR	3.7% (37/994)	5.4% (6/111)	11.2% (106/947)	13.5% (14/104)
TLR	2.1% (21/994)	3.6% (4/111)	5.3% (50/947)	9.6% (10/104)
TLR, PCI	1.8% (18/994)	3.6% (4/111)	4.5% (43/947)	9.6% (10/104)
TLR, CABG	0.3% (3/994)	0.0% (0/111)	0.7% (7/947)	0.0% (0/104)
Non-TL TVR	1.8% (18/994)	2.7% (3/111)	7.4% (70/947)	6.7% (7/104)
Non-TL TVR, PCI	1.5% (15/994)	1.8% (2/111)	6.7% (63/947)	3.8% (4/104)
Non-TL TVR, CABG	0.3% (3/994)	0.9% (1/111)	0.7% (7/947)	2.9% (3/104)
SAFETY				
Total Death	1.0% (10/994)	0.9% (1/111)	8.8% (83/947)	7.7% (8/104)
Cardiac Death	0.5% (5/994)	0.0% (0/111)	3.3% (31/947)	4.8% (5/104)
Non-Cardiac Death	0.5% (5/994)	0.9% (1/111)	5.5% (52/947)	2.9% (3/104)
Cardiac Death or TVMI	1.7% (17/994)	1.8% (2/111)	5.9% (56/947)	6.7% (7/104)
TVMI	1.2% (12/994)	1.8% (2/111)	3.3% (31/947)	2.9% (3/104)
Q wave MI	0.2% (2/994)	0.0% (0/111)	0.4% (4/947)	0.0% (0/104)
Non-Q wave MI	1.0% (10/994)	1.8% (2/111)	2.9% (27/947)	2.9% (3/104)
Stent Thrombosis ARC defined				
Definite/Probable	0.0% (0/994)	0.0% (0/111)	0.5% (5/947)	0.0% (0/104)
Definite	0.0% (0/994)	0.0% (0/111)	0.3% (3/947)	0.0% (0/104)
Probable	0.0% (0/994)	0.0% (0/111)	0.2% (2/947)	0.0% (0/104)
ACUTE SUCCESS				
Procedure Success	98.7% (982/995)	98.2% (108/110)		

Notes

* Included in the 111 subject dual lesion subset are 95 subjects with 1 treated lesion within 2 different vessels, 13 subjects with 2 treated lesions within a single vessel, 1 subject with 3 treated lesions within a single vessel, and 2 subjects with 1 treated lesion within a single vessel plus 2 treated lesions within a different single vessel.

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

2.25 mm Cohort

Demographics and clinical characteristics: There were 150 subjects. The mean age of all subjects was 66.3 years with 64.7% (97/150) 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 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% of lesions (133/196) were characterized as ACC/AHA type B2/C.

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 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.

Results: The Resolute stent 2.25 mm Cohort met the 12-month TLF rate primary endpoint performance goal of 20%, with a rate of 4.8% (7/147) 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 9-6: RESOLUTE US 2.25mm Cohort - Primary Endpoint Analysis,
- Table 9-7: RESOLUTE US 2.25mm Cohort - Principal Safety and Effectiveness
- Table 9-8: RESOLUTE US 2.25mm Cohort - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

Table 9-6: RESOLUTE US 2.25 mm Cohort - Primary Endpoint Analysis

2.25 mm Cohort	Resolute (N = 150)	Performance Goal	Upper One-sided 95% CI ¹	P-value ²
12-month TLF	4.8% (7/147)	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 \pm 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 \pm 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 9-7: RESOLUTE US 2.25mm Cohort – Principal Safety and Effectiveness

	2.25 mm Cohort (N = 150)	2.25 mm Cohort (N = 150)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Month	60 Months
TLF	5.4% (8/147)	18.5% (27/146)
TVF	8.2% (12/147)	27.4% (40/146)
MACE	6.8% (10/147)	23.3% (34/146)
EFFECTIVENESS		
Clinically Driven TVR	6.8% (10/147)	19.9% (29/146)
TLR	4.1% (6/147)	8.2% (12/146)
TLR, PCI	4.1% (6/147)	8.2% (12/146)
TLR, CABG	0.0% (0/147)	0.0% (0/146)
Non-TL TVR	2.7% (4/147)	13.7% (20/146)
Non-TL TVR, PCI	2.7% (4/147)	11.6% (17/146)
Non-TL TVR, CABG	0.0% (0/147)	2.1% (3/146)
SAFETY		
Total Death	2.7% (4/147)	15.1% (22/146)
Cardiac Death	1.4% (2/147)	10.3% (15/146)
Non-Cardiac Death	1.4% (2/147)	4.8% (7/146)
Cardiac Death or TVMI	2.0% (3/147)	12.3% (18/146)
TVMI	0.7% (1/147)	3.4% (5/146)
Q wave MI	0.0% (0/147)	0.7% (1/146)
Non-Q wave MI	0.7% (1/147)	2.7% (4/146)
Stent Thrombosis ARC defined		
Definite/Probable	1.4% (2/147)	1.4% (2/146)
Definite	0.7% (1/147)	0.7% (1/146)
Probable	0.7% (1/147)	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.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-8: RESOLUTE US 2.25mm Cohort - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	2.25 mm Cohort (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)
Very Late (361 – 1800 days)	0.0% (0/146)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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

Demographics and clinical characteristics: 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 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% of lesions (79/104) were characterized as ACC/AHA type B2/C.

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.

Results: 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 8-month in-stent late LL historical control 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 9-9: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Primary Endpoint Analysis
- Table 9-10: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Principal Safety and Effectiveness
- Table 9-11: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 60 Months
- Table 9-12: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Angiographic and IVUS Results

Table 9-9: 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, M =104)	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.

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 0.16 mm, to be compared at a 0.05 significance level.

Table 9-10: RESOLUTE US 2.25-3.5mm Angio/IVUS Sub-study - Principal Safety and Effectiveness

	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	12.1% (12/99)	18.6% (18/97)
TVF	13.1% (13/99)	20.6% (20/97)
MACE	13.1% (13/99)	21.6% (21/97)
EFFECTIVENESS		
Clinically Driven TVR	10.1% (10/99)	16.5% (16/97)
TLR	8.1% (8/99)	12.4% (12/97)
TLR, PCI	7.1% (7/99)	3.1% (3/97)
TLR, CABG	1.0% (1/99)	11.3% (11/97)
Non-TL TVR	4.0% (4/99)	8.2% (8/97)
Non-TL TVR, PCI	4.0% (4/99)	7.2% (7/97)
Non-TL TVR, CABG	0.0% (0/99)	2.1% (2/97)
SAFETY		
Total Death	4.0% (4/99)	10.3% (10/97)
Cardiac Death	3.0% (3/99)	6.2% (6/97)
Non-Cardiac Death	1.0% (1/99)	4.1% (4/97)
Cardiac Death or TVMI	4.0% (4/99)	7.2% (7/97)
TVMI	1.0% (1/99)	2.1% (2/97)
Q wave MI	0.0% (0/99)	0.0% (0/97)
Non-Q wave MI	1.0% (1/99)	2.1% (2/97)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/99)	0.0% (0/97)
Definite	0.0% (0/99)	0.0% (0/97)
Probable	0.0% (0/99)	0.0% (0/97)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-11: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months.

	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)
Stent Thrombosis	0.0% (0/97)
Acute (0 - 1 day)	0.0% (0/97)
Subacute (2 - 30 days)	0.0% (0/97)
Late (31 - 360 days)	0.0% (0/97)
Very Late (361 - 1440 days)	0.0% (0/97)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-12: 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

Demographics and clinical characteristics: 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 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% of lesions (57/72) were characterized as ACC/AHA type B2/C.

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 the ENDEAVOR II trial (8-month late LL).

Results: 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 9-13: RESOLUTE US 4.0 mm Sub-study - Primary Endpoint Analyses
- Table 9-14: RESOLUTE US 4.0 mm Sub-study – Principal Safety and Effectiveness
- Table 9-15: RESOLUTE US 4.0 mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 60 Months
- Table 9-16: RESOLUTE US 4.0 mm Sub-study - Angiographic Results

Table 9-13: 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% CI ¹	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 ± standard error (number of evaluable lesions).

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 4.0 mm 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 9-14: RESOLUTE US 4.0 mm Sub-study – Principal Safety and Effectiveness

	4.0 mm Sub-Study (N = 60)	4.0 mm Sub-Study (N = 60)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	6.8% (4/59)	12.7% (7/55)
TVF	6.8% (4/59)	14.5% (8/55)
MACE	8.5% (5/59)	23.6% (13/55)
EFFECTIVENESS		
Clinically Driven TVR	3.4% (2/59)	9.1% (5/55)
TLR	3.4% (2/59)	7.3% (4/55)
TLR, PCI	3.4% (2/59)	7.3% (4/55)
TLR, CABG	0.0% (0/59)	0.0% (0/55)
Non-TL TVR	1.7% (1/59)	7.3% (4/55)
Non-TL TVR, PCI	1.7% (1/59)	5.5% (3/55)
Non-TL TVR, CABG	0.0% (0/59)	1.8% (1/55)
SAFETY		
Total Death	1.7% (1/59)	10.9% (6/55)
Cardiac Death	0.0% (0/59)	0.0% (0/55)
Non-Cardiac Death	1.7% (1/59)	10.9% (6/55)
Cardiac Death or TVMI	3.4% (2/59)	5.5% (3/55)
TVMI	3.4% (2/59)	5.5% (3/55)
Q wave MI	0.0% (0/59)	0.0% (0/55)
Non-Q wave MI	3.4% (2/59)	5.5% (3/55)
Stent Thrombosis defined	ARC	
Definite/Probable	0.0% (0/59)	0.0% (0/55)
Definite	0.0% (0/59)	0.0% (0/55)
Probable	0.0% (0/59)	0.0% (0/55)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-15: RESOLUTE US 4.0mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	4.0 mm Sub-study (N = 60)
Stent Thrombosis	0.0% (0/55)
Acute (0 - 1 day)	0.0% (0/55)
Subacute (2 - 30 days)	0.0% (0/55)
Late (31 – 360 days)	0.0% (0/55)
Very Late (361 - 1440 days)	0.0% (0/55)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-16: RESOLUTE US 4.0 mm 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.

RESOLUTE US – Primary Enrollment Group - Gender Analysis

Table 9-17 shows the baseline demographic and clinical characteristics stratified by gender for subjects in the pooled RESOLUTE US analysis, 445/1402 (31.7%) subjects were female and 957/1402 (68.3%) were male. Consistent with other DES clinical studies, female patients were older, had a higher rate of diabetes and hypertension and had smaller reference vessel diameters (RVD).

Table 9-17: RESOLUTE US Baseline Demographic and Lesion Characteristics – Male vs. Female

Patient Characteristics	Male (N=957)	Female (N=445)	p-value
Age (Years)	63.14±10.48 (957)	66.23±10.76 (445)	<.001
History of smoking/tobacco use	67.0% (641/957)	52.8% (235/445)	<.001
Prior PCI	34.2% (327/957)	29.4% (131/445)	0.087
Hyperlipidemia	88.5% (847/957)	86.1% (383/445)	0.221
Diabetes Mellitus	31.3% (300/957)	40.9% (182/445)	<.001
Insulin Dependent	7.2% (69/957)	14.8% (66/445)	<.001
Hypertension	82.2% (787/957)	88.3% (393/445)	0.004
Prior MI	24.6% (232/943)	15.1% (66/436)	<.001
Prior CABG	10.6% (101/957)	5.2% (23/445)	<.001
Ejection fraction - Qualitative			0.028
< 30%	0.12% (1/823)	0.26% (1/386)	
30 - 40%	6.68% (55/823)	3.37% (13/386)	
> 40%	93.20% (767/823)	96.37% (372/386)	
Lesion Class			0.022
A	5.55% (60/1082)	7.64% (37/484)	
B1	17.10% (185/1082)	22.11% (107/484)	
B2	30.87% (334/1082)	27.48% (133/484)	
C	46.49% (503/1082)	42.77% (207/484)	
Moderate/Severe Calcification	26.0% (281/1082)	28.9% (140/484)	0.241
Pre procedure RVD	2.62±0.48 (1082)	2.53±0.44 (484)	<.001
Pre procedure MLD	0.75±0.35 (1082)	0.79±0.34 (484)	0.058
Pre procedure Diameter Stenosis	71.43±11.57 (1082)	68.98±11.24 (484)	<.001
Lesion Length	13.27±5.89 (1082)	12.60±5.83 (484)	0.036

The 12 month rate of TLF was 4.5% in males and 5.0% in females (Table 9-18). 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 9-18: RESOLUTE US Primary Enrollment Group - Clinical Endpoints by Gender – Principal Safety and Effectiveness to 60 Months

	Male (N = 957)	Female (N = 445)
Safety Measures to 12 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.5% (43/952)	5.0% (22/438)
TVF	5.7% (54/952)	7.3% (32/438)
MACE	5.6% (53/952)	5.5% (24/438)
EFFECTIVENESS		
Clinically Driven TVR	4.4% (42/952)	5.0% (22/438)
Clinically Driven TLR	3.0% (29/952)	2.5% (11/438)
SAFETY		
Death	1.4% (13/952)	1.4% (6/438)
Cardiac Death	0.6% (6/952)	0.9% (4/438)
Non Cardiac Death	0.7% (7/952)	0.5% (2/438)
TVMI (Extended Historical Definition)	1.1% (10/952)	1.8% (8/438)
Cardiac Death or Target Vessel MI (TVMI)	1.7% (16/952)	2.7% (12/438)
Stent Thrombosis ARC defined		
Definite/Probable	0.2% (2/952)	0.0% (0/438)
Definite	0.1% (1/952)	0.0% (0/438)
Probable	0.1% (1/952)	0.0% (0/438)
Safety Measures to 60 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	12.4% (113/909)	12.1% (51/420)
TVF	17.5% (159/909)	17.6% (74/420)
MACE	18.0% (164/909)	17.9% (75/420)
EFFECTIVENESS		
Clinically Driven TVR	12.7% (115/909)	12.1% (51/420)
Clinically Driven TLR	6.9% (63/909)	5.5% (23/420)
SAFETY		
Death	9.4% (85/909)	10.0% (42/420)
Cardiac Death	4.0% (36/909)	4.5% (19/420)
Non Cardiac Death	5.4% (49/909)	5.5% (23/420)
TVMI (Extended Historical Definition)	2.8% (25/909)	4.3% (18/420)
Cardiac Death or Target Vessel MI (TVMI)	6.2% (56/909)	7.9% (33/420)
Stent Thrombosis ARC defined		
Definite/Probable	0.6% (5/909)	0.5% (2/420)
Definite	0.2% (2/909)	0.5% (2/420)
Probable	0.3% (3/909)	0.0% (0/420)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 60-month timeframe includes follow-up window (1800 days ± 30 days).
 See Table 9-4 for the definition of the ARC defined Stent Thrombosis

See **Section 9.9.1 - Gender Analysis from the RESOLUTE Pooled On-label Dataset** for the comprehensive gender analysis.

RESOLUTE 38 mm Length Group

The 38 mm Length Group was designed to demonstrate the safety and effectiveness of the Resolute 38 mm stent and consisted of subjects with ischemic heart disease due to a stenotic lesion in a de novo native coronary artery with a reference vessel diameter between 3.0 and 4.2 mm and a lesion length \leq 35 mm amenable to percutaneous treatment with a 38 mm Resolute stent. The 38 mm Length Group was made up of 38 mm subjects pooled from the RESOLUTE US and RESOLUTE ASIA studies. 223 subjects were enrolled at 47 sites with 114 subjects at 29 sites in the US and 109 subjects at 17 sites in Asia: Bangladesh, India, Hong Kong, Malaysia, Singapore, and Thailand.

Demographics and clinical characteristics: There were 223 subjects. The mean age of all subjects was 60.9 years with 78.9% (176/223) being males. 32.4% (70/216) had a prior history of MI, 27.4% (61/223) had a prior history of PCI and 7.2% (16/223) had previous CABG surgery. 37.7% (84/223) were diabetics, with 10.3% (23/223) being insulin dependent diabetics. Past medical history of subjects indicated 58.7% (131/223) had hyperlipidemia, 74.9% (167/223) had hypertension, and 18.8% (42/223) were current smokers. The mean RVD by QCA was 2.78 ± 0.42 mm, the lesion length was 25.22 ± 8.83 mm and the average percentage diameter stenosis was $71.33 \pm 11.61\%$. 91.2% of lesions (240/263) were characterized as ACC/AHA type B2/C.

Primary Endpoint: The primary endpoint of the 38 mm Length Group was Target Lesion Failure (TLF) at 12 months post-procedure, defined as 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 that was derived from a logistic regression of TLF rates in subjects treated with Endeavor or Driver stents pooled from the Endeavor stent clinical program: ENDEAVOR I, ENDEAVOR II, ENDEAVOR II CA, ENDEAVOR III, ENDEAVOR IV and ENDEAVOR PK. The performance goal was set at 19%, which was 48% above the expected TLF rate for a drug-eluting stent and preserved 51% of the benefit of a drug-eluting stent vs. a bare metal stent.

Results: The 38 mm Length Group 12-month TLF rate was 4.5% (10/223) with an upper one-sided 95% CI of 7.5%, which met the performance goal of 19%, (P-value < 0.001). The 12 month and 60 month follow-up rates were 99.1% (221/223) and 93.7% (209/223) respectively.

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

- **Table 9-19: 38 mm Length Group – Primary Endpoint Analyses**
- **Table 9-20: 38 mm Length Group - Principal Safety and Effectiveness Through 60 Months**
- **Table 9-21: 38 mm Length Group – ARC Defined/Probable Stent Thrombosis Through 60 Months**
- **Table 9-22: Pooled Resolute Analysis including the 38 mm Length Group**

Table 9-19: 38 mm Length Group - Primary Endpoint Analysis

38 mm Length Group	Resolute (N=223)	Performance Goal	Upper One-sided 95% CI ¹	P-value ²
12-month TLF	4.5% (10/223)	19.00%	7.5%	< 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).

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 38 mm lesions.

12-month timeframe includes follow-up window (360 days \pm 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 9-20: 38 mm Length Group – Principal Safety and Effectiveness

	38 mm Length Group (N = 223)	R-US Sub-study (N = 114)	R-Asia Cohort (N = 109)	38 mm Length Group (N = 223)
COMPOSITE SAFETY AND EFFECTIVENESS	Outcomes at 12 Months	Outcomes at 12 Months	Outcomes at 12 Months	Outcomes at 60 Months
TLF	5.4% (12/222)	7.1% (8/113)	3.7% (4/109)	13.8% (30/217)
TVF	6.8% (15/222)	9.7% (11/113)	3.7% (4/109)	17.1% (37/217)
MACE	6.3% (14/222)	8.8% (10/113)	3.7% (4/109)	17.5% (38/217)
EFFECTIVENESS				
Clinically-driven TVR	2.7% (6/222)	4.4% (5/113)	0.9% (1/109)	9.7% (21/217)
TLR	1.4% (3/222)	1.8% (2/113)	0.9% (1/109)	6.0% (13/217)
TLR, PCI	1.4% (3/222)	1.8% (2/113)	0.9% (1/109)	5.5% (12/217)
TLR, CABG	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)	0.5% (1/217)
Non-TL TVR	1.4% (3/222)	2.7% (3/113)	0.0% (0/109)	3.7% (8/217)
Non-TL TVR, PCI	1.4% (3/222)	2.7% (3/113)	0.0% (0/109)	3.2% (7/217)
Non-TL TVR, CABG	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)	0.5% (1/217)
SAFETY				
Total Death	0.9% (2/222)	1.8% (2/113)	0.0% (0/109)	6.5% (14/217)
Cardiac Death	0.9% (2/222)	1.8% (2/113)	0.0% (0/109)	4.1% (9/217)
Non Cardiac Death	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)	2.3% (5/217)
Cardiac Death or TVMI	4.5% (10/222)	5.3% (6/113)	3.7% (4/109)	8.8% (19/217)
TVMI	3.6% (8/222)	3.5% (4/113)	3.7% (4/109)	6.0% (13/217)
Q wave MI	0.9% (2/222)	0.9% (1/113)	0.9% (1/109)	0.9% (2/217)
Non-Q wave MI	2.7% (6/222)	2.7% (3/113)	2.8% (3/109)	5.1% (11/217)
Side Branch Occlusion†	5.4% (12/222)	7.1% (8/113)	3.7% (4/109)	5.5% (12/217)
Stent Thrombosis ARC Defined				
Definite/Probable	0.9% (2/222)	0.9% (1/113)	0.9% (1/109)	1.4% (3/217)
Definite	0.5% (1/222)	0.0% (0/113)	0.9% (1/109)	0.5% (1/217)
Probable	0.5% (1/222)	0.9% (1/113)	0.0% (0/109)	0.9% (2/217)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

† 5 subjects with side branch occlusion had a TVMI

See Table 9-4: RESOLUTE US 2.5-3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months for the definition of the ARC defined Stent Thrombosis.

Table 9-21: 38 mm Length Group – ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	38 mm Length Group (N = 223)
Stent Thrombosis	1.4% (3/217)
Acute (0-1 day)	0.0% (0/217)
Subacute (2-30 days)	0.9% (2/217)
Late (31-360 days)	0.0% (0/217)
Very Late (361 - 1800 days)	0.5% (1/217)

**Table 9-21: 38 mm Length Group – ARC Defined
Definite/Probable Stent Thrombosis Through 60 Months**

	38 mm Length Group (N = 223)
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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).
 60-month timeframe includes follow-up window (1800 days ± 30 days).
 See Table 9-4 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 9-22 shows the Pooled Resolute Analysis including the 38 mm Length Groups. The safety and efficacy data from the 38 mm Length Group and five (5) Resolute studies; Resolute FIM, Resolute US (PEG), Resolute International, Resolute All-Corners and Resolute Japan are presented to 60 Months.

**Table 9-22: Pooled Resolute Analysis including the 38 mm Length Groups -
Through 60 Months**

Pooled Resolute analysis with the 38mm Length Group	(N=5353)
Safety Measures to 12 Months	
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	6.5% (348/5321)
TVF	7.5% (397/5321)
MACE	7.5% (398/5321)
EFFECTIVENESS	
Clinically Driven TVR	4.2% (226/5321)
Clinically Driven TLR	3.2% (169/5321)
SAFETY	
Death	1.9% (100/5321)
Cardiac Death	1.2% (62/5321)
Non Cardiac Death	0.7% (38/5321)
TVMI (Extended Historical Definition)	3.0% (157/5321)
Cardiac Death or Target Vessel MI (TVMI)	3.9% (210/5321)
Stent Thrombosis ARC defined	
Definite/Probable	0.8% (42/5321)
Definite	0.6% (30/5321)
Probable	0.3% (14/5321)
Safety Measures to 36 Months	
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	10.7% (562/5234)
TVF	13.0% (681/5234)
MACE	13.5% (708/5234)
EFFECTIVENESS	
Clinically Driven TVR	7.9% (413/5234)
Clinically Driven TLR	5.3% (276/5234)
SAFETY	
Death	5.4% (284/5234)
Cardiac Death	3.1% (161/5234)
Non Cardiac Death	2.4% (123/5234)
TVMI (Extended Historical Definition)	3.8% (200/5234)

Table 9-22: Pooled Resolute Analysis including the 38 mm Length Groups - Through 60 Months

Pooled Resolute analysis with the 38mm Length Group	(N=5353)
Cardiac Death or Target Vessel MI (TVMI)	6.5% (339/5234)
Stent Thrombosis ARC defined	
Definite/Probable	1.1% (56/5234)
Definite	0.7% (38/5234)
Probable	0.4% (20/5234)
Safety Measures to 60 Months*	
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	14.0% (406/2905)
TVF	18.0% (523/2905)
MACE	19.2% (559/2905)
EFFECTIVENESS	
Clinically Driven TVR	11.3% (327/2905)
Clinically Driven TLR	6.6% (192/2905)
SAFETY	
Death	9.6% (280/2905)
Cardiac Death	4.8% (140/2905)
Non Cardiac Death	4.8% (140/2905)
TVMI (Extended Historical Definition)	4.6% (133/2905)
Cardiac Death or Target Vessel MI (TVMI)	8.7% (253/2905)
Stent Thrombosis ARC defined	
Definite/Probable	1.3% (37/2905)
Definite	0.8% (23/2905)
Probable	0.5% (15/2905)
Notes	
N = The total number of subjects enrolled.	
Numbers are % (Count/Number of Eligible Subjects).	
Subjects are only counted once for each time period.	
The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.	
12-month timeframe includes follow-up window (360 days ± 30 days).	
36-month timeframe includes follow-up window (1080 days ± 30 days).	
60-month timeframe includes follow-up window (1800 days ± 30 days).	
* Note: R-Int. follow-up ends at three years and is not included in this analysis.	
See Table 9-4 for the definition of the ARC defined Stent Thrombosis	

Table 9-23 shows the baseline demographic and clinical characteristics stratified by gender for subjects in the 38 mm Length Group analysis, 47/223 (21.1%) subjects were female and 176/223 (78.9%) were male. Consistent with other DES clinical studies, female patients were older, and there was no other significant difference in baseline demographic and clinical characteristics observed between gender groups.

Table 9-23: RESOLUTE 38 mm Length Group - Baseline Demographic and Lesion Characteristics Male vs. Female

Patient Characteristics	Male (N = 176)	Female (N = 47)	p-value
Age (Years)	60.1±10.7	64.0±10.2	0.028
History of smoking/tobacco use	20.5% (36/176)	12.8% (6/47)	0.469
Prior PCI	25.0% (44/176)	36.2% (17/47)	0.142
Hyperlipidemia	56.3% (99/176)	68.1% (32/47)	0.182

Table 9-23: RESOLUTE 38 mm Length Group - Baseline Demographic and Lesion Characteristics Male vs. Female

Patient Characteristics	Male (N = 176)	Female (N = 47)	p-value
Diabetes Mellitus	36.4% (64/176)	42.6% (20/47)	0.499
Insulin Dependent	9.1% (16/176)	14.9% (7/47)	0.280
Hypertension	72.2% (127/176)	85.1% (40/47)	0.088
Prior MI	32.4% (55/170)	32.6% (15/46)	1.000
Prior CABG	7.4% (13/176)	6.4% (3/47)	1.000
Ejection fraction - Qualitative			0.389
<30%	0.0% (0/144)	0.0% (0/40)	
30-40%	4.2% (6/144)	7.5% (3/40)	
>40%	95.8% (138/144)	92.5% (37/40)	
Lesion Class			0.634
A	1.9% (4/209)	0.0% (0/54)	
B1	8.1% (17/209)	3.7% (2/54)	
B2	9.6% (20/209)	9.3% (5/54)	
C	80.4% (168/209)	87.0% (47/54)	
Moderate/Severe Calcification	32.5% (68/209)	44.4% (24/54)	0.111
Pre procedure RVD (mm)	2.79±0.44	2.75±0.37	0.504
Pre procedure MLD (mm)	0.80±0.36	0.80±0.36	0.912
Pre procedure Diameter Stenosis (%)	71.42±11.49	70.98±12.15	0.805
Lesion Length (mm)	25.16±8.45	25.48±10.27	0.808

The 12 month rate of TLF was 4.0% in males and 10.9% in females (Table 9-24). Although event rates were numerically higher in women, the number of women in the study was small. Further, the RESOLUTE 38 mm Length study was not designed or powered to study the safety or effectiveness of the 38 mm Resolute stent in gender-specific subgroups, so these post hoc analyses are considered hypothesis-generating.

Table 9-24: RESOLUTE 38 mm Length Group - 12 Month Clinical Endpoints by Gender – Principal Safety and Effectiveness

	Male (N = 176)	Female (N = 47)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.0% (7/176)	10.9% (5/46)
TVF	5.1% (9/176)	13.0% (6/46)
MACE	5.1% (9/176)	10.9% (5/46)
EFFECTIVENESS		
Clinically Driven TVR	1.7% (3/176)	6.5% (3/46)
TLR	0.6% (1/176)	4.3% (2/46)
SAFETY		
Total Death	0.6% (1/176)	2.2% (1/46)
Cardiac Death	0.6% (1/176)	2.2% (1/46)
Non-Cardiac Death	0.0% (0/176)	0.0% (0/46)
TVMI	2.8% (5/176)	6.5% (3/46)
Cardiac Death or TVMI	3.4% (6/176)	8.7% (4/46)
Stent Thrombosis defined		
ARC		
Definite/Probable	0.6% (1/176)	2.2% (1/46)
Definite	0.0% (0/176)	2.2% (1/46)
Probable	0.6% (1/176)	0.0% (0/46)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

See Table 9-4 for the definition of the ARC defined Stent Thrombosis

9.2 Results of the RESOLUTE All Comers (AC) Clinical Trial

Primary Objective: 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, clinically indicated TLR at 12 months.

The data from the RESOLUTE AC trial were used to support the 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. See **Section 8.1 – Observed Adverse Events.**

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. 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 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.

Demographics and clinical characteristics: Refer to Table 9-25: R-AC – Baseline Characteristics

Table 9-25: R-AC - Baseline Characteristics

Baseline Characteristics	Resolute (N = 1140 subjects; M = 1661 lesions)	Xience V (N = 1152 subjects; M = 1705 lesions)
Mean Age (years)	64.4	64.2
Male Enrollment	76.67% (873/1140)	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)
* 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).		
The remaining baseline clinical features were well-matched between both arms.		

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

- Table 9-26: R-AC Principal Safety and Effectiveness (All subjects)
- Table 9-27: R-AC Principal Safety and Effectiveness (Complex cohort)
- Table 9-28: R-AC Principal Safety and Effectiveness (Non-Complex cohort)
- Table 9-29: R-AC ARC Defined Definite/Probable Stent Thrombosis through 60 Months (Complex and Non-Complex)

The 12 month and 5 year follow-up rates for the RESOLUTE All Comers study were 99.5% (2280/2292) and 98.8% (2265/2292) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in a randomized study in an all comer population. A limitation was that this trial was not sized to determine the rate of low frequency events with a pre-specified precision.

The published RESOLUTE All-Comers trial results are available in *Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010; 363: 136-46.*

Table 9-26: R-AC Principal Safety and Effectiveness (All subjects)

COMPOSITE SAFETY AND EFFECTIVENESS	All subjects			
	12 Months		60 Months	
	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 1140)	Xience V (N = 1152)
TLF	8.1% (92/1132)	8.5% (97/1142)	17.0% (191/1123)	16.2% (183/1133)
TVF	8.9% (101/1132)	9.7% (111/1142)	20.0% (225/1123)	19.1% (216/1133)
MACE	8.6% (97/1132)	9.8% (112/1142)	21.9% (246/1123)	21.6% (245/1133)
EFFECTIVENESS				
Clinically Driven TVR	4.9% (55/1132)	4.8% (55/1142)	11.4% (128/1123)	10.9% (123/1133)
TLR	3.9% (44/1132)	3.4% (39/1142)	7.8% (88/1123)	7.1% (81/1133)
TLR, PCI	3.4% (38/1132)	2.7% (31/1142)	6.9% (77/1123)	6.0% (68/1133)
TLR, CABG	0.5% (6/1132)	0.8% (9/1142)	1.4% (16/1123)	1.4% (16/1133)
Non-TL TVR	1.9% (21/1132)	2.2% (25/1142)	6.1% (68/1123)	6.1% (69/1133)
Non-TL TVR, PCI	1.5% (17/1132)	1.9% (22/1142)	5.2% (58/1123)	5.2% (59/1133)
Non-TL TVR, CABG	0.4% (4/1132)	0.4% (4/1142)	0.9% (10/1123)	1.0% (11/1133)
SAFETY				
Total Death	1.6% (18/1132)	2.7% (31/1142)	11.0% (123/1123)	10.8% (122/1133)
Cardiac Death	1.3% (15/1132)	1.7% (19/1142)	6.5% (73/1123)	5.7% (65/1133)
Non-Cardiac Death	0.3% (3/1132)	1.1% (12/1142)	4.5% (50/1123)	5.0% (57/1133)
Cardiac Death or TVMI	5.3% (60/1132)	5.5% (63/1142)	11.5% (129/1123)	10.6% (120/1133)
TVMI	4.2% (48/1132)	4.2% (48/1142)	5.7% (64/1123)	5.7% (65/1133)
Q wave MI	0.8% (9/1132)	0.4% (5/1142)	1.3% (15/1123)	0.8% (9/1133)
Non-Q wave MI	3.5% (40/1132)	3.8% (43/1142)	4.6% (52/1123)	4.9% (56/1133)
Stent Thrombosis ARC defined				
Definite/Probable	1.6% (18/1132)	0.7% (8/1142)	2.4% (27/1123)	1.7% (19/1133)
Definite	1.1% (13/1132)	0.3% (3/1142)	1.6% (18/1123)	0.8% (9/1133)
Probable	0.5% (6/1132)	0.4% (5/1142)	0.9% (10/1123)	0.9% (10/1133)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-27: R-AC Principal Safety and Effectiveness (Complex cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Complex cohort			
	12 Months		60 Months	
	Resolute (N = 764)	Xience V (N = 756)	Resolute (N = 764)	Xience V (N = 756)
TLF	8.8% (67/760)	10.0% (75/750)	18.2% (137/751)	18.4% (137/745)
TVF	9.7% (74/760)	11.3% (85/750)	22.1% (166/751)	21.3% (159/745)
MACE	9.1% (69/760)	11.7% (88/750)	22.5% (169/751)	24.6% (183/745)
EFFECTIVENESS				
Clinically Driven TVR	5.5% (42/760)	5.6% (42/750)	13.4% (101/751)	11.7% (87/745)
TLR	4.3% (33/760)	4.1% (31/750)	8.9% (67/751)	8.1% (60/745)
TLR, PCI	3.9% (30/760)	3.2% (24/750)	8.1% (61/751)	6.7% (50/745)
TLR, CABG	0.4% (3/760)	1.1% (8/750)	1.2% (9/751)	1.7% (13/745)
SAFETY				
Total Death	1.4% (11/760)	3.3% (25/750)	10.4% (78/751)	13.2% (98/745)
Cardiac Death	1.3% (10/760)	2.1% (16/750)	6.4% (48/751)	7.4% (55/745)
Non-Cardiac Death	0.1% (1/760)	1.2% (9/750)	4.0% (30/751)	5.8% (43/745)
Cardiac Death or TVMI	5.4% (41/760)	6.4% (48/750)	11.9% (89/751)	12.2% (91/745)
TVMI	4.2% (32/760)	4.7% (35/750)	5.9% (44/751)	6.0% (45/745)
Q wave MI	0.7% (5/760)	0.5% (4/750)	1.3% (10/751)	0.9% (7/745)
Non-Q wave MI	3.7% (28/760)	4.1% (31/750)	4.8% (36/751)	5.1% (38/745)
Stent Thrombosis ARC defined				
Definite/Probable	1.7%(13/759)	0.9%(7/749)	2.5% (19/751)	2.0% (15/745)
Definite	1.2%(9/759)	0.4%(3/749)	1.7% (13/751)	0.9% (7/745)
Probable	0.7%(5/759)	0.5%(4/749)	0.9% (7/751)	1.1% (8/745)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-28: R-AC Principal Safety and Effectiveness (Non-Complex Cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Non-Complex cohort			
	12 Months		60 Months	
	Resolute (N = 376)	Xience V (N = 396)	Resolute (N = 376)	Xience V (N = 396)
TLF	6.7% (25/372)	5.6% (22/392)	14.5% (54/372)	11.9% (46/388)
TVF	7.3% (27/372)	6.6% (26/392)	15.9% (59/372)	14.7% (57/388)
MACE	7.5% (28/372)	6.1% (24/392)	20.7% (77/372)	16.0% (62/388)
EFFECTIVENESS				
Clinically Driven TVR	3.5% (13/372)	3.3% (13/392)	7.3% (27/372)	9.3% (36/388)
TLR	3.0% (11/372)	2.0% (8/392)	5.6% (21/372)	5.4% (21/388)
TLR, PCI	2.2% (8/372)	1.8% (7/392)	4.3% (16/372)	4.6% (18/388)
TLR, CABG	0.8% (3/372)	0.3% (1/392)	1.9% (7/372)	0.8% (3/388)
SAFETY				
Total Death	1.9% (7/372)	1.5% (6/392)	12.1% (45/372)	6.2% (24/388)
Cardiac Death	1.3% (5/372)	0.8% (3/392)	6.7% (25/372)	2.6% (10/388)
Non-Cardiac Death	0.5% (2/372)	0.8% (3/392)	5.4% (20/372)	3.6% (14/388)
Cardiac Death or TVMI	5.1% (19/372)	3.8% (15/392)	10.8% (40/372)	7.5% (29/388)
TVMI	4.3% (16/372)	3.3% (13/392)	5.4% (20/372)	5.2% (20/388)
Q wave MI	1.1% (4/372)	0.3% (1/392)	1.3% (5/372)	0.5% (2/388)
Non-Q wave MI	3.2% (12/372)	3.1% (12/392)	4.3% (16/372)	4.6% (18/388)
Stent Thrombosis ARC defined				
Definite/Probable	1.3%(5/372)	0.3%(1/392)	2.2% (8/372)	1.0% (4/388)
Definite	1.1%(4/372)	0.0%(0/392)	1.3% (5/372)	0.5% (2/388)
Probable	0.3%(1/372)	0.3%(1/392)	0.8% (3/372)	0.5% (2/388)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-29: R-AC ARC Defined Definite/Probable Stent Thrombosis Through 60 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% (18/1132)	0.7% (8/1142)	1.3% (5/372)	0.3% (1/392)	1.7%(13/760)	0.9%(7/750)
Cumulative Stent Thrombosis Through 5 -Years	2.4% (27/1123)	1.7% (19/1133)	2.2% (8/372)	1.0% (4/388)	2.5% (19/751)	2.0% (15/745)
Acute (0 - 1 day)	0.4% (5/1123)	0.2% (2/1133)	0.3% (1/372)	0.0% (0/388)	0.5% (4/751)	0.3% (2/745)
Subacute (2 - 30 days)	0.7% (8/1123)	0.4% (4/1133)	0.3% (1/372)	0.3% (1/388)	0.9% (7/751)	0.4% (3/745)
Late (31 – 360 days)	0.6% (7/1123)	0.2% (2/1133)	0.8% (3/372)	0.0% (0/388)	0.5% (4/751)	0.3% (2/745)
Very Late (361 – 1800 days)	0.8% (9/1123)	1.0% (11/1133)	0.8% (3/372)	0.8% (3/388)	0.8% (6/751)	1.1% (8/745)

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)

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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).

9.3 Results of the RESOLUTE International Study

Primary Objective: 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.

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. 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 9.2 - Results of the RESOLUTE All Comers (AC) Clinical Trial**.

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 6 months and up to 12 months in subjects who were not at a high risk of bleeding.

Demographics and clinical characteristics: 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.

Results: These analyses are based on the intent-to-treat population. The 12 month and 3 year follow-up rates for the RESOLUTE International study were 97.7% (2295/2349) and 96.7% (2271/2349) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in an all comer population. A limitation was that this trial was not sized to determine the rate of low frequency events with a pre-specified precision.

The results are presented in the following tables:

- Table 9-30: RESOLUTE International - Principal Safety and Effectiveness
- Table 9-31: RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis Through 36 Months

Table 9-30: RESOLUTE International - Principal Safety and Effectiveness

	(N = 2349)	(N = 2349)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	36 Months
TLF	7.1% (165/2337)	11.4% (261/2284)
TVF	7.7% (180/2337)	12.9% (294/2284)
MACE	8.3% (193/2337)	14.4% (329/2284)
EFFECTIVENESS		
Clinically Driven TVR	4.2% (99/2337)	7.4% (168/2284)
TLR	3.5% (81/2337)	5.7% (130/2284)
TLR, PCI	3.1% (72/2337)	5.2% (118/2284)
TLR, CABG	0.4% (10/2337)	0.6% (14/2284)
Non-TL TVR	1.2% (27/2337)	2.6% (59/2284)
Non-TL TVR, PCI	1.2% (27/2337)	2.5% (56/2284)
Non-TL TVR, CABG	0.0% (0/2337)	0.2% (4/2284)
SAFETY		
Total Death	2.4% (57/2337)	6.1% (139/2284)
Cardiac Death	1.5% (34/2337)	3.6% (82/2284)
Non-Cardiac Death	1.0% (23/2337)	2.5% (57/2284)
Cardiac Death or MI	4.2% (99/2337)	7.0% (161/2284)
TVMI	3.0% (71/2337)	3.9% (89/2284)
Q wave MI	0.5% (12/2337)	0.9% (20/2284)
Non-Q wave MI	2.5% (59/2337)	3.0% (69/2284)
Stent Thrombosis ARC defined		
Definite/Probable	0.9% (20/2337)	1.1% (26/2284)
Definite	0.6% (15/2337)	0.8% (19/2284)
Probable	0.3% (6/2337)	0.4% (8/2284)

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).

36-month timeframe includes follow-up window (1080 days ± 30 days)

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-31: RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis Through 36 Months

	Resolute (N = 2349)
Stent Thrombosis	1.1% (26/2284)
Acute (0 - 1 day)	0.1% (3/2284)
Subacute (2 - 30 days)	0.6% (14/2284)
Late (31 – 360 days)	0.1% (3/2284)
Very Late (361 – 1080 days)	0.3% (6/2284)

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).
 36-month timeframe includes follow-up window (1080 days ± 30 days)
 See Table 9-4 for the definition of the ARC defined Stent Thrombosis

9.4 Results of the RESOLUTE FIM Clinical Trial

Primary Objective: 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.

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 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 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.

Primary Endpoint: The primary endpoint was in-stent late lumen loss (LL) at 9 months post-procedure as measured by QCA.

Control Group and Statistical Analysis Plan: 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.

Demographics and clinical characteristics: 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 ± 6.13mm and the average percentage diameter stenosis was 70.30 ± 11.37%. The ACC/AHA lesion classification was reported by sites as type B2/C for 81.4% (114/140) of the lesions.

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, $p_{\text{non-inferiority}} < 0.001$. The 12 month and 5 year follow-up rates were 99.3% (138/139) and 97.1% (135/139) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that it was a single arm feasibility study.

These analyses are based on the intent-to-treat population. PK results are presented in **Section 6.3** for the **Pharmacokinetics of the Resolute Stent**. The results are presented in the following tables:

- Table 9-32: RESOLUTE FIM - Primary Endpoint Analysis
- Table 9-33: RESOLUTE FIM - Principal Safety and Effectiveness
- Table 9-34: RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis through 60 Months
- Table 9-35: RESOLUTE FIM - Angiographic and IVUS Results

Table 9-32: 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 ± 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 9-33: RESOLUTE FIM - Principal Safety and Effectiveness

	Outcomes at 9 Months (N = 139)	Outcomes at 12 Months (N = 139)	Outcomes at 60 Months (N = 139)
COMPOSITE SAFETY AND EFFECTIVENESS			
TVF	6.5% (9/139)	7.2% (10/139)	13.2% (18/136)
MACE	7.2% (10/139)	8.6% (12/139)	16.2% (22/136)
EFFECTIVENESS			
Clinically Driven TVR	0.0% (0/139)	0.7% (1/139)	5.1% (7/136)
TLR	0.0% (0/139)	0.7% (1/139)	2.9% (4/136)
TLR, PCI	0.0% (0/139)	0.7% (1/139)	2.2% (3/136)
TLR, CABG	0.0% (0/139)	0.0% (0/139)	0.7% (1/136)
Non-TL TVR	0.0% (0/139)	0.0% (0/139)	2.2% (3/136)
Non-TL TVR, PCI	0.0% (0/139)	0.0% (0/139)	2.2% (3/136)
Non-TL TVR, CABG	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
SAFETY			
Total Death	1.4% (2/139)	2.2% (3/139)	6.6% (9/136)
Cardiac Death	0.7% (1/139)	0.7% (1/139)	1.5% (2/136)
Non-Cardiac Death	0.7% (1/139)	1.4% (2/139)	5.1% (7/136)
Cardiac Death or MI	6.5% (9/139)	6.5% (9/139)	8.1% (11/136)
MI	5.8% (8/139)	5.8% (8/139)	6.6% (9/136)
Q wave MI	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
Non-Q wave MI	5.8% (8/139)	5.8% (8/139)	6.6% (9/136)
Stent Thrombosis ARC defined			
Definite/Probable	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
Definite	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
Probable	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-34: RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	Resolute (N = 139)
Stent Thrombosis	0.0% (0/136)
Acute (0 - 1 day)	0.0% (0/136)
Subacute (2 - 30 days)	0.0% (0/136)
Late (31 - 360 days)	0.0% (0/136)
Very late (361 - 1800 days)	0.0% (0/136)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis

Table 9-35: 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)
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 Evaluable Lesions) or Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

9.5 Results of the RESOLUTE Japan Clinical Trial

Primary Objective: 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 \leq 27 mm.

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.

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 8 months post-procedure. 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 subjects who were not at a high risk of bleeding.

Primary Endpoint: The primary endpoint was in-stent late LL at 8 months post-procedure measured by 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 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.

Demographics and clinical characteristics: The mean age was 67.7 years with 77.0% (77/100) of subjects 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 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 $69.17 \pm 7.80\%$.

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. The 12 month and 5 year follow-up rates were 100% (100/100) and 96% (96/100) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

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

Table 9-36: RESOLUTE Japan - Primary Endpoint Analysis

Table 9-37: RESOLUTE Japan - Principal Safety and Effectiveness

Table 9-38: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis through 60 Months

Table 9-39: RESOLUTE Japan - Angiographic and IVUS Results

Table 9-36: 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 9-37: RESOLUTE Japan - Principal Safety and Effectiveness

	(N = 100)	(N = 100)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	4.0% (4/100)	6.1% (6/98)
TVF	5.0% (5/100)	10.2% (10/98)
MACE	5.0% (5/100)	14.3% (14/98)
EFFECTIVENESS		
Clinically Driven TVR	1.0% (1/100)	5.1% (5/98)
TLR	0.0% (0/100)	1.0% (1/98)
TLR, PCI	0.0% (0/100)	1.0% (1/98)
TLR, CABG	0.0% (0/100)	0.0% (0/98)
Non-TL TVR	1.0% (1/100)	4.1% (4/98)
Non-TL TVR, PCI	1.0% (1/100)	3.1% (3/98)
Non-TL TVR, CABG	0.0% (0/100)	1.0% (1/98)
SAFETY		
Total Death	1.0% (1/100)	7.1% (7/98)
Cardiac Death	0.0% (0/100)	1.0% (1/98)
Non-Cardiac Death	1.0% (1/100)	6.1% (6/98)
Cardiac Death or MI	4.0% (4/100)	5.1% (5/98)
TVMI	4.0% (4/100)	4.1% (4/98)
Q wave MI	0.0% (0/100)	0.0% (0/98)
Non-Q wave MI	4.0% (4/100)	4.1% (4/98)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/100)	0.0% (0/98)
Definite	0.0% (0/100)	0.0% (0/98)
Probable	0.0% (0/100)	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).

60-month timeframe includes follow-up window (1800 days ± 30 days)

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-38: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	Resolute (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 - 360 days)	0.0% (0/98)
Very late (361 - 1800 days)	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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-39: 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)	3.19 ± 4.53 (99)
% Volume Obstruction	2.33 ± 3.51 (99)
Incomplete Apposition	
Persistent	4.9% (5/103)
Late Acquired	2.9% (3/103)

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.

9.6 Results of the RESOLUTE INTEGRITY US Post Market Study

The RESOLUTE INTEGRITY US Post Market Study is a post approval study of the Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries with a Reference Vessel Diameter of 2.25 mm to 4.2 mm.

Primary Objective: The objective of this study is to assess the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm in two groups of patients, specifically those patients receiving stents \leq 30 mm in length, referred to as the Primary Enrollment Group (PEG) and those patients who receive extended length stents (34 mm or 38 mm) referred to as the Extended Length (XL) Sub-study.

Design: The RESOLUTE INTEGRITY US Post Market Study is a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects that are treated with the commercially available Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System.

This study enrolled 286 patients with *de novo* lesions in native coronary arteries who met the eligibility criteria and signed the informed consent form to participate in this study of which 230 patients were part of the PEG and 56 patients in the XL Sub-study.

For the PEG, centers were allowed to enroll a maximum of 40 subjects per center until study enrollment has been completed, whichever came first. For the XL Sub study, centers were allowed to enroll a maximum of 16 subjects per center until study enrollment was completed, whichever comes first.

The expected time of participation in the studies for each subject is two years for the PEG and five years for the XL Sub-study.

Patient follow up occurs at: 30 days \pm 5 days (Contact); 6 months \pm 14 days (Contact); 12 months \pm 30 days (Clinic Visit with 12-lead ECG); 24 months \pm 30 days (Contact). The XL Sub-study has additional visits at 3-5 years \pm 30 days (Contact).

Primary Endpoint: The primary endpoint for this study was composite rate of cardiac death and target vessel myocardial infarction (MI) at 12 months.

Control Group and Statistical Analysis Plan: The primary analysis sample was based on intent-to-treat (ITT): For this study, all subjects who sign the written informed consent and are enrolled in the study will be counted in the ITT set, which will be the primary analysis set.

Demographics and Clinical Characteristics for the RESOLUTE Integrity-US PEG: Baseline demographics and clinical characteristics showed a mean age of 64.4 years with 69.6% (160/230) of subjects being males. Of the subjects enrolled, 42.2% (97/230) had diabetes mellitus, 18.3% (42/230) were current smokers, 24.4% (55/225) had prior MI, 35.7% (82/230) had prior PCI, 86.5% (199/230) had hypertension, and 82.6% (190/230) reported hyperlipidemia. Baseline lesion characteristics include 40.9% (94/230) LAD lesions, a mean lesion length of 13.03 ± 5.76 mm, 82.9% (200/241) ACC/AHA type B2/C lesions and 36.5% (88/241) lesions involving a bifurcation. The mean RVD was 2.60 ± 0.45 mm and the percentage diameter stenosis was $66.84 \pm 10.37\%$.

Results for the RESOLUTE Integrity-US PEG: These analyses are based on the intent-to-treat population.

The results specifically for the RI-US PEG are presented in the following tables:

Table 9-40: RESOLUTE Integrity US (PEG) - Primary Endpoint Analysis

Table 9-41: RESOLUTE Integrity US (PEG) - Principal Safety and Effectiveness

Table 9-42: RESOLUTE Integrity US (PEG) - ARC Defined Definite/Probable Stent Thrombosis through 24 Months

Table 9-40: RESOLUTE Integrity US (PEG) - Primary Endpoint Analysis

	Resolute Integrity US (PEG) (N=230)	95% Confidence Interval ¹
Primary Endpoint - Cardiac Death/TVMI at 12-month- ITT set	3.5% (8/226)	[1.5%, 6.9%]
¹ The two-sided 95% CI is calculated by binomial (exact) distribution.		

Table 9-41: RESOLUTE Integrity US (PEG) - Principal Safety and Effectiveness		
	RESOLUTE INTEGRITY US (PEG) (N=230 Patients) (N=251 Lesions) (m/n) ¹	
Clinical Outcomes	Outcomes at 12 Months	Outcomes at 24 Months
Target Lesion Failure (TLF)	4.9% (11/226)	9.1% (20/219)
Target Vessel Failure (TVF)	7.1% (16/226)	12.3% (27/219)
MACE	5.8% (13/226)	11.0% (24/219)
Cardiac Death or Target Vessel MI (TVMI)	3.5% (8/226)	5.9% (13/219)
Death	1.8% (4/226)	2.7% (6/219)
Cardiac Death	1.3% (3/226)	1.8% (4/219)
Non Cardiac Death	0.4% (1/226)	0.9% (2/219)
TVMI (Extended historical definition)	2.2% (5/226)	4.1% (9/219)
Clinically Driven TLR	2.2% (5/226)	5.0% (11/219)
Clinically Driven TVR	4.4% (10/226)	8.2% (18/219)
Stent Thrombosis (ARC) Definite/Probable	0.9% (2/220)	1.8% (4/219)
Early Thrombosis (<=30 days)	0.9% (2/226)	0.9% (2/219)
Late Thrombosis (31-360 days)	0.0% (0/226)	0.0% (0/219)
Very Late Thrombosis (361-720 days)	N/A	0.9% (2/219)
Effectiveness Measures		
Lesion Success (Definition 1) ²	100.0% (245/245)	
Lesion Success (Definition 2) ³	99.2% (243/245)	
Device Success (Definition 1) ⁴	100.0% (245/245)	
Device Success (Definition 2) ⁵	99.2% (243/245)	
Procedure Success (Definition 1) ⁶	98.2% (223/227)	
Procedure Success (Definition 2) ⁷	97.4% (221/227)	
Device Specific Procedure Success (Definition 1) ⁸	98.2% (223/227)	
Device Specific Procedure Success (Definition 2) ⁹	97.4% (221/227)	
¹ Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage (%) was calculated as 100 × (m/n) ² The attainment of <50% residual stenosis of the target lesion using any percutaneous method. ³ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method. ⁴ The attainment of <50% residual stenosis of the target lesion using only the assigned device. ⁵ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only. ⁶ The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE. ⁷ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay. ⁸ The attainment of <50% residual stenosis of the target lesion using only the assigned device and no in-hospital MACE. ⁹ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only, and no in-hospital MACE.		

Table 9-42: RESOLUTE Integrity US (PEG) - ARC Defined Definite/Probable Stent Thrombosis through 24 Months

	Resolute Integrity (N = 230)
Stent Thrombosis	1.8% (4/219)
Acute (0 - 1 day)	0.0% (0/219)

Table 9-42: RESOLUTE Integrity US (PEG) - ARC Defined Definite/Probable Stent Thrombosis through 24 Months

	Resolute Integrity (N = 230)
Subacute (2 - 30 days)	0.9% (2/219)
Late (31 – 360 days)	0.0% (0/219)
Very Late Thrombosis (361-720 days)	0.9% (2/219)

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).
 24-month time frame includes follow-up window (720 days ± 30 days).
 See Table 9-4 for the definition of the ARC defined Stent Thrombosis

The 12 month and 24 month follow-up rates for the RESOLUTE Integrity US Post Market Study PEG were 94.3% (217/230) and 94.8% (218/230) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

Results for the RESOLUTE Integrity-US XL Sub-study: These analyses are based on the intent-to-treat population.

The results specifically for the RESOLUTE Integrity-US XL Sub-study are presented in the following tables:

Table 9-43: RESOLUTE Integrity US (XL Sub-study) - Primary Endpoint Analysis

Table 9-44: RESOLUTE Integrity US (XL Sub-study) - Principal Safety and Effectiveness

Table 9-45: RESOLUTE Integrity US (XL Sub-study) - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 9-43: RESOLUTE Integrity US (XL Sub-study) - Primary Endpoint Analysis

	Resolute Integrity US (XL Sub-study) (N=56)	95% Confidence Interval ¹
Primary Endpoint - Cardiac Death/TVMI at 12-month- ITT set	7.4% (4/54)	[2.1%, 17.9%]

¹ The two-sided 95% CI is calculated by binomial (exact) distribution.

Table 9-44: RESOLUTE Integrity US (XL Sub-study) - Principal Safety and Effectiveness

	RESOLUTE INTEGRITY US (XL Sub-study) (N=56 Patients) (N=69 Lesions) (m/n) ¹
Clinical Outcomes	Outcomes at 12 Months
Target Lesion Failure (TLF)	7.4% (4/54)
Target Vessel Failure (TVF)	7.4% (4/54)
MACE	9.3% (5/54)
Cardiac Death or Target Vessel MI (TVMI)	7.4% (4/54)
Death	1.9% (1/54)

Table 9-44: RESOLUTE Integrity US (XL Sub-study) - Principal Safety and Effectiveness	
	RESOLUTE INTEGRITY US (XL Sub-study) (N=56 Patients) (N=69 Lesions) (m/n)¹
Clinical Outcomes	Outcomes at 12 Months
Cardiac Death	1.9% (1/54)
Non Cardiac Death	0.0% (0/54)
TVMI (Extended historical definition)	5.6% (3/54)
Clinically Driven TLR	1.9% (1/54)
Clinically Driven TVR	1.9% (1/54)
Stent Thrombosis (ARC) Definite/Probable	1.9% (1/54)
Early Thrombosis (<=30 days)	1.9% (1/54)
Late Thrombosis (31-360 days)	0.0% (0/54)
Effectiveness Measures	
Lesion Success (Definition 1) ²	100.0% (67/67)
Lesion Success (Definition 2) ³	98.6% (68/69)
Device Success (Definition 1) ⁴	97.0% (65/67)
Device Success (Definition 2) ⁵	95.7% (66/69)
Procedure Success (Definition 1) ⁶	98.2% (55/56)
Procedure Success (Definition 2) ⁷	96.4% (54/56)
Device Specific Procedure Success (Definition 1) ⁸	94.6% (53/56)
Device Specific Procedure Success (Definition 2) ⁹	92.9% (52/56)
¹ Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage (%) was calculated as 100 × (m/n) ² The attainment of <50% residual stenosis of the target lesion using any percutaneous method. ³ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method. ⁴ The attainment of <50% residual stenosis of the target lesion using only the assigned device. ⁵ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only. ⁶ The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE. ⁷ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay. ⁸ The attainment of <50% residual stenosis of the target lesion using only the assigned device and no in-hospital MACE. ⁹ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only, and no in-hospital MACE.	

Table 9-45: RESOLUTE Integrity US (XL Sub-study) - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	Resolute Integrity (N = 56)
Stent Thrombosis	1.9% (1/54)
Acute (0 - 1 day)	0.0% (0/54)
Subacute (2 - 30 days)	1.9% (1/54)

Table 9-45: RESOLUTE Integrity US (XL Sub-study) - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	Resolute Integrity (N = 56)
Late (31 – 360 days)	0.0% (0/54)

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 9 4 for the definition of the ARC defined Stent Thrombosis

The 12 month follow-up rate for the RESOLUTE Integrity US Post Market Study XL Sub-study was 96.4% (54/56).

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

9.7 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.

Primary Objective: 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 diabetes mellitus cohort:

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

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 FIM 2.7% (24/878).

Subjects from the 38 mm Length sub-study are not included in this Resolute Pooled Analysis of Subjects with Diabetes Mellitus. Additional information is provided in **Section 9.7.1** for the Resolute US 38 mm Length Group for subjects with Diabetes Mellitus.

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.

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 stent 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 the 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 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. 28.5% (250/878) of the subjects were insulin dependent diabetics. Of the subjects included in this analysis, 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 9-46: RESOLUTE Diabetes Mellitus Cohort - Primary Endpoint Analysis
- Table 9-47: 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
- Table 9-48: RESOLUTE Diabetes Mellitus Cohort - ARC Defined Definite/Probable Stent Thrombosis Events through 12 Months

Table 9-46: 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 timeframe includes follow-up window (360 days ± 30 days).

¹ One-sided confidence interval using exact method.

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

Table 9-47: 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).

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-48: 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 9-4 for the definition of the ARC defined Stent Thrombosis.

9.7.1 Subjects with Diabetes Mellitus in the RESOLUTE 38 mm Length Stent Sub-study

Additional information is provided in Table 9-49 for the RESOLUTE US 38 mm Length Group in subjects with Diabetes Mellitus.

Table 9-49: RESOLUTE 38 mm Length Group: All 38 mm Subjects, Insulin-Dependent DM Subjects (IDDM), Non-Insulin Dependent DM Subjects (Non-IDDM), and Non-DM Subjects – Principal Safety and Effectiveness through 12 Months

	All Diabetic 38 mm Length Group Subjects (N = 84 Patients)	38 mm Length Group IDDM (N = 23 Patients)	38 mm Length Group – Non-IDDM (N = 61 Patients)	38 mm Length Group – Non-DM (N = 139 Patients)
COMPOSITE SAFETY AND EFFECTIVENESS				
TLF	6.0% (5/84)	4.3% (1/23)	6.6% (4/61)	5.1% (7/138)
TVF	7.1% (6/84)	4.3% (1/23)	8.2% (5/61)	6.5% (9/138)
MACE	8.3% (7/84)	4.3% (1/23)	9.8% (6/61)	5.1% (7/138)
EFFECTIVENESS				
Clinically-driven TVR	3.6% (3/84)	0.0% (0/23)	4.9% (3/61)	2.2% (3/138)
TLR	2.4% (2/84)	0.0% (0/23)	3.3% (2/61)	0.7% (1/138)
SAFETY				
Total Death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Cardiac Death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Non Cardiac Death	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)
Cardiac Death or TVMI	3.6% (3/84)	4.3% (1/23)	3.3% (2/61)	5.1% (7/138)
TVMI	2.4% (2/84)	4.3% (1/23)	1.6% (1/61)	4.3% (6/138)
Stent Thrombosis ARC defined				
Stent Thrombosis (ARC def/prob)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Early (<= 30 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Late (> 30 and <=360 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)

9.8 Subjects with Chronic Total Occlusion

The PERSPECTIVE Study – RESOLUTE CTO Cohort

The PERSPECTIVE Study included a retrospective and a prospective study arm. Both arms of this study enrolled approximately 250 patients at a single center experienced in CTO procedures. The prospective arm essentially comprised a separate substudy designed to evaluate procedural and 1-year clinical outcomes among consecutive patients undergoing attempted percutaneous Chronic Total Occlusion (CTO) revascularization. The prospective arm of the PERSPECTIVE study included a pre-specified subgroup analysis of patients treated with the Resolute family of drug eluting stents (all were Resolute Integrity).

Primary Objective: To assess the safety and effectiveness of the Resolute Zotarolimus-eluting Coronary Stent System (Resolute ZES) for the treatment of chronic total occlusions.

Population: The population consisted of prospectively enrolled subjects undergoing attempted percutaneous CTO revascularization and treated with the Resolute ZES.

Design: The PERSPECTIVE Study (Prospective Arm/Prespecified Resolute ZES for CTO Analysis) was a single-center, investigator-initiated, observational study which prospectively enrolled approximately 250 subjects undergoing attempted CTO. Assessment of use of Resolute ZES stents in CTO revascularization was based on prospectively enrolled CTO patients compared to a pre-specified performance goal.

An estimated MACE rate was derived based on a weighted average of the reported rates for drug-eluting stents from the PRISON II⁶ and EXPERT CTO⁷ studies. Due to difference in the definition of myocardial infarction used in the PRISON II study, an adjustment for the MACE rate was made to approximate the MACE rate if the ARC definition of myocardial infarction had been applied. The weighted average produced an estimated MACE rate of 16.6% using the ARC definition of MI. The performance goal (PG) for the pre-specified RESOLUTE CTO Cohort analysis was 25.2% based on the estimated MACE rate of 16.6% and a one-sided 95% CI.

Demographics: In the RESOLUTE CTO Cohort of the PERSPECTIVE Study, the mean age was 63.4 ± 9.5, 79.8% (146/183) were male, 98.4% (180/183) reported dyslipidemia, 88.5% (162/183) had hypertension, 18.0% (31/172) were current smokers, 35.5% (65/183) were diabetic including 12.6% (23/182) reported as insulin dependent, 33.3% (61/183) had a prior MI, and 80.9% (140/173) were classified as having stable angina.

Primary Endpoint: Major Adverse Cardiac Events (MACE) at one year; a composite of death, myocardial infarction (MI) (ARC defined), and clinically-driven target lesion revascularization (TLR).

Results: The observed MACE rate at one year for the RESOLUTE CTO Cohort was 18.2% (33/181) for the ITT population. The ITT population met the primary endpoint. The upper limit of the 95% confidence interval was 23.6% which is lower than the pre-specified performance goal (25.2%). A post hoc gender subgroup analysis of the primary endpoint resulted in MACE rates at one year of 18.8% (27/144) in male subjects and 16.2% (6/37) in female subjects.

The PERSPECTIVE Study results are presented in Table 9-50, Table 9-51, and Table 9-52:

Table 9-50: Primary Endpoint Analysis – MACE at 12 Months (ITT)

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

⁶ Suttrop MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation* 2006; 114(9): 921 – 928.

⁷ Kandzari DE, Kini AS, Karpaliotis D, et al. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results From the EXPERT CTO Multicenter Trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions). *J Am Coll Cardiol Intv* 2015; 8(6): 761 – 769.

Table 9-51: Principal Safety and Effectiveness Results

Safety and Effectiveness Measures	RESOLUTE CTO cohort (N=183 Subjects) %(m/n)
Safety Measures (In-hospital)	
TLF	15.3% (28/183)
TVF	15.3% (28/183)
MACE	15.3% (28/183)
Cardiac Death or MI	15.3% (28/183)
Death or MI	15.3% (28/183)
Death	1.1% (2/183)
Cardiac Death	1.1% (2/183)
Non-Cardiac Death	0.0% (0/183)
MI	14.8% (27/183)
TLR	0.0% (0/183)
TVR	0.0% (0/183)
Safety Measures (to 6 Months/183 days)	
TLF	17.5% (32/183)
TVF	17.5% (32/183)
MACE	17.5% (32/183)
Cardiac Death or MI	17.5% (32/183)
Death or MI	17.5% (32/183)
Death	2.7% (5/183)
Cardiac Death	2.2% (4/183)
Non-Cardiac Death	0.5% (1/183)
MI	15.8% (29/183)
TLR	0.5% (1/183)
TVR	0.5% (1/183)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.6% (3/183)
Stent Thrombosis ARC Definite/Probable	0.6% (1/183)
Stent Thrombosis ARC Possible	1.1% (2/183)
Early Stent Thrombosis (0 to 30 days)	0.6% (1/183)
Definite	0.6% (1/183)
Probable	0.0% (0/183)
Possible	0.0% (0/183)
Late Stent Thrombosis (31 days – 6 months)	1.1% (2/183)
Definite	0.0% (0/183)
Probable	0.0% (0/183)
Possible	1.1% (2/183)
Safety Measures (to 1 year/365 days)	
TLF	18.2% (33/181)
TVF	18.2% (33/181)
MACE	18.2% (33/181)
Cardiac Death or MI	17.7% (32/181)
Death or MI	17.7% (32/181)
Death	2.8% (5/181)
Cardiac Death	2.2% (4/181)
Non-Cardiac Death	0.6% (1/181)
MI	16.0% (29/181)
TLR	1.1% (2/181)
TVR	1.1% (2/181)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.7% (3/181)

Table 9-51: Principal Safety and Effectiveness Results

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

¹CTO procedural success as defined by achievement of <50% residual stenosis with ≥TIMI 2 antegrade flow

²Successful guidewire crossing with placement in distal true lumen of CTO target lesion

Table 9-52: RESOLUTE CTO Cohort – Primary Endpoint Analysis by Gender

Primary Endpoint	Male Subjects RESOLUTE CTO cohort (N=146 Subjects) % (m/n)	Female Subjects RESOLUTE CTO cohort (N=37 Subjects) % (m/n)
MACE at 12 months	18.8% (27/144)	16.2% (6/37)

Global RESOLUTE Clinical Program – RESOLUTE Pooled CTO

Population: In order to provide additional support for the performance of the Resolute family of stents in the treatment of CTOs, a retrospective, pooled analysis was performed which was comprised of pooled CTO patients from the Global RESOLUTE Clinical Program.

The following Global RESOLUTE Clinical Trials contributed subjects to the CTO cohort:

- RESOLUTE International
The RESOLUTE International Study (R-Int) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real world subject population. A total 2349 subjects were enrolled into the study. Subjects were followed for 3 years post-procedure. A total of 186 subjects from the R-Int study were included in the RESOLUTE Pooled CTO analysis.
- RESOLUTE China Randomized Controlled Trial
The RESOLUTE China Randomized Controlled Trial (R-China RCT) was a prospective, multi-center, randomized, open-label study designed to assess the non-inferiority of the Resolute stent compared to the Taxus Liberte stent for in-stent late lumen loss. A total of 198 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 15 subjects from the R-China RCT study were included in the RESOLUTE Pooled CTO analysis.
- RESOLUTE China Registry

The RESOLUTE China Registry (R-China Registry) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real-world patient population requiring stent implantation. A total of 1800 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 157 subjects from the R-China Registry were included in the RESOLUTE Pooled CTO Analysis.

Design: The Resolute stent performance for the treatment of CTO lesions was analyzed from data collected in the R-Int, R-China RCT, and R-China Registry studies. The results pooled datasets from the 5-year data of R-China RCT, 4-year data of R-China Registry, and 3-year data from R-Int. In total, 358 subjects were evaluable for this CTO subset.

Demographics: The average age in the RESOLUTE Pooled CTO subset (n=358) was 60.4 ± 11.3 years and 84.4% (302/358) were male. For this population, 37.7% (133/353) experienced a prior MI, 65.1% (233/358) had hypertension, 50.3% (180/358) had hyperlipidemia and 26.5% (95/358) had diabetes.

Global RESOLUTE Clinical Program results are presented in the following table:

Table 9-53: RESOLUTE Pooled CTO Analysis – Safety and Effectiveness Results

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) % (m/n) ⁹
Effectiveness Measures	
Lesion Success ⁶	100.0% (526/526)
Device Success ⁷	94.1% (496/527)
Procedure Success ⁸	97.5% (348/357)
1 Year	
TLF ¹	4.5% (16/352)
TVF ²	4.8% (17/352)
MACE ³	5.7% (20/352)
Composite Endpoint ⁴	12.2% (43/352)
Cardiac Death or TVMI	3.1% (11/352)
Death or TVMI	4.0% (14/352)
Death	1.7% (6/352)
Cardiac Death	0.9% (3/352)
Non Cardiac Death	0.9% (3/352)
TVMI (Extended historical definition)	2.3% (8/352)
Clinically Driven TLR	2.0% (7/352)
Clinically Driven TVR	2.3% (8/352)
Stent Thrombosis (ARC) Definite/Probable)	0.6% (2/352)
Early Thrombosis(<=30 days)	0.3% (1/352)
Late Thrombosis(>30 and <=360 days)	0.3% (1/352)
Significant Bleeding Complications ⁵	1.1% (4/352)
Stroke	0.9% (3/352)
3 Years	
TLF ¹	8.9% (31/347)
TVF ²	10.1% (35/347)
MACE ³	10.1% (35/347)
Composite Endpoint ⁴	18.4% (64/347)
Cardiac Death or TVMI	6.6% (23/347)
Death or TVMI	7.8% (27/347)
Death	5.5% (19/347)
Cardiac Death	4.3% (15/347)
Non Cardiac Death	1.2% (4/347)
TVMI (Extended historical definition)	3.2% (11/347)
Clinically Driven TLR	3.2% (11/347)
Clinically Driven TVR	4.3% (15/347)
Stent Thrombosis (ARC) Definite/Probable)	1.2% (4/347)

Table 9-53: RESOLUTE Pooled CTO Analysis – Safety and Effectiveness Results

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n) ⁹
Early Thrombosis(<=30 days)	0.3% (1/347)
Late Thrombosis(>30 and <=360 days)	0.3% (1/347)
Very Late Thrombosis(>360 days)	0.9% (3/347)
Significant Bleeding Complications ⁵	1.2% (4/347)
Stroke	1.7% (6/347)
<p>1.Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.</p> <p>2.Cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization.</p> <p>3.Death, myocardial infarction, (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically driven/clinically indicated) by percutaneous or surgical methods.</p> <p>4.The combined clinical outcome of (all cause) mortality, Myocardial Infarction (Q-wave and non Q-wave), or (any) revascularization.</p> <p>5.Bleeding complication is defined as a procedure related hemorrhagic event that requires a transfusion or surgical repair. These may include a hematoma requiring treatment of retroperitoneal bleed.</p> <p>Significant Bleeding complication is defined as the bleeding complication that has at least one of the following scenarios:</p> <ul style="list-style-type: none"> • Bleedings that led to an interruption of anti-platelet medication; • Bleedings that require transfusion; • Intracerebral bleedings; or • Bleedings that resulted in substantial hemodynamic compromise requiring treatment <p>6.The attainment of <50% residual stenosis of the target lesion using any percutaneous method.</p> <p>7.The attainment of <50% residual stenosis of the target lesion using only the assigned device.</p> <p>8.The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.</p> <p>9.Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage () was calculated as $100 \times (m/n)$</p> <p>Extended historical definition of MI is used for all the composite endpoints.</p>	

9.9 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, a subject-level pooled analysis was conducted. Table 9-54 below provides the total number of subjects included in the analyses.

Table 9-54: Subjects Included in the Analyses by Clinical Study

	All Subjects	On-label
RESOLUTE FIM	139	139
RESOLUTE All-Comers – Resolute	1140	376
RESOLUTE International	2349	763
RESOLUTE US	1402	1402
RESOLUTE Japan	100	100
Pooled Resolute Dataset	5130	2780
Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis presented here		

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 (ISR) target lesion, 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 of > 2.5 mg/dl, a lesion length > 27 mm, 2 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 9-55: Resolute Pooled Analysis - Principal Safety and Effectiveness
- Table 9-56 Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis* through 60 Months

Table 9-55: Resolute Pooled Analysis - Principal Safety and Effectiveness Through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
Outcomes at 12 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	6.6% (336/5098)	5.4% (150/2759)
TVF	7.5% (382/5098)	6.6% (181/2759)
MACE	7.5% (384/5098)	6.3% (174/2759)
EFFECTIVENESS		
Clinically Driven TVR	4.3% (220/5098)	3.7% (103/2759)
Clinically Driven TLR	3.3% (166/5098)	2.5% (69/2759)
SAFETY		
Total Death	1.9% (98/5098)	1.6% (44/2759)
Cardiac Death	1.2% (60/5098)	0.9% (26/2759)
Non-Cardiac Death	0.7% (38/5098)	0.7% (18/2759)
TVMI	2.9% (149/5098)	2.4% (66/2759)
Cardiac Death or TVMI	3.9% (200/5098)	3.3% (90/2759)
Stent Thrombosis ARC defined		
Definite/Probable	0.8% (40/5098)	0.3% (9/2759)
Definite	0.6% (29/5098)	0.2% (6/2759)
Probable	0.3% (13/5098)	0.1% (3/2759)
Outcomes at 36 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	10.8% (539/5012)	9.2% (249/2709)
TVF	13.0% (652/5012)	12.0% (324/2709)
MACE	13.5% (679/5012)	12.0% (325/2709)
EFFECTIVENESS		
Clinically Driven TVR	7.9% (397/5012)	7.5% (204/2709)
Clinically Driven TLR	5.3% (267/5012)	4.4% (119/2709)
SAFETY		
Total Death	5.5% (275/5012)	5.0% (135/2709)
Cardiac Death	3.1% (156/5012)	2.6% (70/2709)
Non-Cardiac Death	2.4% (119/5012)	2.4% (65/2709)
TVMI	3.8% (188/5012)	3.1% (84/2709)
Cardiac Death or TVMI	6.5% (324/5012)	5.4% (145/2709)

Table 9-55: Resolute Pooled Analysis - Principal Safety and Effectiveness Through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
Stent Thrombosis ARC defined		
Definite/Probable	1.1% (54/5012)	0.5% (13/2709)
Definite	0.7% (37/5012)	0.3% (7/2709)
Probable	0.4% (19/5012)	0.2% (6/2709)
Outcomes at 60 Months*		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	14.0% (376/2688)	12.3% (239/1937)
TVF	18.1% (486/2688)	16.5% (320/1937)
MACE	19.4% (521/2688)	18.2% (352/1937)
EFFECTIVENESS		
Clinically Driven TVR	11.4% (306/2688)	10.6% (205/1937)
Clinically Driven TLR	6.7% (179/2688)	5.8% (112/1937)
SAFETY		
Total Death	9.9% (266/2688)	9.7% (188/1937)
Cardiac Death	4.9% (131/2688)	4.3% (83/1937)
Non-Cardiac Death	5.0% (135/2688)	5.4% (105/1937)
TVMI	4.5% (120/2688)	3.9% (76/1937)
Cardiac Death or TVMI	8.7% (234/2688)	7.5% (145/1937)
Stent Thrombosis ARC defined		
Definite/Probable	1.3% (34/2688)	0.8% (15/1937)
Definite	0.8% (22/2688)	0.5% (9/1937)
Probable	0.5% (13/2688)	0.3% (6/1937)

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).

36-month timeframe includes follow-up window (1080 days ± 30days).

60-month timeframe includes follow-up window (1800 days ± 30days)

* Note: R-Int. follow-up ends at three years and is not included in this analysis.

The definitions of the outcomes are presented as table notes to Table 8-1 - Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-56: Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	All Subjects* (N = 2781)	On-label* (N = 2017)
Stent Thrombosis	1.3% (34/2688)	0.8% (15/1937)
Early (0 - 30 days)	0.5% (13/2688)	0.2% (3/1937)
Late (31 – 360 days)	0.3% (8/2688)	0.2% (4/1937)
Very Late (361 – 1800 days)*	0.5% (14/2688)	0.4% (8/1937)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

* Note: R-Int. follow-up ends at three years and is not included in this analysis.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

9.9.1 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).⁸ 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 pathophysiology⁹, 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 coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease.

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis.

Table 9-57 describes the baseline and demographic characteristics by gender for subjects in the pooled on-label analysis. 784/2780 (28.2%) subjects were female and 1996/2780 (71.8%) were male. Female patients at baseline were older, had higher rates of diabetes and hypertension, and had smaller reference vessel diameters (RVD).

Table 9-57: Baseline Characteristics of Male vs. Female for Pooled On-Label Resolute Patients

Patient Characteristics	Male N=1996	Female N=784	p-value
Age(years)	62.9±10.5 (1996)	67.1±10.6 (784)	<.001
History of Smoking/Tobacco use	64.1% (1280/1996)	45.5% (357/784)	<.001
Prior PCI	32.4% (646/1996)	28.1% (220/784)	0.029
Hyperlipidemia	78.6% (1568/1996)	80.9% (634/784)	0.194
Diabetes Mellitus	29.2% (582/1996)	37.6% (295/784)	<.001
Insulin Dependent	7.0% (140/1996)	13.9% (109/784)	<.001
History of Hypertension	75.1% (1499/1996)	84.3% (661/784)	<.001
Prior MI	28.1% (556/1977)	18.3% (141/772)	<.001
Prior CABG	9.4% (187/1996)	5.7% (45/784)	0.002

⁸ 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.

⁹ 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.

Table 9-57: Baseline Characteristics of Male vs. Female for Pooled On-Label Resolute Patients

Patient Characteristics	Male N=1996	Female N=784	p-value
Ejection Fraction (%)			0.059
<30%	0.1% (1/1463)	0.2% (1/593)	
30-40%	6.9% (101/1463)	4.6% (27/593)	
>40%	93.0% (1361/1463)	95.3% (565/593)	
Lesion Class ACC/AHA			0.133
A	7.8% (172/2219)	9.5% (81/857)	
B1	25.8% (573/2219)	27.5% (236/857)	
B2	32.0% (710/2219)	29.8% (255/857)	
C	34.4% (764/2219)	33.3% (285/857)	
Moderate/Severe Calcification	39.1% (867/2216)	39.2% (335/855)	1.000
Pre procedure RVD (mm)	2.7±0.5 (2201)	2.6±0.5 (855)	<.001
Pre procedure MLD (mm)	0.7±0.4 (2212)	0.8±0.4 (856)	0.025
Pre procedure Diameter Stenosis (%)	73.0±13.8 (2212)	70.5±13.5 (856)	<.001
Lesion Length (mm)	13.8±5.8 (2201)	12.9±5.7 (855)	<.001

The pooled Resolute stent on-label use data were evaluated retrospectively for gender-based clinical outcomes. Table 9-58 shows a post-hoc analysis of the principal 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. The event rates were numerically higher in women (except for non-cardiac death) at 12 months; although after 60 months are evenly distributed among the two groups. These results suggest that the safety and effectiveness profile of the Resolute stent is generalizable to both males and females.

Table 9-58: Resolute Pooled On-Label Gender (Male vs. Female) – Principal Safety and Effectiveness Through 60 Months

	Male (N=1996)	Female (N=784)
Safety Outcomes to 12 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.9% (97/1983)	6.8% (53/776)
TVF	5.8% (115/1983)	8.5% (66/776)
MACE	6.0% (118/1983)	7.2% (56/776)
EFFECTIVENESS		
Clinically Driven TVR	3.3% (66/1983)	4.8% (37/776)
Clinically Driven TLR	2.3% (46/1983)	3.0% (23/776)
SAFETY		
Death	1.5% (30/1983)	1.8% (14/776)
Cardiac Death	0.8% (15/1983)	1.4% (11/776)
Non Cardiac Death	0.8% (15/1983)	0.4% (3/776)
TVMI (Extended Historical Definition)	2.1% (41/1983)	3.2% (25/776)
Cardiac Death or Target Vessel MI (TVMI)	2.8% (55/1983)	4.5% (35/776)
Stent Thrombosis ARC defined		
Definite/Probable	0.3% (5/1983)	0.5% (4/776)
Definite	0.2% (4/1983)	0.3% (2/776)
Probable	0.1% (1/1983)	0.3% (2/776)
Safety Measures to 36 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	8.8% (172/1949)	10.1% (77/760)
TVF	11.4% (222/1949)	13.4% (102/760)
MACE	11.8% (230/1949)	12.5% (95/760)
EFFECTIVENESS		
Clinically Driven TVR	7.3% (142/1949)	8.2% (62/760)
Clinically Driven TLR	4.4% (86/1949)	4.3% (33/760)
SAFETY		
Death	5.0% (98/1949)	4.9% (37/760)
Cardiac Death	2.5% (48/1949)	2.9% (22/760)
Non Cardiac Death	2.6% (50/1949)	2.0% (15/760)
TVMI (Extended Historical Definition)	2.6% (51/1949)	4.3% (33/760)
Cardiac Death or Target Vessel MI (TVMI)	4.8% (94/1949)	6.7% (51/760)
Stent Thrombosis ARC defined		
Definite/Probable	0.4% (7/1949)	0.8% (6/760)
Definite	0.3% (5/1949)	0.3% (2/760)
Probable	0.1% (2/1949)	0.5% (4/760)
Outcomes to 60 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	12.4% (169/1363)	12.2% (70/574)
TVF	16.6% (226/1363)	16.4% (94/574)
MACE	18.3% (249/1363)	17.9% (103/574)
EFFECTIVENESS		
Clinically Driven TVR	10.6% (144/1363)	10.6% (61/574)
Clinically Driven TLR	5.9% (80/1363)	5.6% (32/574)
SAFETY		
Death	9.8% (133/1363)	9.6% (55/574)
Cardiac Death	4.3% (58/1363)	4.4% (25/574)
Non Cardiac Death	5.5% (75/1363)	5.2% (30/574)
TVMI (Extended Historical Definition)	3.6% (49/1363)	4.7% (27/574)
Cardiac Death or Target Vessel MI (TVMI)	7.3% (99/1363)	8.0% (46/574)
Stent Thrombosis ARC defined		
Definite/Probable	0.7% (9/1363)	1.0% (6/574)

Table 9-58: Resolute Pooled On-Label Gender (Male vs. Female) – Principal Safety and Effectiveness Through 60 Months

	Male (N=1996)	Female (N=784)
Definite	0.4% (6/1363)	0.5% (3/574)
Probable	0.2% (3/1363)	0.5% (3/574)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

36-month timeframe includes follow-up window (1080 days ± 30 days).

60-month timeframe includes follow-up window (1800 days ± 30 days).

* Note: R-Int. follow-up ends at three years and is not included in this analysis. See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis

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

9.9.2 Subset Analyses from the Resolute Pooled Dataset

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 studies 33% of enrolled subjects who 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 Tables below (Table 9-59, Table 9-60, Table 9-61). Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis.

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 9-59: 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 ≥ 27 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 defined							
ARC							
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 9-60: 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 defined					
ARC					
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 9-61: 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)
TVMI	5.9% (41/690)	2.4% (12/497)	7.1% (4/56)	5.3% (7/133)	2.4% (19/788)
Cardiac Death or TVMI	7.1% (49/690)	3.4% (17/497)	10.7% (6/56)	9.8% (13/133)	3.8% (30/788)
Stent Thrombosis defined					
ARC					
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).

The definitions of the outcomes are presented as table notes to Table 8-1 - Principal Adverse Events.

See Table 9-4 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.

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis

10 PATIENT SELECTION AND TREATMENT

See also **Section 5.5 Use in Special Populations**. The risks and benefits described above should be carefully considered for each patient before use of the Resolute Integrity Stent System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anti-thrombotic therapy. In the clinical studies reviewed to support the approval of the Resolute Integrity Stent System, subjects were prescribed DAPT for at least 6 months post-procedure, and most patients who were not at a high risk of bleeding used DAPT for at least 12 months.

Post-Resolute Integrity Stent implantation, aspirin should be continued indefinitely, and a P2Y12 platelet inhibitor should be given for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS). A longer duration of DAPT may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at a high bleeding risk. In patients who are at a high risk of bleeding, or who develop significant bleeding during DAPT treatment, a shorter DAPT duration may be reasonable (see **Section 5.1 - Pre- and Post-Procedure Antiplatelet Regimen**). However, definitive evidence supporting the safety of short DAPT duration has not been established in prospective clinical studies. The safety and effectiveness of the Resolute Integrity stent have not been evaluated in patients at high bleeding risk.

11 PATIENT COUNSELING INFORMATION

Physicians should consider the following in counseling the patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a zotarolimus-eluting stent implant
- Discuss the risks/benefits issues for the particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following patient materials will be provided to physicians to educate their patients about the options available for treating coronary artery disease and provide contact information to the patient after their stent implant procedure:

- A Patient Guide which includes information on the Resolute Integrity Zotarolimus-Eluting Coronary Stent System, coronary artery disease, and the stent implantation procedure.
- A Stent Patient Implant Card that includes patient information, stent implant information and MRI guidelines. All patients should be instructed to keep this card in their possession at all times for procedure/stent identification.

12 HOW SUPPLIED

STERILE: This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use if the package is opened or damaged. Do not resterilize. If the product or package is opened or damaged, return to Medtronic Returned Goods. Contact your local Medtronic Inc. Representative for return information.

CONTENTS: Package contains one (1) Resolute Integrity Zotarolimus-Eluting Coronary Stent mounted on a Rapid Exchange (RX) stent delivery system.

STORAGE: Store in the original container. Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). Use by the "Use By" date noted on the package.

DISPOSAL INSTRUCTIONS: After use, dispose of product and packaging in accordance with hospital, administrative and/ or local government policy.

13 DIRECTIONS FOR USE

13.1 Access to Package Holding Sterile Stent Delivery System

Remove the stent delivery system from the package. Special care must be taken not to handle the stent or in any way disrupt its placement on the balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through the rotating hemostatic valve and

guiding catheter hub. Excessive manipulation, e.g., rolling the mounted stent, may cause dislodgement of the stent from the delivery balloon.

13.2 Inspection Prior to Use

Before opening the product, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Do not use after the "Use By" date. If the sterile package is intact, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging or system is noted.

A protective sheath covers the stent mounted on the balloon. After removal of the sheath, visually inspect the stent to ensure that it has not been damaged or displaced from its original position (between proximal and distal marker bands) on the balloon.

13.3 Materials Required

Quantity	Material
N/A	Guide catheter [\geq 5 F (1.42 mm, 0.056 inch) inner diameter]
2-3	20 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [\leq 0.014 inch (0.36 mm) outer diameter]
1	Rotating hemostatic valve
N/A	Contrast medium diluted 1:1 with heparinized normal saline
1	Inflation device
1	Stopcock (3-way minimum)
1	Torque device
N/A	Appropriate anticoagulation and antiplatelet drugs

13.4 Preparation Precaution

- DO NOT use product if the protective sheath is not present or the stent is damaged/displaced.
- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply positive pressure to the balloon during the delivery system preparation.

13.4.1 Guidewire Lumen Flush

Flush the stent system guidewire lumen with heparinized normal saline until the fluid exits the distal tip.

13.4.2 Delivery System Preparation

Step Action

1. Prepare the guide catheter and guidewire according to the manufacturer's instructions.
2. Remove the stent delivery system from the package.
3. Remove protective sheath covering from the stent/balloon. Removing the protective sheath will also remove the stylette.
4. Inspect the stent to assure it has not been damaged or displaced from its original position on the balloon. Verify that the stent is positioned between the proximal and distal balloon markers. Verify that there is no visible damage to the stent or the balloon.
Note: Should there be movement of or damage to the stent, do not use.
5. Flush Stent Delivery System guidewire lumen with heparinized normal saline in routine manner.
6. Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1).
7. Attach to delivery system and apply negative pressure for 20 - 30 seconds.
8. Slowly release pressure to allow negative pressure to draw mixture into balloon lumen.
9. Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen.
10. Prepare inflation device in standard manner and purge to remove all air from syringe and tubing.

Step Action

- 11 Attach inflation device to catheter directly ensuring no bubbles remain at connection.
- 12 Leave on ambient pressure (neutral position).

Note: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

13.5 Delivery Procedure

Step	Action
------	--------

1. Prepare the vascular access site according to standard practice.
2. **Pre-dilate the lesion with a PTCA catheter.** Pre-dilatation must be performed using a balloon with the following three characteristics:
 - A diameter at least 0.5 mm smaller than the treatment stent.
 - A length equal to or shorter than the lesion length to be dilated.
 - A length shorter than the stent to be implanted.
3. Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible.

Note: If resistance is encountered, **do not force passage.** Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine.
4. Ensure guide catheter stability before advancing the Resolute Integrity System into the coronary artery. Carefully advance the Resolute Integrity System into the hub of the guide catheter.
5. Advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. If the position of the stent is not optimal, it should be carefully repositioned or removed (see **Precautions – 5 Stent/System Removal Precautions**). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
6. Sufficiently tighten the rotating hemostatic valve. Stent is now ready to be deployed.

Note: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system before stent implantation, do not force passage. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. See **Precautions –5 Stent/System Removal Precautions** for specific stent delivery system removal instructions. In the event the stent is not deployed, contact your local Medtronic, Inc. representative for return information and avoid handling stent with bare hands.

13.6 Deployment Procedure

Step	Action
------	--------

1. Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning.
2. Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3. **Do not exceed Rated Burst Pressure (RBP). The RBP is 16atm for the 2.25mm – 3.5mm stent diameters and 15atm for the 4.0mm stent diameter. The Resolute Integrity stents should not be expanded to a diameter beyond the maximum labeled diameter listed on the label. Do not dilate the 2.25 mm - 2.75 mm stents to greater than 3.50 mm. Do not dilate the 3.0 mm - 4.0 mm stents to greater than 4.75mm.**
4. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

13.7 Removal Procedures

Step	Action
------	--------

1. Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 30 seconds, for full balloon deflation. Longer stents may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast within the balloon.
2. Open the hemostatic valve to allow removal of the delivery system.
3. Maintain position of guide catheter and guidewire. Very slowly, withdraw the balloon from the stent, maintaining negative pressure, allowing movement of the myocardium to gently dislodge the balloon from the stent.

4. After removal of the delivery system, tighten the hemostatic valve.
5. Repeat angiography and visually assess the vessel and the stent for proper expansion.

13.8 *In-vitro* Information:

Table 13-1: Inflation Pressure Recommendations

Pressure		Nominal and Rated Burst Pressure*	Stent Nominal Inner Diameter (mm)**					
ATM	kPa		2.25	2.5	2.75	3.0	3.5	4.0
6	608		2.20	2.45	2.70	2.90	3.30	3.75
7	709		2.20	2.45	2.70	2.95	3.35	3.80
8	811		2.25	2.50	2.75	3.00	3.40	3.90
9	912	Nominal	2.30	2.55	2.80	3.05	3.50	3.95
10	1013		2.30	2.60	2.85	3.10	3.55	4.05
11	1115		2.35	2.60	2.90	3.15	3.60	4.10
12	1216		2.40	2.65	2.95	3.20	3.65	4.15
13	1317		2.40	2.70	3.00	3.20	3.70	4.20
14	1419		2.45	2.70	3.05	3.25	3.75	4.25
15	1520	RBP for 4.0 mm	2.50	2.75	3.10	3.30	3.80	4.30
16	1621	RBP*	2.55	2.80	3.15	3.35	3.85	4.35
17	1723		2.60	2.80	3.20	3.40	3.90	4.40
18	1824		2.60	2.85	3.25	3.45	3.95	4.45
19	1925			2.90	3.30	3.50	4.00	4.50
20	2027			2.95	3.40	3.55	4.05	

*Do not exceed the rated burst pressure (RBP). The RBP for 4.0 mm diameter is 15 ATM.

** The shaded cells at pressures 19 ATM and 20 ATM signify that 99% of the balloons did not pass at the listed pressure beyond RBP with 95% confidence.

13.9 Further Dilatation of Stented Segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed at the physician's discretion with appropriately sized (length and diameter) balloons to ensure that the stent is in full contact with the vessel wall. To achieve this, a balloon to artery ratio of 1.0 to 1.1:1.0 should be used to leave a residual diameter stenosis of near 0% (with a recommended maximum of no greater than 10%). Whenever possible, avoid the use of grossly oversized balloons (balloon:artery ratio > 1.2).

Precaution: Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilatation Limits
2.25 mm	3.50 mm
2.50 mm	3.50 mm
2.75 mm	3.50 mm
3.00 mm	4.75 mm
3.50 mm	4.75 mm
4.00 mm	4.75 mm

All efforts should be taken to assure that the stent is not under dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. This further expansion should be performed using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging or displacing the stent. The balloon should be centered within the stent and should not extend outside of the stented region. **The Resolute Integrity stents should not be expanded to a diameter beyond the maximum labeled diameter listed on the label. Do not dilate the 2.25 mm - 2.75 mm stents to greater than 3.50 mm. Do not dilate the 3.0 mm - 4.0 mm stents to greater than 4.75 mm.**

14 REUSE PRECAUTION STATEMENT

For single use only.

Do not Resterilize or Reuse.

DISCLAIMER OF WARRANTY

NOTE: ALTHOUGH THE MEDTRONIC RESOLUTE INTEGRITY ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM, HEREAFTER REFERRED TO AS "PRODUCT," HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, MEDTRONIC, INC., MEDTRONIC VASCULAR, INC. AND THEIR AFFILIATES (COLLECTIVELY, "MEDTRONIC") HAVE NO CONTROL OVER CONDITIONS UNDER WHICH THIS PRODUCT IS USED. MEDTRONIC, THEREFORE, DISCLAIMS ALL WARRANTIES, BOTH EXPRESSED AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. MEDTRONIC SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT OR OTHERWISE. NO PERSON HAS ANY AUTHORITY TO BIND MEDTRONIC TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.

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M724130B001 Rev 1J

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Medtronic

**Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System
Over the Wire Delivery System**

INSTRUCTIONS FOR USE

CAUTION – Federal (USA) law restricts this device for sale by or on the order of a physician.

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THE COMPONENTS OF THE RESOLUTE INTEGRITY ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM ARE STERILE.

1 RESOLUTE INTEGRITY™ ZOTAROLIMUS ELUTING CORONARY STENT SYSTEM

The Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System (Resolute Integrity System) is a device/drug combination product comprised of the following device components: The Integrity Coronary Stent and MicroTrac delivery systems and a drug component (a formulation of zotarolimus in a polymer coating). The characteristics of the Resolute Integrity System are described in Table 1-1.

Table 1-1: Device Component Description and Nominal Dimensions

Component	Resolute Integrity Zotarolimus-Eluting Coronary Stent System Over the Wire Delivery System	
	Small Vessel	Medium/Large Vessel
Available Stent Diameters (mm):	2.25, 2.5, 2.75	3.0, 3.5, 4.0
Available Stent Lengths Unexpanded (mm):	8, 12, 14, 18, 22, 26, 30	9, 12, 15, 18, 22, 26, 30, 34, 38
Stent Material & Geometry:	A cobalt-based alloy conforming to ASTM F562 and ISO 5832-6:1997 with 1.0 mm length elements, 7.5 alternating crowns and 0.0035" strut thickness; the stent utilizes a single helix fusion pattern. The coronary stent is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are provided in multiple lengths and diameters.	A cobalt-based alloy conforming to ASTM F562 and ISO 5832-6:1997 with 0.9 mm length elements, 9.5 alternating crowns and 0.0035" strut thickness; utilizes a helical u-joint fusion pattern. The coronary stent is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are provided in multiple lengths and diameters.
Drug Component:	A coating of polymers loaded with zotarolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.6 µg/mm ² which results in a maximum nominal drug content of 380 µg on the largest stent (4.0 mm x 38 mm).	
Delivery System Working Length:	140 cm	
Delivery System Luer Adapter Ports:	Two-arm luer (side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire less than or equal to 0.36 mm (0.014 inch).	
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 Pressure: 9 ATM (912 kPa) Rated Burst Pressure: 16 ATM (1621 kPa) for 2.25 - 3.5 mm diameters 15 ATM (1520 kPa) for 4.0 mm diameter	
Minimum Guide Catheter Inner Diameter:	≥ 5 F (1.42 mm, 0.056 inch)	
Catheter Shaft Outer Diameter:	Proximal OD: 3.4 F (1.1 mm, 0.044 inch) Distal Section OD: 2.7 F (0.91 mm, 0.036 inch)	

1.1 Device Component Description

The Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System (Resolute Integrity System) consists of a balloon-expandable intracoronary drug-eluting stent pre-mounted on the MicroTrac Over the Wire (OTW) stent delivery system. The Resolute Integrity Stent is manufactured from a cobalt alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are available in multiple lengths and diameters. The delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014 inch (0.36 mm) guidewires. The MicroTrac OTW delivery system (Figure 1-1) has an effective length of 140 cm.

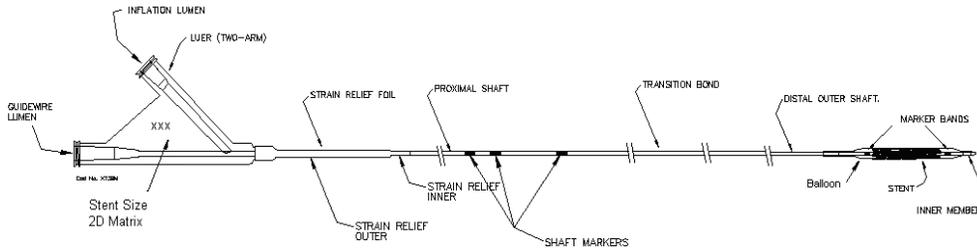


Figure 1-1: MicroTrac OTW Delivery System (with Stent)

The stent is crimped on various size delivery catheter balloons, which are sized from 2.25 to 4.0 mm. The Resolute Integrity available stent sizes are listed in Table 1-2.

Table 1-2: Resolute Integrity Stent Sizes

Diameter (mm)	Stent Length (mm)										
	8	9	12	14	15	18	22	26	30	34	38
2.25	✓	---	✓	✓	---	✓	✓	✓	✓	---	---
2.5	✓	---	✓	✓	---	✓	✓	✓	✓	---	---
2.75	✓	---	✓	✓	---	✓	✓	✓	✓	---	---
3.0	---	✓	✓	---	✓	✓	✓	✓	✓	✓	✓
3.5	---	✓	✓	---	✓	✓	✓	✓	✓	✓	✓
4.0	---	✓	✓	---	✓	✓	✓	✓	✓	✓	✓

Note: "—" indicates sizes not offered; "✓" indicates sizes offered.

1.2 Drug Component Description

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

1.2.1 Zotarolimus

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

The chemical structure of zotarolimus is shown in Figure 1-2:

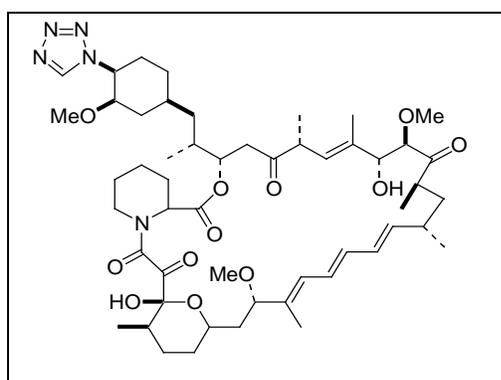


Figure 1-2: Zotarolimus Chemical Structure

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

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

1.2.2 Polymer System Description

The Resolute Integrity stent is comprised of a bare metal stent with a Parylene C primer coat and a coating that consists of a blend of the drug zotarolimus and the BioLinx polymer system. BioLinx is a blend of the Medtronic proprietary components C10 and C19, and PVP (polyvinyl pyrrolidone). The structural formula of the BioLinx polymer subunits are shown in Figure 1-3:

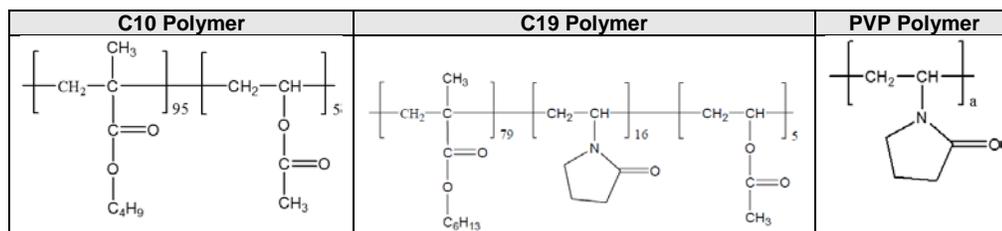


Figure 1-3: Chemical Structure of the BioLinx Polymer Subunits

1.2.3 Product Matrix and Zotarolimus Content

Table 1-3: Resolute Integrity Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number OTW	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSINT22508W	2.25	8	59
RSINT25008W	2.5	8	59
RSINT27508W	2.75	8	59
RSINT30009W	3.0	9	90
RSINT35009W	3.5	9	90
RSINT40009W	4.0	9	90
RSINT22512W	2.25	12	85
RSINT25012W	2.5	12	85
RSINT27512W	2.75	12	85
RSINT30012W	3.0	12	120
RSINT35012W	3.5	12	120
RSINT40012W	4.0	12	120
RSINT22514W	2.25	14	102
RSINT25014W	2.5	14	102
RSINT27514W	2.75	14	102
RSINT30015W	3.0	15	150
RSINT35015W	3.5	15	150
RSINT40015W	4.0	15	150
RSINT22518W	2.25	18	128
RSINT25018W	2.5	18	128
RSINT27518W	2.75	18	128
RSINT30018W	3.0	18	180
RSINT35018W	3.5	18	180
RSINT40018W	4.0	18	180
RSINT22522W	2.25	22	153
RSINT25022W	2.5	22	153
RSINT27522W	2.75	22	153
RSINT30022W	3.0	22	220
RSINT35022W	3.5	22	220
RSINT40022W	4.0	22	220
RSINT22526W	2.25	26	188
RSINT25026W	2.5	26	188
RSINT27526W	2.75	26	188
RSINT30026W	3.0	26	260
RSINT35026W	3.5	26	260
RSINT40026W	4.0	26	260
RSINT22530W	2.25	30	213
RSINT25030W	2.5	30	213
RSINT27530W	2.75	30	213

Table 1-3: Resolute Integrity Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number OTW	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RSINT30030W	3.0	30	300
RSINT35030W	3.5	30	300
RSINT40030W	4.0	30	300
RSINT30034W	3.0	34	340
RSINT35034W	3.5	34	340
RSINT40034W	4.0	34	340
RSINT30038W	3.0	38	380
RSINT35038W	3.5	38	380
RSINT40038W	4.0	38	380

2 INDICATIONS

The Resolute Integrity Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length \leq 35 mm in native coronary arteries with reference vessel diameters of 2.25 to 4.2 mm. In addition, the Resolute Integrity Zotarolimus-Eluting Coronary Stent System is indicated for treating *de novo* chronic total occlusions.

3 CONTRAINDICATIONS

The Resolute Integrity System is contraindicated for use in:

- Patients with known hypersensitivity or allergies to aspirin, heparin, bivalirudin, clopidogrel, prasugrel, ticagrelor, ticlopidine, drugs such as zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Patients with a known hypersensitivity to the BioLinx polymer or its individual components (see details in **Section 1.2.2 – Polymer System Description**).

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.

4 WARNINGS

- Please ensure that the inner package has not been opened or damaged as this would indicate the sterile barrier has been breached.
- The use of this product carries the same risks associated with coronary artery stent implantation procedures which include subacute and late vessel thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

5 PRECAUTIONS

- Only physicians who have received adequate training should perform implantation of the stent.
- Subsequent stent restenosis or occlusion may require repeat catheter-based treatments (including balloon dilatation) of the arterial segment containing the stent. The long-term outcome following repeat catheter-based treatments of previously implanted stents is not well characterized.
- The risks and benefits of stent implantation should be assessed for patients with a history of severe reaction to contrast agents.

- Do not expose or wipe the product with organic solvents such as alcohol.
- When drug eluting stents (DES) are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the RESOLUTE pivotal clinical trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.
- Care should be taken to control the position of the guide catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that is frequently associated with myocardial infarction (MI) or death. Data from the RESOLUTE clinical trials have been prospectively evaluated and adjudicated using the definition developed by the Academic Research Consortium (ARC) (see **Section 9.8 – Pooled Results of the Global RESOLUTE Clinical Trial Program (RESOLUTE FIM, RESOLUTE US, RESOLUTE AC, RESOLUTE International, RESOLUTE Japan)** for more information).

5.1 Pre- and Post-Procedure Antiplatelet Regimen

In the Medtronic RESOLUTE US Clinical Trial, RESOLUTE AC Clinical Trial, RESOLUTE International Study, RESOLUTE First-In-Man (FIM) Clinical Trial and RESOLUTE Japan Clinical Trial, the protocol specified administration of clopidogrel or ticlopidine prior to the procedure and for a period of at least 6 months post-procedure and up to 12 months in patients who were not at high risk of bleeding. Aspirin was administered prior to the procedure concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis. In the Medtronic RESOLUTE US Primary Enrollment Group, 95.9%, 93.8% and 46.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE AC Clinical Trial, 93.1%, 84.2% and 11.0% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE International Study, 95.9%, 91.1% and 34.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 36 months, respectively. In the RESOLUTE FIM Clinical Trial, 79.1%, 58.1% and 39.4% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE Japan Clinical Trial, 99.0%, 94.9% and 62.5% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE 38 mm Length Group, 92.8%, 91.4% and 61.5% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. See **Section 9 - CLINICAL STUDIES**, for more information.

5.1.1 Oral Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) using a combination treatment of aspirin with a P2Y₁₂ platelet inhibitor after percutaneous coronary intervention (PCI), reduces the risk of stent thrombosis and ischemic cardiac events, but may increase the risk of bleeding complications. The optimal duration of DAPT, specifically a P2Y₁₂ platelet inhibitor in addition to aspirin, following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. It is very important that the patient is compliant with the post-procedural antiplatelet recommendations.

Per 2016 ACC/AHA guidelines,¹ a daily aspirin dose of 81 mg is recommended indefinitely after PCI. A P2Y₁₂ platelet inhibitor should be given daily for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS).

In pivotal trials of current generation DES, subjects were prescribed DAPT for at least 6 months post-procedure, and most patients who were not at high risk of bleeding used DAPT for at least 12 months.

Consistent with the 2016 ACC/AHA guidelines,¹ and the DAPT Study,² longer duration of DAPT may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at high

¹ Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016; doi:10.1016/j.jacc.2016.03.513. For full text, please refer to the following website: <http://content.onlinejacc.org/article.aspx?doi=10.1016/j.jacc.2016.03.513>

bleeding risk. In patients who are at a high risk of bleeding or who develop significant bleeding during DAPT treatment, these guidelines suggest that a shorter DAPT duration may be reasonable. However, definitive evidence supporting the safety of short DAPT duration has not been established in prospective clinical studies.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of ischemic and bleeding risks, and patient preference.

Premature discontinuation or interruption of prescribed antiplatelet medication could result in an increased risk of stent thrombosis, MI or death.

Prior to PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient whether a DES and its associated recommended DAPT regimen is the appropriate PCI choice.

Following PCI, if elective noncardiac surgery requiring suspension of antiplatelet therapy is considered, the risks and benefits of the procedure should be weighed against the possible risk associated with interruption of antiplatelet therapy.

Patients who require premature DAPT discontinuation should be carefully monitored for cardiac events. At the discretion of the patient's treating physician(s), the antiplatelet therapy should be restarted as soon as possible.

5.2 Use of Multiple Stents

The long-term effects of zotarolimus are currently unknown. The extent of the patient's exposure to zotarolimus drug and the stent and polymer coating is directly related to the number of stents and total stent length implanted.

When multiple stents are required, stent materials should be of similar composition. Placing multiple stents of different materials in contact with each other may increase potential for corrosion. To avoid the possibility of dissimilar metal corrosion, do not implant stents of different materials in tandem where overlap or contact is possible.

Potential interactions of the Resolute Integrity stent with other drug-eluting or coated stents have not been evaluated and should be avoided whenever possible.

When using two wires, care should be taken when introducing, torquing and removing one or both guidewires to avoid entanglement. In this situation, it is recommended that one guidewire be completely withdrawn from the patient before removing any additional equipment.

5.3 Use in Conjunction with Other Procedures

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with Resolute Integrity stent implantation have not been established.

5.4 Brachytherapy

The safety and effectiveness of the Resolute Integrity stent in target lesions treated patients with prior brachytherapy, or the use of brachytherapy to treat in-stent restenosis of a Resolute Integrity stent, have not been established.

5.5 Use in Special Populations

Information on use of the Resolute Integrity stent in certain special patient populations is derived from clinical studies of the Resolute stent system, which uses the same drug (zotarolimus) – see **Section 7 OVERVIEW OF CLINICAL TRIALS** for a description of the other features of the Resolute Stent System compared to the Resolute Integrity Stent System.

5.5.1 Pregnancy

Pregnancy Category C. See **Section 6.6 Pregnancy** under **Drug Information**. There are no well-controlled studies in pregnant women or men intending to father children. The Resolute Integrity stent

² Mauri L, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. N Engl J Med. 2014;371:2155–66.

should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo or fetus. Effective contraception should be initiated before implanting a Resolute Integrity stent and for 1 year after implantation.

5.5.2 Lactation

It is not known whether zotarolimus is excreted in human milk. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant a Resolute Integrity stent, taking into account the importance of the stent to the mother. See **Section 6.7 – Lactation** under **Drug Information**.

5.5.3 Gender

Clinical studies of the Resolute stent did not suggest any significant differences in safety and effectiveness for male and female patients. See **Section 9.9.1 – Gender Analysis from the RESOLUTE Pooled On-label Dataset**.

5.5.4 Ethnicity

Clinical studies of the Resolute stent did not include sufficient numbers of patients to assess for differences in safety and effectiveness due to ethnicity.

5.5.5 Pediatric Use

The safety and effectiveness of the Resolute Integrity stent in patients below the age of 18 years have not been established.

5.5.6 Geriatric Use

Clinical studies of the Resolute stent did not have an upper age limit. Among the 1242 patients treated with the Resolute stent in the Resolute US Main Study that included 2.25 - 3.5 mm stents, 617 patients were age 65 or older and 88 patients were age 80 or older. A post hoc analysis of patients treated with the Resolute stent showed no significant differences between subjects under age 65 vs. age 65 and older in the rates of cardiac death, target vessel MI, target lesion revascularization, ARC definite or probable stent thrombosis, or target lesion failure at 12 months. The rate of all-cause death at 12 months was 0.3% in patients under age 65 vs. 1.8% in patients age 65 or older.

5.5.7 Lesion/Vessel Characteristics

The safety and effectiveness of the Resolute Integrity stent have not been established in the cerebral, carotid, or peripheral vasculature or in the following coronary disease patient populations:

- Patients with coronary artery reference vessel diameters < 2.25 mm or > 4.2 mm.
- Patients with coronary artery lesions longer than 35 mm or requiring more than one Resolute Integrity stent.
- Patients with evidence of an acute MI within 72 hours of intended stent implantation.
- Patients with vessel thrombus at the lesion site.
- Patients with lesions located in a saphenous vein graft, in the left main coronary artery, ostial lesions, or bifurcation lesions.
- Patients with diffuse disease or poor flow distal to identified lesions.
- Patients with tortuous vessels in the region of the target vessel or proximal to the lesion.
- Patients with in-stent restenosis.
- Patients with moderate or severe lesion calcification at the target lesion.
- Patients with occluded target lesions including chronic total occlusions.
- Patients with 3 vessel disease.
- Patients with a left ventricular ejection fraction of < 30%.
- Patients with a serum creatinine of > 2.5 mg/dl.
- Patients with longer than 24 months of follow-up.

5.6 Drug Interactions

The effect of potential drug interactions on the safety or effectiveness of the Resolute Integrity stent has not been investigated. While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP12) may interfere with the efficacy of zotarolimus. Zotarolimus is

metabolized by CYP3A4, a human cytochrome P450 enzyme. When administered concomitantly with 200 mg ketoconazole bid, a strong inhibitor of CYP3A4, zotarolimus produces less than a 2-fold increase in AUC_{0-inf} with no effect on C_{max} . Therefore, consideration should be given to the potential for drug interactions when deciding to place a Resolute Integrity stent in a patient who is taking drugs that are known substrates or inhibitors of the cytochrome P450 isoenzyme CYP3A4. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

Formal drug interaction studies have not been conducted with the Resolute Integrity stent.

5.7 Magnetic Resonance Imaging (MRI)

Non-clinical testing has demonstrated the Resolute Integrity Stent up to a total length of 120 mm is MR Conditional. It 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
- 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.

1.5 T

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 were 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.

3 T

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 were 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 14\LX\MR 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.

1.5 T and 3 T

The Resolute Integrity Stent should not move or migrate when exposed to MR scanning immediately post-implantation. MRI at 3 Tesla and 1.5 Tesla may be performed immediately following the implantation of the stent. Non-clinical testing at field strength greater than 3 Tesla 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 stent. The image artifact extends approximately 1 cm 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 ASTM F2119-01; the device lumen was always observed during scanning. This testing was completed using a GE SIGNA HDx with software version 14\LX\MR release 14.0.M5A.0828.b.

5.8 Stent Handling Precautions

- For single use only. The Resolute Integrity System is provided sterile. Do not resterilize or reuse this product. Note the "Use By" date on the product label. Do not use if package or product has been opened or damaged.
- Only the contents of the pouch should be considered sterile. The outside surface of the pouch is not sterile.
- Do not remove the contents of the pouch until the device will be used immediately.
- Do not remove the stent from the delivery balloon; removal may damage the stent and polymer coating and/or lead to stent embolization. The Resolute Integrity System is intended to perform as a system. The stent is not designed to be crimped onto another delivery device.
- Special care must be taken not to handle or in any way disrupt the stent on the balloon. This is most important while removing the catheter from the packaging, placing it over the guidewire, and advancing it through the rotating hemostatic valve and guide catheter hub.
- Do not try to straighten a kinked shaft or hypotube. Straightening a kinked metal shaft may result in breakage of the shaft.
- Stent manipulation (e.g., rolling the mounted stent with your fingers) may cause coating damage, contamination or dislodgement of the stent from the delivery system balloon.
- The Resolute Integrity System must not be exposed to any direct handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug elution.
- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in deployment of the stent.
- The Resolute Integrity stent delivery system should not be used in conjunction with any other stents or for post-dilatation.

5.9 Stent Placement Precautions

- The vessel must be pre-dilated with an appropriate sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 13.5 – Delivery Procedure**. Failure to do so may increase the risk of placement difficulty and procedural complications.
- Do not prepare or pre-inflate the balloon prior to stent deployment other than as directed. Use the balloon purging technique described in **Section 13 – DIRECTIONS FOR USE**.
- Guide catheters used must have lumen sizes that are suitable to accommodate the stent delivery system (see **Device Component Description** in Table 1-1).
- After preparation of the stent delivery system, do not induce negative pressure on the delivery catheter prior to placement of the stent across the lesion. This may cause premature dislodgment of the stent from the balloon or delivery difficulties.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as indicated on the product label. Use of pressures higher than those specified on the product label may result in a ruptured balloon with possible intimal damage and dissection.
- In small or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
- Implanting a stent may lead to a dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilatation, placement of additional stents, or other intervention).
- Do not expand the stent if it is not properly positioned in the vessel (see **Section 5 PRECAUTIONS-Stent/System Removal Precautions**).
- Placement of the stent has the potential to compromise side branch patency.
- Do not attempt to pull an unexpanded stent back through the guide catheter, as dislodgement of the stent from the balloon may occur. Remove as a single unit per instructions in **Section 5 PRECAUTIONS -Stent/System Removal Precautions**.
- Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure that the stent is in full contact with the arterial wall upon deflation of the balloon.
- Stent retrieval methods (e.g., use of additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Ensure full coverage of the entire lesion/dissection site so that there are no gaps between stents.
- Administration of appropriate anticoagulant, antiplatelet and coronary vasodilator therapy is critical to successful stent implantation.

5.10 Stent/System Removal Precautions

If removal of a stent system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the stent delivery system and cautiously withdraw the stent delivery system into the guide catheter. Should unusual resistance be felt at any time when withdrawing the stent towards the guide catheter, the stent delivery system and the guide catheter should be removed as a single unit. This must be done under direct visualization with fluoroscopy.

When removing the stent delivery system and guide catheter as a single unit:

- Do not retract the stent delivery system into the guide catheter. Maintain guidewire placement across the lesion and carefully pull back the stent delivery system until the proximal balloon marker of the stent delivery system is aligned with the distal tip of the guide catheter.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guide catheter enters into the arterial sheath, the catheter will straighten, allowing safe withdrawal of the stent delivery system into the guide catheter and the subsequent removal of the stent delivery system and the guide catheter from the arterial sheath.

Failure to follow these steps and/or applying excessive force to the stent delivery system can potentially result in loss or damage to the stent and/or stent delivery system components such as the balloon.

5.11 Post-Procedure

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, an optical coherence tomography (OCT) catheter, a coronary guidewire or a balloon catheter to avoid disrupting the stent placement, apposition, geometry, and/or coating.

- Post-dilatation: All efforts should be made to assure that the stent is not under dilated. If the deployed stent is not fully apposed to the vessel wall, the stent may be expanded further with a larger diameter balloon that is slightly shorter (about 2 mm) than the stent. The post-dilatation can be done using a low-profile, high pressure, non-compliant balloon catheter. The balloon should not extend outside of the stented region. **Do not use the stent delivery balloon for post-dilatation.**
- If patient requires MR imaging, refer to **Section 5.7 – Magnetic Resonance Imaging (MRI)**, above.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – Section 5.1 Pre- and Post-Procedure Antiplatelet Regimen**). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding), should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, antiplatelet therapy should be restarted as soon as possible.

6 DRUG INFORMATION

6.1 Mechanisms of Action

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 results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control.

6.2 Metabolism

Zotarolimus undergoes oxidative metabolism in the liver to form the demethyl and hydroxylated metabolites of the parent drug. Further metabolism can lead to the formation of hydroxyl-demethyl and dihydroxyl-demethyl metabolites. Enzymes of the CYP3A family are the major catalysts of oxidative metabolism of zotarolimus. Zotarolimus is a competitive inhibitor of CYP3A-dependent activities; however, the IC_{50} values (3 μ M and above) are many fold higher than the systemic concentrations expected following implantation of a drug-eluting stent. The anticipated zotarolimus blood levels in stented patients are expected to be less than 0.004 μ M, suggesting that clinically significant drug-drug interactions are unlikely.

6.3 Pharmacokinetics of the Resolute Stent

The pharmacokinetics information for the Resolute Integrity stent system is derived from a study conducted on the Resolute stent system. The Resolute Integrity stent system is similar to the Resolute stent system with regards to the stent design, 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 pharmacokinetics information from the RESOLUTE FIM PK Sub-study, as described below, is applicable to the Resolute Integrity stent system.

The pharmacokinetics (PK) of zotarolimus delivered from the Resolute Stent has been determined in patients with coronary artery disease after stent implantation in the Medtronic RESOLUTE FIM Clinical Trial. The dose of zotarolimus was calculated per stent unit surface area and the key pharmacokinetic parameters determined from these patients are provided in Table 6-1.

Table 6-1: Zotarolimus Pharmacokinetics in the Medtronic 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
β [§]	(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 _d /F [§]	(L)	1161.2	1449.3 ± 221.6	1181.2 ± 336.4	1658.6 ± 494.8

Notes

C _{max}	Maximum observed blood concentration	a	Primary dose groups
T _{max}	Time to C _{max}	†	No SD was reported when N = 1
AUC _{0-last}	Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration	‡	Harmonic mean ± pseudo-standard deviation
AUC _{0-inf}	AUC from time 0 to infinity (AUC _{0-inf}).	#	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
t _{1/2}	Harmonic mean half-life		
CL/F	Mean apparent clearance		
V _d /F	Apparent volume of distribution	\$	Not a true sample

The results in Table 6-1 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 and intravenous administration. Based on available zotarolimus pharmacokinetic data, systemic safety margins of ≥ 78-fold have been established for the Resolute stent at 380 µg due to the extended elution of zotarolimus from the BioLinx polymer.

6.4 Pharmacokinetics following Multi-dose Intravenous Administration of Zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. Table 6-2 provides a summary of the pharmacokinetic analysis.

Table 6-2: Pharmacokinetic Parameters (Mean ± Standard Deviation) in Patients Following Multi-dose Intravenous Administration of Zotarolimus

PK Parameters	Units	200 µg QD N = 15		400 µg QD N = 16		800 µg QD N = 16	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C _{max}	(ng/mL)	11.41 ± 1.38 ^y	11.93 ± 1.25	21.99 ± 3.79	23.31 ± 3.15	37.72 ± 7.00	41.79 ± 6.68
T _{max}	(h)	1.05 ± 0.04 ^y	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
AUC ₀₋₂₄	(ng•h/mL)	34.19 ± 4.39 ^y	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
t _{1/2} ^z	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL ^b	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

Notes

^x N = 16;

^y Harmonic mean ± pseudo-standard deviation

^z Clearance data is calculated using compartmental methods.

All other data presented in is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400 and 800 µg, zotarolimus was generally well tolerated by the subjects. No clinically significant abnormalities in physical examinations, vital signs or laboratory measurements were observed during the study.

6.5 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.5.1 Mutagenesis

Zotarolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the human peripheral lymphocyte chromosomal aberration assay, or the *in vivo* mouse micronucleus assay.

6.5.2 Carcinogenicity

No long-term studies in animals have been performed to evaluate the carcinogenic potential of zotarolimus. The carcinogenic potential of the Resolute stent is expected to be minimal based on the types and quantities of materials present.

6.5.3 Reproductive Toxicology

No effect on fertility or early embryonic development in female rats was observed following the IV administration of zotarolimus at dosages up to 100 µg/kg/day (approximately 19 times the cumulative blood exposure provided by Resolute stents coated with 300 µg zotarolimus).

For male rats, there was no effect on the fertility rate at IV dosages up to 30 µg/kg/day (approximately 21 times the cumulative blood exposure provided by Resolute stents coated with 300 µg zotarolimus). Reduced sperm counts and motility, and failure in sperm release were observed in male rats following the IV administration of zotarolimus for 28 days at dosages of > 30 µg/kg/day. Testicular germ cell degeneration and histological lesions were observed in rats following IV dosages of 30 µg/kg/day and above.

6.6 Pregnancy

Pregnancy Category C: There are no well-controlled studies in pregnant women, lactating women, or men intending to father children for this product.

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day resulted in embryoletality. Fetal ossification delays were also observed at this dosage, but no major fetal malformations or minor fetal anomalies were observed in this study. A 60 µg/kg/day dose in rats results in approximately 47 times the maximum blood level and about 11 times the cumulative blood exposure in patients receiving Resolute Integrity stents coated with 300 µg zotarolimus total dose.

No embryo-fetal effects were observed in pregnant rabbits administered zotarolimus in a developmental toxicity study at intravenous dosages up to 100 µg/kg/day. This dose in rabbits results in approximately 215 times the maximum blood level and about 37 times the cumulative blood exposure in patients receiving Resolute Integrity stents coated with 300 µg zotarolimus total dose.

Effective contraception should be initiated before implanting a Resolute Integrity stent and continued for one year post-stent implantation. The Resolute Integrity stent should be used in pregnant women only if potential benefits justify potential risks.

6.7 Lactation

It is not known whether zotarolimus is excreted in human milk. The potential adverse reactions in nursing infants from zotarolimus have not been determined. The pharmacokinetic and safety profiles of zotarolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from zotarolimus, a decision should be made whether to discontinue nursing or to implant the stent, taking into account the importance of the stent to the mother.

7 OVERVIEW OF CLINICAL TRIALS

Clinical Trials in support of Pre-market Approval:

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

The principal safety and effectiveness information for the Resolute stent was derived from the Global RESOLUTE Clinical Trial Program, which consists of the following clinical trials – the RESOLUTE United States Clinical Trial(R-US), the RESOLUTE All-Corners Clinical Trial(R-AC), the RESOLUTE International Study(R-Int), the RESOLUTE First-in-Man (FIM) Clinical Trial and the RESOLUTE Japan Clinical Trial(R-J). These five studies have evaluated the performance of the Resolute stent in improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to *de novo* lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 4.2 mm. Key elements of these studies are summarized below and in Table 7-1. The Resolute 38 mm Length Group was derived from subjects enrolled in the R-US and the RESOLUTE Asia study (R-Asia) (For 38 mm Length Group data see Table 7-1).

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 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 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 analysis, in which the cohort was derived from subjects treated with the 2.25 mm Resolute stent in the 2.25 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 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 6 months and up to 12 months in subjects who were not at a high risk of bleeding.

The 38 mm Length Group: In addition to the primary enrollment group, the 38 mm Length Group is made up of 38 mm subjects from RESOLUTE US 38 mm Length Sub-study pooled with subjects from the RESOLUTE Asia (R-Asia) 38 mm cohort (see description of the R-Asia study below).

- 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 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' patient 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 clinically indicated TLR within 12 months post-implantation. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 6 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 6 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 6 months. This trial had a subset of subjects undergoing pharmacokinetic (PK) assessments (see **Section 6.3** for the **Pharmacokinetics 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 6 months and up to 12 months in subjects who were not at a high risk of bleeding.

The RESOLUTE Asia (R Asia) study is a prospective, multi-center, non-randomized study. The primary objective of this study was to document the safety and effectiveness of the Endeavor Resolute Zotarolimus-Eluting Coronary Stent system in a patient population with long lesion(s). The Primary endpoint for the 38 mm cohort was target lesion failure (TLF) at 12 months post-procedure, defined as composite of cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. The RESOLUTE Asia trial was designed to be included in the pooled dataset for the RESOLUTE 38 mm Length Group

(38 mm subjects from RESOLUTE US and RESOLUTE Asia). A total of 109 subjects were enrolled in the 38 mm cohort across 17 clinical research sites from six (6) countries throughout Asia.

All 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.

Post-market Approval Study:

The RESOLUTE INTEGRITY US Post Market Study is a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects that are treated with the commercially available Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System. The objective of this study is to assess the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm in two groups of patients, specifically those patients receiving stents \leq 30 mm in length, referred to as the Primary Enrollment Group (PEG) and those patients who receive extended length stents (34 mm or 38 mm) referred to as the Extended Length (XL) Sub-study. The primary endpoint for this study is composite rate of cardiac death and target vessel myocardial infarction (MI) at 12 months.

Table 7-1 summarizes the clinical trial designs for the Global RESOLUTE Clinical Trial Program and Post-market Approval Study.

Table 7-1: Clinical Trial Comparisons

	Pre-market Approval Studies; Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	Post-market Approval Study	
	RESOLUTE US*	RESOLUTE AC ¹	RESOLUTE Int ²	RESOLUTE FIM ³	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG) ⁴	RESOLUTE INTEGRITY US (XL Sub-study) ⁵
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 	<ul style="list-style-type: none"> ■ Prospective ■ Multi-center ■ Non-randomized 	<ul style="list-style-type: none"> ■ Prospective ■ Multi-center ■ Non-randomized ■ Post approval 	<ul style="list-style-type: none"> ■ Prospective ■ Multi-center ■ Non-randomized ■ Post approval
Number of Subjects Enrolled	Total: 1516 - 2.25-3.5 mm Main Study -1242 subjects - 2.25 mm Cohort- 150 subjects - 2.25-3.5 mm Angio/IVUS sub-study - 100 subjects - 4.0 mm Sub-study -60 subjects - 38 mm Sub-study 114 subjects (38 mm Sub-study Total patient population was 223 subjects with 114 from RESOLUTE US and 109 from RESOLUTE Asia)	Total: 2292 (Resolute: 1140, Xience V: 1152)	Total: 2349	Total: 139	Total: 100	Total: 109	Total: 230	Total: 56
Lesion Criteria	<ul style="list-style-type: none"> ■ Single or two <i>de novo</i> lesions located in separate target vessels ■ Lesion(s) length ≤27 mm for the Primary Enrollment Group, ≤35 mm for the 38-mm Length Group ■ Target vessel with RVD between 2.25 to 4.2 mm 	<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 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 to 4.0 mm 	<ul style="list-style-type: none"> ■ Single <i>de novo</i> lesion ■ Lesion length from 14 to 27 mm ■ Target vessel with RVD between 2.5 and 3.5 mm 	<ul style="list-style-type: none"> ■ Single or two <i>de novo</i> lesions located in separate coronary arteries ■ Lesion(s) length ≤27 mm ■ Target vessel with RVD between 2.5 to 3.5 mm 	<ul style="list-style-type: none"> ■ Single or two <i>de novo</i> lesions located in separate target vessels ■ Lesion(s) length ≤35 mm ■ Target vessel with RVD between 3.0 to 4.0 mm ■ Patients may have received treatment of up to two lesions second lesion RVD (2.25 to 4.2 mm), if the lesions were located in separate target vessels. 	<ul style="list-style-type: none"> ■ Single target lesion or two target lesions located in separate target vessels ■ PEG: <ul style="list-style-type: none"> ■ Target lesion ≤27 mm ■ Target vessel with RVD between 2.25 to 4.2 mm. 	<ul style="list-style-type: none"> ■ Single target lesion or two target lesions located in separate target vessels ■ XL: <ul style="list-style-type: none"> ■ Target lesion ≤ 35 mm treated or lesion length ■ Target vessel with RVD between 2.25 to 4.2 mm.
Stent Sizes (Resolute)	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 38 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 38 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 34-38 mm
Product Used	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange AV100 Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System
Post-procedure Antiplatelet Therapy	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine ≥ 6 months	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine, for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated

Table 7-1: Clinical Trial Comparisons

	Pre-market Approval Studies; Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	Post-market Approval Study	
	RESOLUTE US*	RESOLUTE AC ¹	RESOLUTE Int ²	RESOLUTE FIM ³	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG) ⁴	RESOLUTE INTEGRITY US (XL Sub-study) ⁵
Follow-up	2.25-3.5 mm Main Study: 30 days and 9 months: clinical; 6, 12 and 18 months, 2.5 years: telephone 4.0 mm Sub-study: 8 months: clinical and angiographic; 6, 12 and 18 months, 2.5 years: telephone 2.25 - 3.5 mm Angio/IVUS Sub-study: 8 months: clinical and angiographic/IVUS 6, 12 and 18 months, 2.5 years: telephone 38 mm Length Sub-study: 30 days (R-US) and 9 months clinical visits (preferred), or patient contact 30 days (R-Asia); 6, 12, 18 months then annually at 2, 3, 4, 5 years	30 days and 12 months: clinical 13 months (455 subject subset): angiographic 6 months and 2.5 years: telephone	30 days, 6 months, 1-3 years: clinical or telephone	30 days: clinical 4 (30 subject subset) and 9 months (100 subject subset): clinical and angiographic/IVUS 6 months and 1-5 years: telephone	30 days and 12 months: clinical 8 months: angiographic/IVUS 6, 9 and 18 months and 2.5 years: telephone	30 days, 6, 9 (Clinical Visit), 12, 18 months then annually at 2 - 5 years	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact)	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact) 3-5 years (contact)
Status	60-month follow-up is complete. 551 subjects qualified for 18-month follow-up.	60-month follow-up is complete.	36-month follow-up is complete.	60-month follow-up complete.	60-month follow-up is complete.	60-month follow-up is complete	24-month follow-up is complete	12-month follow-up is complete

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

- ¹ The term 'AC' refers to All-comers.
- ² The term 'Int' refers to International.
- ³ The term 'FIM' refers to First-In-Man.
- ⁴ The term 'PEG' refers to Primary Enrollment Group.
- ⁵ The term 'XL' refers to Extended Length.

8 ADVERSE EVENTS

8.1 Observed Adverse Events

Observed adverse event experience with the Resolute stent is derived from the following five clinical trials: the RESOLUTE US, RESOLUTE AC, RESOLUTE Int, RESOLUTE FIM and RESOLUTE Japan. In addition, the adverse event experience from the Resolute Integrity US Primary Enrollment Group (PEG) Post-market Approval Study and the Extended Length (XL) Sub-study have been included.

See Section 9 CLINICAL STUDIES for a more complete description of the trial designs and results.

The Global RESOLUTE Clinical Trial Program has evaluated the performance of the Resolute stent in subjects, including those with diabetes mellitus, with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. The Resolute Integrity US Post-market Approval Study assessed the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries. Principal adverse events are shown in Table 8-1 below.

Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US ¹	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
	Resolute (N = 1402)	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)	Resolute Integrity (PEG) (N = 230)	RESOLUTE INTEGRITY US (XL Sub-study) (N = 56)
In-Hospital									
TLF ²	1.3% (18/1402)	3.7% (42/1140)	4.5% (52/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
TVF ³	1.3% (18/1402)	3.8% (43/1140)	4.7% (54/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
MACE ⁴	1.3% (18/1402)	3.8% (43/1140)	4.9% (56/1152)	2.7% (63/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
Total Death	0.0% (0/1402)	0.1% (1/1140)	0.8% (9/1152)	0.3% (7/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Cardiac Death	0.0% (0/1402)	0.1% (1/1140)	0.6% (7/1152)	0.3% (6/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Cardiac Death	0.0% (0/1402)	0.0% (0/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
TVMI ⁵	1.1% (16/1402)	3.1% (35/1140)	3.6% (42/1152)	2.2% (51/2349)	4.3% (6/139)	2.0% (2/100)	3.1% (7/223)	1.7% (4/230)	1.8% (1/56)
Q wave MI	0.1% (1/1402)	0.3% (3/1140)	0.4% (5/1152)	0.3% (8/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Q Wave MI	1.1% (15/1402)	2.8% (32/1140)	3.2% (37/1152)	1.8% (43/2349)	4.3% (6/139)	2.0% (2/100)	2.7% (6/223)	1.7% (4/230)	1.8% (1/56)
Cardiac Death or TVMI ⁶	1.1% (16/1402)	3.2% (36/1140)	4.0% (46/1152)	2.4% (56/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
Clinically Driven TVR ⁷	0.1% (2/1402)	0.9% (10/1140)	0.9% (10/1152)	0.4% (10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
TLR ⁸	0.1% (2/1402)	0.7% (8/1140)	0.7% (8/1152)	0.4% (10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
Non-TL TVR	0.0% (0/1402)	0.4% (4/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
ARC Del/Prob ST ⁹	0.0% (0/1402)	0.6% (7/1140)	0.3% (4/1152)	0.4% (9/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	1.8% (1/56)
30 Day									
MACE	1.4% (20/1399)	4.4% (50/1133)	5.2% (60/1146)	3.3% (78/2345)	4.3% (6/139)	3.0% (3/100)	4.5% (10/223)	3.0% (7/230)	3.6% (2/56)
12 Months									
TLF	4.7% (65/1390)	8.1% (92/1132)	8.5% (97/1142)	7.1% (165/2337)	7.2% (10/139)	4.0% (4/100)	5.4% (12/222)	4.9% (11/226)	7.4% (4/54)
TVF	6.2% (86/1390)	8.9% (101/1132)	9.7% (111/1142)	7.7% (180/2337)	7.2% (10/139)	5.0% (5/100)	6.8% (15/222)	7.1% (16/226)	7.4% (4/54)
MACE	5.5% (77/1390)	8.6% (97/1132)	9.8% (112/1142)	8.3% (193/2337)	8.6% (12/139)	5.0% (5/100)	6.3% (14/222)	5.8% (13/226)	9.3% (5/54)
Total Death	1.4% (19/1390)	1.6% (18/1132)	2.7% (31/1142)	2.4% (57/2337)	2.2% (3/139)	1.0% (1/100)	0.9% (2/222)	1.8% (4/226)	1.9% (1/54)
Cardiac Death	0.7% (10/1390)	1.3% (15/1132)	1.7% (19/1142)	1.5% (34/2337)	0.7% (1/139)	0.0% (0/100)	0.9% (2/222)	1.3% (3/226)	1.9% (1/54)
Non-Cardiac Death	0.6% (9/1390)	0.3% (3/1132)	1.1% (12/1142)	1.0% (23/2337)	1.4% (2/139)	1.0% (1/100)	0.0% (0/222)	0.4% (1/226)	0.0% (0/54)
TVMI	1.3% (18/1390)	4.2% (48/1132)	4.2% (48/1142)	3.0% (71/2337)	5.8% (8/139)	4.0% (4/100)	3.6% (8/222)	2.2% (5/226)	5.6% (3/54)
Q wave MI	0.1% (2/1390)	0.8% (9/1132)	0.4% (5/1142)	0.5% (12/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.0% (0/226)	1.9% (1/54)
Non-Q Wave MI	1.2% (16/1390)	3.5% (40/1132)	3.8% (43/1142)	2.5% (59/2337)	5.8% (8/139)	4.0% (4/100)	2.7% (6/222)	2.2% (5/226)	3.7% (2/54)
Cardiac Death or TVMI	2.0% (28/1390)	5.3% (60/1132)	5.5% (63/1142)	4.2% (99/2337)	6.5% (9/139)	4.0% (4/100)	4.5% (10/222)	3.5% (8/226)	7.4% (4/54)
Clinically Driven TVR	4.6% (64/1390)	4.9% (55/1132)	4.8% (55/1142)	4.2% (99/2337)	0.7% (1/139)	1.0% (1/100)	2.7% (6/222)	4.4% (10/226)	1.9% (1/54)
TLR	2.9% (40/1390)	3.9% (44/1132)	3.4% (39/1142)	3.5% (81/2337)	0.7% (1/139)	0.0% (0/100)	1.4% (3/222)	2.2% (5/226)	1.9% (1/54)
Non-TL TVR	2.2% (30/1390)	1.9% (21/1132)	2.2% (25/1142)	1.2% (27/2337)	0.0% (0/139)	1.0% (1/100)	1.4% (3/222)	2.2% (5/226)	0.0% (0/54)
ARC Del/Prob ST ⁹	0.1% (2/1390)	1.6% (18/1132)	0.7% (8/1142)	0.9% (20/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.9% (2/226)	1.9% (1/54)
Latest Follow-up									
	60 Months	60 Months		36 Months	60 Months	60 Months	60 Months	24 Months	
TLF	12.3% (164/1329)	17.0% (191/1123)	16.2% (183/1133)	11.4% (261/2284)	11.0% (15/136)	6.1% (6/98)	13.8% (30/217)	9.1% (20/219)	
TVF	17.5% (233/1329)	20.0% (225/1123)	19.1% (216/1133)	12.9% (294/2284)	13.2% (18/136)	10.2% (10/98)	17.1% (37/217)	12.3% (27/219)	
MACE	18.0% (239/1329)	21.9% (246/1123)	21.6% (245/1133)	14.4% (329/2284)	16.2% (22/136)	14.3% (14/98)	17.5% (38/217)	11.0% (24/219)	
Total Death	9.6% (127/1329)	11.0% (123/1123)	10.8% (122/1133)	6.1% (139/2284)	6.6% (9/136)	7.1% (7/98)	6.5% (14/217)	2.7% (6/219)	
Cardiac Death	4.1% (55/1329)	6.5% (73/1123)	5.7% (65/1133)	3.6% (82/2284)	1.5% (2/136)	1.0% (1/98)	4.1% (9/217)	1.8% (4/219)	
Non-Cardiac Death	5.4% (72/1329)	4.5% (50/1123)	5.0% (57/1133)	2.5% (57/2284)	5.1% (7/136)	6.1% (6/98)	2.3% (5/217)	0.9% (2/219)	
TVMI	3.2% (43/1329)	5.7% (64/1123)	5.7% (65/1133)	3.9% (89/2284)	6.6% (9/136)	4.1% (4/98)	6.0% (13/217)	4.1% (9/219)	
Q wave MI	0.4% (5/1329)	1.3% (15/1123)	0.8% (9/1133)	0.9% (20/2284)	0.0% (0/136)	0.0% (0/98)	0.9% (2/217)	0.9% (2/219)	
Non-Q Wave MI	2.9% (38/1329)	4.6% (52/1123)	4.9% (56/1133)	3.0% (69/2284)	6.6% (9/136)	4.1% (4/98)	5.1% (11/217)	3.2% (7/219)	

Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US ¹	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
	Resolute (N = 1402)	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)	Resolute Integrity (PEC) (N= 230)	RESOLUTE INTEGRITY US (XL Sub-study) (N=56)
Cardiac Death or TVMI	6.7% (89/1329)	11.5% (129/1123)	10.6% (120/1133)	7.0% (161/2284)	8.1% (11/136)	5.1% (5/98)	8.8% (19/217)	5.9% (13/219)	
Clinically Driven TVR	12.5% (166/1329)	11.4% (128/1123)	10.9% (123/1133)	7.4% (168/2284)	5.1% (7/136)	5.1% (5/98)	9.7% (21/217)	8.2% (18/219)	
TLR	6.5% (86/1329)	7.8% (88/1123)	7.1% (81/1133)	5.7% (130/2284)	2.9% (4/136)	1.0% (1/98)	6.0% (13/217)	5.0% (11/219)	
Non-TL TVR	8.1% (107/1329)	6.1% (68/1123)	6.1% (69/1133)	2.6% (59/2284)	2.2% (3/136)	4.1% (4/98)	3.7% (8/217)	4.1% (9/219)	
ARC Del/Prob ST	0.5% (7/1329)	2.4% (27/1123)	1.7% (19/1133)	1.1% (26/2284)	0.0% (0/136)	0.0% (0/98)	1.4% (3/217)	1.8% (4/219)	

Notes

N = The total number of subjects enrolled.

The numbers are % (Count/Number of Eligible Subjects).

Subjects are only counted once for each time period.

NA = Not applicable; variable and/or time point not calculated

In-hospital is defined as hospitalization less than or equal to the discharge date

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

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

36-month timeframe includes follow-up window (1080 days ± 30 days).

60-month timeframe includes follow-up window (1800 days ± 30 days).

¹ Primary Enrollment Group consisted of 1402 subjects, including 1242 subjects in the 2.25 - 3.5 mm Main Study, 100 subjects in the 2.25 - 3.5 mm Angio/IVUS Sub-study and 60 subjects in the 4.0 mm Sub-study. The Primary Enrollment Group does not include the 38 mm Length Sub-study

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

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

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

⁵ TVMI is composed of both Q wave and non-Q wave MI which are not clearly attributable to a non-target vessel.

Q wave MI defined when any occurrence of chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data, or new pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data, the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.

Non-Q Wave MI is defined as elevated CK ≥ 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves.

[Note: Periprocedural MIs (events < 48 hours post-PCI) that did not fulfill the criteria for Q-wave MI are included in Non-Q Wave MI category.

Periprocedural MIs did not require clinical symptoms or ECG evidence of myocardial ischemia, and in the absence of CK measurements, were based on an elevated CKMB > 3 X the upper laboratory normal, an elevated troponin > 3 X the upper laboratory normal, or CEC adjudication of the clinical scenario.]

⁶ Cardiac death/TVMI is defined as Cardiac Death or Myocardial Infarction not clearly attributable to a non-target vessel.

⁷ Target Vessel Revascularization (TVR) is defined as any clinically-driven repeat intervention of the target vessel by PCI or CABG.

⁸ Target Lesion Revascularization (TLR) is defined as a clinically-driven repeat intervention of the target lesion by PCI or CABG

⁹ See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

8.2 Potential Adverse Events

8.2.1 Potential Adverse Events Related to Zotarolimus

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted. The actual side effects/complications that may be associated with the use of zotarolimus are not fully known.

The 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

8.2.2 Potential Adverse Events Related to BioLinx polymer

Although the type of risks of the BioLinx polymer coating are expected to be no different than those of other stent coatings, the potential for these risks are currently unknown as the coating has limited previous use in humans. These risks may include but are not limited to the following:

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

8.2.3 Potential Risks Associated with Percutaneous Coronary Diagnostic and Treatment Procedures

Other risks associated with using this device are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks (in alphabetical order) may include but are not limited to the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias, including ventricular fibrillation
- Balloon rupture
- Bleeding
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension / hypertension
- Incomplete stent apposition
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis
- Peripheral ischemia / peripheral nerve injury
- Renal Failure
- Restenosis of the stented artery

- Shock / pulmonary edema
- Stable or Unstable angina
- Stent deformation, collapse, or fracture
- Stent migration or embolization
- Stent misplacement
- Stroke / transient ischemic attack
- Thrombosis (acute, subacute or late)

9 CLINICAL STUDIES

9.1 Results of the RESOLUTE US Trial

Primary Objective: 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 to 4.2 mm.

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 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 and 4.2 mm, lesions with stenosis $\geq 50\%$ but $< 100\%$, lesion length ≤ 27 mm (≤ 35 for the 38 mm Length Group), 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 analysis
- The 2.25 mm to 3.5 mm Angio/IVUS Sub-study
- The 4.0 mm stent Sub-study
- The 38 mm Length Group³

Figure 9-1 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.

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 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 Angio/IVUS Sub-study were consented to angiographic and IVUS follow-up at 8 months post-procedure. All subjects enrolled in the 4.0 mm Sub-study were consented to angiographic follow-up at 8 months post-procedure. 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 subjects who were not at a high risk of bleeding.

The 12 month and 5 year follow-up rates for the primary enrollment group were 97.3% (1364/1402) and 92.2% (1293/1402) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

³ The 38 mm data was analyzed separately from the R-US Primary Enrollment Group.

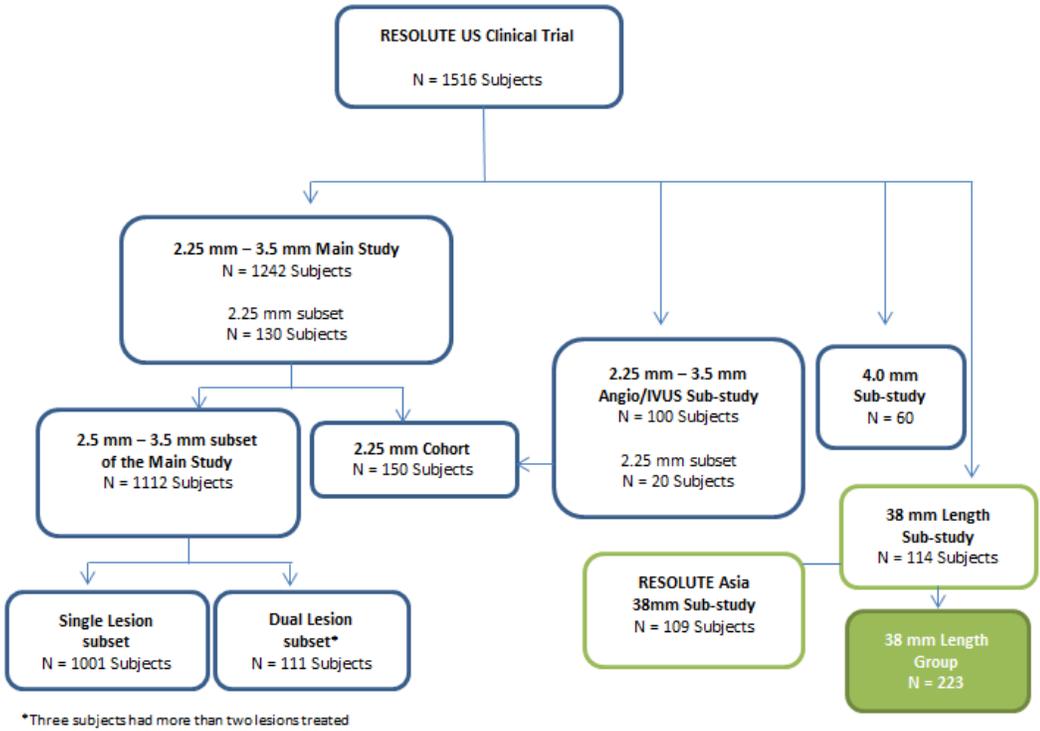


Figure 9-1: Study Designation of RESOLUTE US Clinical Trial

2.5 mm – 3.5 mm Subset of the Main Study

Demographics and clinical characteristics: There were 1112 subjects (1001 single lesion subjects and 111 dual vessel subjects). The 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 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% of lesions (921/1215) were characterized as ACC/AHA type B2/C.

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. TLF was defined as the 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.

Results: 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 3.6% (36/994) 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 9-1: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - Primary Endpoint Analysis)
- Table 9-2: 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 9-3: 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 9-4: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months
- Table 9-5: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study Clinical Results – Single versus Dual Lesion Subjects

Table 9-1: 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	3.6% (36/994)	6.5% (70/1076)	-2.9%	-1.4%	< 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 \pm 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 \pm 30 days).

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 3.3%, to be compared at a 0.05 significance level.

Table 9-2: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - Principal Safety and Effectiveness - Single Lesion Outcome versus Historical Control (Endeavor)

Outcomes at 12 Months	Single Lesion 2.5 mm - 3.5 mm Subset of Main study (N = 1001 subjects)	Single Lesion Historical Control (Endeavor) (N = 1092 subjects)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	3.6% (36/994)	6.5% (70/1076)
TVF	5.0% (50/994)	8.3% (89/1076)
MACE	4.3% (43/994)	7.0% (75/1076)
EFFECTIVENESS		
Clinically Driven TVR	3.7% (37/994)	6.0% (65/1076)
TLR	2.1% (21/994)	4.0% (43/1076)
TLR, PCI	1.8% (18/994)	3.7% (40/1076)
TLR, CABG	0.3% (3/994)	0.5% (5/1076)
Non-TL TVR	1.8% (18/994)	2.5% (27/1076)
Non-TL TVR, PCI	1.5% (15/994)	2.1% (23/1076)
Non-TL TVR, CABG	0.3% (3/994)	0.5% (5/1076)
SAFETY		
Total Death	1.0% (10/994)	1.3% (14/1076)
Cardiac Death	0.5% (5/994)	0.8% (9/1076)
Non-Cardiac Death	0.5% (5/994)	0.5% (5/1076)
Cardiac Death or TVMI	1.7% (17/994)	3.2% (34/1076)
TVMI	1.2% (12/994)	2.4% (26/1076)
Q wave MI	0.2% (2/994)	0.3% (3/1076)
Non-Q wave MI	1.0% (10/994)	2.1% (23/1076)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/994)	0.7% (7/1076)
Definite	0.0% (0/994)	0.5% (5/1076)
Probable	0.0% (0/994)	0.2% (2/1076)
ACUTE SUCCESS		
Procedure Success	98.7% (982/995)	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.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

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

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-3: 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 Through 60 Months

2.5 mm – 3.5 mm subset of the Main Study (N = 1112)	Outcomes at 12 Months	Outcomes at 60 Months
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	3.8% (42/1105)	10.9% (115/1051)
TVF	5.2% (58/1105)	16.1% (169/1051)
MACE	4.6% (51/1105)	16.7% (175/1051)
EFFECTIVENESS		
Clinically Driven TVR	3.9% (43/1105)	11.4% (120/1051)
TLR	2.3% (25/1105)	5.7% (60/1051)
TLR, PCI	2.0% (22/1105)	5.0% (53/1051)
TLR, CABG	0.3% (3/1105)	0.7% (7/1051)
Non-TL TVR	1.9% (21/1105)	7.3% (77/1051)
Non-TL TVR, PCI	1.5% (17/1105)	6.4% (67/1051)
Non-TL TVR, CABG	0.4% (4/1105)	1.0% (10/1051)
SAFETY		
Total Death	1.0% (11/1105)	8.8% (92/1051)
Cardiac Death	0.5% (5/1105)	3.4% (36/1051)
Non-Cardiac Death	0.5% (6/1105)	5.3% (56/1051)
Cardiac Death or TVMI	1.7% (19/1105)	6.0% (63/1051)
TVMI	1.3% (14/1105)	3.2% (34/1051)
Q wave MI	0.2% (2/1105)	0.4% (4/1051)
Non-Q wave MI	1.1% (12/1105)	2.9% (30/1051)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/1105)	0.5% (5/1051)
Definite	0.0% (0/1105)	0.3% (3/1051)
Probable	0.0% (0/1105)	0.2% (2/1051)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-4: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	2.5 mm - 3.5 mm subset of the Main Study (N = 1112)
Stent Thrombosis	0.5% (5/1051)
Acute (0 - 1 day)	0.0% (0/1051)
Subacute (2 - 30 days)	0.0% (0/1051)
Late (31 - 360 days)	0.0% (0/1051)
Very Late (361 - 1800 days)	0.5% (5/1051)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

60-month timeframe includes follow-up window (1800 days \pm 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 9-5: RESOLUTE US 2.5 mm - 3.5 mm Subset of the Main Study Clinical Results – Single versus Dual Lesion Subjects

	Single Lesion 2.5 mm -3.5 mm Subset of Main study (N=1001 subjects)	Dual Lesion* 2.5 mm - 3.5 mm Subset of Main study (N=111 subjects)	Single Lesion 2.5-3.5 mm Subset of Main study (N = 1001 subjects)	Dual Lesion* 2.5-3.5 mm Subset of Main study (N = 111 subjects)
COMPOSITE SAFETY AND EFFECTIVENESS	Outcomes at 12 Months		Outcomes at 60 Months	
TLF	3.6% (36/994)	5.4% (6/111)	10.3% (98/947)	16.3% (17/104)
TVF	5.0% (50/994)	7.2% (8/111)	15.7% (149/947)	19.2% (20/104)
MACE	4.3% (43/994)	7.2% (8/111)	16.3% (154/947)	20.2% (21/104)
EFFECTIVENESS				
Clinically Driven TVR	3.7% (37/994)	5.4% (6/111)	11.2% (106/947)	13.5% (14/104)
TLR	2.1% (21/994)	3.6% (4/111)	5.3% (50/947)	9.6% (10/104)
TLR, PCI	1.8% (18/994)	3.6% (4/111)	4.5% (43/947)	9.6% (10/104)
TLR, CABG	0.3% (3/994)	0.0% (0/111)	0.7% (7/947)	0.0% (0/104)
Non-TL TVR	1.8% (18/994)	2.7% (3/111)	7.4% (70/947)	6.7% (7/104)
Non-TL TVR, PCI	1.5% (15/994)	1.8% (2/111)	6.7% (63/947)	3.8% (4/104)
Non-TL TVR, CABG	0.3% (3/994)	0.9% (1/111)	0.7% (7/947)	2.9% (3/104)
SAFETY				
Total Death	1.0% (10/994)	0.9% (1/111)	8.8% (83/947)	7.7% (8/104)
Cardiac Death	0.5% (5/994)	0.0% (0/111)	3.3% (31/947)	4.8% (5/104)
Non-Cardiac Death	0.5% (5/994)	0.9% (1/111)	5.5% (52/947)	2.9% (3/104)
Cardiac Death or TVMI	1.7% (17/994)	1.8% (2/111)	5.9% (56/947)	6.7% (7/104)
TVMI	1.2% (12/994)	1.8% (2/111)	3.3% (31/947)	2.9% (3/104)
Q wave MI	0.2% (2/994)	0.0% (0/111)	0.4% (4/947)	0.0% (0/104)
Non-Q wave MI	1.0% (10/994)	1.8% (2/111)	2.9% (27/947)	2.9% (3/104)
Stent Thrombosis ARC defined				
Definite/Probable	0.0% (0/994)	0.0% (0/111)	0.5% (5/947)	0.0% (0/104)
Definite	0.0% (0/994)	0.0% (0/111)	0.3% (3/947)	0.0% (0/104)
Probable	0.0% (0/994)	0.0% (0/111)	0.2% (2/947)	0.0% (0/104)
ACUTE SUCCESS				
Procedure Success	98.7% (982/995)	98.2% (108/110)		

Notes

* Included in the 111 subject dual lesion subset are 95 subjects with 1 treated lesion within 2 different vessels, 13 subjects with 2 treated lesions within a single vessel, 1 subject with 3 treated lesions within a single vessel, and 2 subjects with 1 treated lesion within a single vessel plus 2 treated lesions within a different single vessel.

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

2.25 mm Cohort

Demographics and clinical characteristics: There were 150 subjects. The mean age of all subjects was 66.3 years with 64.7% (97/150) 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 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% of lesions (133/196) were characterized as ACC/AHA type B2/C.

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 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.

Results: The Resolute stent 2.25 mm Cohort met the 12-month TLF rate primary endpoint performance goal of 20%, with a rate of 4.8% (7/147) 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 9-6: RESOLUTE US 2.25 mm Cohort - Primary Endpoint Analysis
- Table 9-7: RESOLUTE US 2.25 mm Cohort - Principal Safety and Effectiveness
- Table 9-8: RESOLUTE US 2.25 mm Cohort - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

Table 9-6: RESOLUTE US 2.25 mm Cohort - Primary Endpoint Analysis

2.25 mm Cohort	Resolute (N = 150)	Performance Goal	Upper One-sided 95% CI ¹	P-value ²
12-month TLF	4.8% (7/147)	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 2.25 mm 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 9-7: RESOLUTE US 2.25 mm Cohort – Principal Safety and Effectiveness

Outcomes at 12 Months	2.25 mm Cohort (N = 150)	2.25 mm Cohort (N = 150)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	5.4% (8/147)	18.5% (27/146)
TVF	8.2% (12/147)	27.4% (40/146)
MACE	6.8% (10/147)	23.3% (34/146)
EFFECTIVENESS		
Clinically Driven TVR	6.8% (10/147)	19.9% (29/146)
TLR	4.1% (6/147)	8.2% (12/146)
TLR, PCI	4.1% (6/147)	8.2% (12/146)
TLR, CABG	0.0% (0/147)	0.0% (0/146)
Non-TL TVR	2.7% (4/147)	13.7% (20/146)
Non-TL TVR, PCI	2.7% (4/147)	11.6% (17/146)
Non-TL TVR, CABG	0.0% (0/147)	2.1% (3/146)
SAFETY		
Total Death	2.7% (4/147)	15.1% (22/146)
Cardiac Death	1.4% (2/147)	10.3% (15/146)
Non-Cardiac Death	1.4% (2/147)	4.8% (7/146)
Cardiac Death or TVMI	2.0% (3/147)	12.3% (18/146)
TVMI	0.7% (1/147)	3.4% (5/146)
Q wave MI	0.0% (0/147)	0.7% (1/146)
Non-Q wave MI	0.7% (1/147)	2.7% (4/146)
Stent Thrombosis ARC defined		
Definite/Probable	1.4% (2/147)	1.4% (2/146)
Definite	0.7% (1/147)	0.7% (1/146)
Probable	0.7% (1/147)	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.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-8: RESOLUTE US 2.25 mm Cohort - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	2.25 mm Cohort (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- 360 days)	0.7% (1/146)
Very Late (361 – 1800 days)	0.0% (0/146)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 - 3.5 mm Angio/IVUS Sub-study

Demographics and clinical characteristics: 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 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% of lesions (79/104) were characterized as ACC/AHA type B2/C.

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.

Results: 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 8-month in-stent late LL historical control 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 9-9: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Primary Endpoint Analysis
- Table 9-10: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Principal Safety and Effectiveness
- Table 9-11: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 60 Months
- Table 9-12: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Angiographic and IVUS Results

Table 9-9: RESOLUTE US 2.25 - 3.5 mm Angio/IVUS Sub-study - Primary Endpoint Analysis

2.25-3.5 mm Angio/IVUS Sub-study	Resolute (N = 100, M =104)	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.

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 0.16 mm, to be compared at a 0.05 significance level.

Table 9-10: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - Principal Safety and Effectiveness

	2.25-3.5 mm Angio/IVUS Sub-study (N = 100)	2.25 mm - 3.5 mm Angio/IVUS Sub-study (N = 100)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	12.1% (12/99)	18.6% (18/97)
TVF	13.1% (13/99)	20.6% (20/97)
MACE	13.1% (13/99)	21.6% (21/97)
EFFECTIVENESS		
Clinically Driven TVR	10.1% (10/99)	16.5% (16/97)
TLR	8.1% (8/99)	12.4% (12/97)
TLR, PCI	7.1% (7/99)	3.1% (3/97)
TLR, CABG	1.0% (1/99)	11.3% (11/97)
Non-TL TVR	4.0% (4/99)	8.2% (8/97)
Non-TL TVR, PCI	4.0% (4/99)	7.2% (7/97)
Non-TL TVR, CABG	0.0% (0/99)	2.1% (2/97)
SAFETY		
Total Death	4.0% (4/99)	10.3% (10/97)
Cardiac Death	3.0% (3/99)	6.2% (6/97)
Non-Cardiac Death	1.0% (1/99)	4.1% (4/97)
Cardiac Death or TVMI	4.0% (4/99)	7.2% (7/97)
TVMI	1.0% (1/99)	2.1% (2/97)
Q wave MI	0.0% (0/99)	0.0% (0/97)
Non-Q wave MI	1.0% (1/99)	2.1% (2/97)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/99)	0.0% (0/97)
Definite	0.0% (0/99)	0.0% (0/97)
Probable	0.0% (0/99)	0.0% (0/97)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-11: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months.

	2.25-3.5 mm Angio/IVUS Sub-study (N = 100)
Stent Thrombosis	0.0% (0/97)
Acute (0 - 1 day)	0.0% (0/97)
Subacute (2 - 30 days)	0.0% (0/97)
Late (31 – 360 days)	0.0% (0/97)
Very Late (361 - 1800 days)	0.0% (0/97)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-12: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study -
Angiographic and IVUS Results**

Outcomes at 8 Months	2.25-3.5 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

Demographics and Clinical Characteristics: 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 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% of lesions (57/72) were characterized as ACC/AHA type B2/C.

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 the ENDEAVOR II trial (8-month late LL).

Results: 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 9-13: RESOLUTE US 4.0 mm Sub-study - Primary Endpoint Analyses
- Table 9-14: RESOLUTE US 4.0 mm Sub-study – Principal Safety and Effectiveness
- Table 9-15: RESOLUTE US 4.0 mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis through 60 Months
- Table 9-16: RESOLUTE US 4.0 mm Sub-study - Angiographic Results

Table 9-13: 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% CI ¹	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 ± standard error (number of evaluable lesions).

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 4.0 mm 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 superiority test using asymptotic test statistic, to be compared at a 0.05 significance level.

Table 9-14: RESOLUTE US 4.0 mm Sub-study – Principal Safety and Effectiveness

	4.0 mm Sub-Study (N = 60)	4.0 mm Sub-Study (N = 60)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	6.8% (4/59)	12.7% (7/55)
TVF	6.8% (4/59)	14.5% (8/55)
MACE	8.5% (5/59)	23.6% (13/55)
EFFECTIVENESS		
Clinically Driven TVR	3.4% (2/59)	9.1% (5/55)
TLR	3.4% (2/59)	7.3% (4/55)
TLR, PCI	3.4% (2/59)	7.3% (4/55)
TLR, CABG	0.0% (0/59)	0.0% (0/55)
Non-TL TVR	1.7% (1/59)	7.3% (4/55)
Non-TL TVR, PCI	1.7% (1/59)	5.5% (3/55)
Non-TL TVR, CABG	0.0% (0/59)	1.8% (1/55)
SAFETY		
Total Death	1.7% (1/59)	10.9% (6/55)
Cardiac Death	0.0% (0/59)	0.0% (0/55)
Non-Cardiac Death	1.7% (1/59)	10.9% (6/55)
Cardiac Death or TVMI	3.4% (2/59)	5.5% (3/55)
TVMI	3.4% (2/59)	5.5% (3/55)
Q wave MI	0.0% (0/59)	0.0% (0/55)
Non-Q wave MI	3.4% (2/59)	5.5% (3/55)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/59)	0.0% (0/55)
Definite	0.0% (0/59)	0.0% (0/55)
Probable	0.0% (0/59)	0.0% (0/55)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-15: RESOLUTE US 4.0 mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	4.0 mm Sub-study (N = 60)
Stent Thrombosis	0.0% (0/55)
Acute (0 - 1 day)	0.0% (0/55)
Subacute (2 - 30 days)	0.0% (0/55)
Late (31 – 360 days)	0.0% (0/55)
Very Late (361 - 1800 days)	0.0% (0/55)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-16: RESOLUTE US 4.0 mm 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.

RESOLUTE US – Primary Enrollment Group - Gender Analysis

Table 9-17 shows the baseline demographic and clinical characteristics stratified by gender for subjects in the pooled RESOLUTE US analysis, 445/1402 (31.7%) subjects were female and 957/1402 (68.3%) were male. Consistent with other DES clinical studies, female patients were older, had a higher rate of diabetes and hypertension and had smaller reference vessel diameters (RVD).

Table 9-17: RESOLUTE US Baseline Demographic and Lesion Characteristics Male vs. Female

Patient Characteristics	Male (N = 957)	Female (N = 445)	p-value
Age (Years)	63.14±10.48 (957)	66.23±10.76 (445)	<.001
History of smoking/tobacco use	67.0% (641/957)	52.8% (235/445)	<.001
Prior PCI	34.2% (327/957)	29.4% (131/445)	0.087
Hyperlipidemia	88.5% (847/957)	86.1% (383/445)	0.221
Diabetes Mellitus	31.3% (300/957)	40.9% (182/445)	<.001
Insulin Dependent	7.2% (69/957)	14.8% (66/445)	<.001
Hypertension	82.2% (787/957)	88.3% (393/445)	0.004
Prior MI	24.6% (232/943)	15.1% (66/436)	<.001
Prior CABG	10.6% (101/957)	5.2% (23/445)	<.001
Ejection fraction - Qualitative			0.028
<30%	0.12% (1/823)	0.26% (1/386)	
30-40%	6.68% (55/823)	3.37% (13/386)	
>40%	93.20% (767/823)	96.37% (372/386)	
Lesion Class			0.022
A	5.55% (60/1082)	7.64% (37/484)	
B1	17.10% (185/1082)	22.11% (107/484)	
B2	30.87% (334/1082)	27.48% (133/484)	
C	46.49% (503/1082)	42.77% (207/484)	
Moderate/Severe Calcification	26.0% (281/1082)	28.9% (140/484)	0.241
Pre procedure RVD	2.62±0.48 (1082)	2.53±0.44 (484)	<.001
Pre procedure MLD	0.75±0.35 (1082)	0.79±0.34 (484)	0.058
Pre procedure Diameter Stenosis	71.43±11.57 (1082)	68.98±11.24 (484)	<.001
Lesion Length	13.27±5.89 (1082)	12.60±5.83 (484)	0.036

The 12 month rate of TLF was 4.5% in males and 5.0% in females (Table 9-18). 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 9-18: RESOLUTE US Primary Enrollment Group - Clinical Endpoints by Gender – Principal Safety and Effectiveness to 60 Months

	Male (N = 957)	Female (N = 445)
Safety Measures to 12 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.5% (43/952)	5.0% (22/438)
TVF	5.7% (54/952)	7.3% (32/438)
MACE	5.6% (53/952)	5.5% (24/438)
EFFECTIVENESS		
Clinically Driven TVR	4.4% (42/952)	5.0% (22/438)
Clinically Driven TLR	3.0% (29/952)	2.5% (11/438)
SAFETY		
Death	1.4% (13/952)	1.4% (6/438)
Cardiac Death	0.6% (6/952)	0.9% (4/438)
Non Cardiac Death	0.7% (7/952)	0.5% (2/438)
TVMI (Extended Historical Definition)	1.1% (10/952)	1.8% (8/438)
Cardiac Death or Target Vessel MI (TVMI)	1.7% (16/952)	2.7% (12/438)
Stent Thrombosis ARC defined		
Definite/Probable	0.2% (2/952)	0.0% (0/438)
Definite	0.1% (1/952)	0.0% (0/438)
Probable	0.1% (1/952)	0.0% (0/438)
Safety Measures to 60 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	12.4% (113/909)	12.1% (51/420)
TVF	17.5% (159/909)	17.6% (74/420)
MACE	18.0% (164/909)	17.9% (75/420)
EFFECTIVENESS		
Clinically Driven TVR	12.7% (115/909)	12.1% (51/420)
Clinically Driven TLR	6.9% (63/909)	5.5% (23/420)
SAFETY		
Death	9.4% (85/909)	10.0% (42/420)
Cardiac Death	4.0% (36/909)	4.5% (19/420)
Non Cardiac Death	5.4% (49/909)	5.5% (23/420)
TVMI (Extended Historical Definition)	2.8% (25/909)	4.3% (18/420)
Cardiac Death or Target Vessel MI (TVMI)	6.2% (56/909)	7.9% (33/420)
Stent Thrombosis ARC defined		
Definite/Probable	0.6% (5/909)	0.5% (2/420)
Definite	0.2% (2/909)	0.5% (2/420)
Probable	0.3% (3/909)	0.0% (0/420)

Notes

N = The total number of subjects enrolled.
 Numbers are % (Count/Number of Eligible Subjects).
 Subjects are only counted once for each time period.
 The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.
 12-month timeframe includes follow-up window (360 days ± 30 days).
 60-month timeframe includes follow-up window (1800 days ± 30 days).
 See Table 9-4 for the definition of the ARC defined Stent Thrombosis

See **Section 9.9.1** Gender Analysis from the RESOLUTE Pooled On-label Dataset for the comprehensive gender analysis.

RESOLUTE 38 mm Length Group

The 38 mm Length Group was designed to demonstrate the safety and effectiveness of the Resolute 38 mm stent and consisted of subjects with ischemic heart disease due to a stenotic lesion in a de novo native coronary artery with a reference vessel diameter between 3.0 mm and 4.2 mm and a lesion length \leq 35 mm amenable to percutaneous treatment with a 38 mm Resolute stent. The 38 mm Length Group was made up of 38 mm subjects pooled from the RESOLUTE US and RESOLUTE ASIA studies. 223 subjects were enrolled at 47 sites with 114 subjects at 29 sites in the US and 109 subjects at 17 sites in Asia (Bangladesh, India, Hong Kong, Malaysia, Singapore and Thailand).

Demographics and clinical characteristics: There were 223 subjects. The mean age of all subjects was 60.9 years with 78.9% (176/223) being males. 32.4% (70/216) had a prior history of MI, 27.4% (61/223) had a prior history of PCI and 7.2% (16/223) had previous CABG surgery. 37.7% (84/223) were diabetics, with 10.3% (23/223) being insulin dependent diabetics. Past medical history of subjects indicated 58.7% (131/223) had hyperlipidemia, 74.9% (167/223) had hypertension, and 18.8% (42/223) were current smokers. The mean RVD by QCA was 2.78 ± 0.42 mm, the lesion length was 25.22 ± 8.83 mm and the average percentage diameter stenosis was $71.33 \pm 11.61\%$. 91.2% of lesions (240/263) were characterized as ACC/AHA type B2/C.

Primary Endpoint: The primary endpoint of the 38 mm Length Group was Target Lesion Failure (TLF) at 12 months post-procedure, defined as 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 that was derived from a logistic regression of TLF rates in subjects treated with Endeavor or Driver stents pooled from the Endeavor stent clinical program: ENDEAVOR I, ENDEAVOR II, ENDEAVOR II CA, ENDEAVOR III, ENDEAVOR IV and ENDEAVOR PK. The performance goal was set at 19%, which was 48% above the expected TLF rate for a drug-eluting stent and preserved 51% of the benefit of a drug-eluting stent vs. a bare metal stent.

Results: The 38 mm Length Group 12-month TLF rate was 4.5% (10/223) with an upper one-sided 95% CI of 7.5%, which met the performance goal of 19%, (P-value < 0.001). The 12 month and 60 month follow-up rates were 99.1% (221/223) and 93.7% (209/223), respectively.

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

- **Table 9-19: 38 mm Length Group – Primary Endpoint Analyses**
- **Table 9-20: 38 mm Length Group - Principal Safety and Effectiveness Through 60 Months**
- **Table 9-21: 38 mm Length Group – ARC Defined/Probable Stent Thrombosis Through 60 Months**
- **Table 9-22: Pooled Resolute Analysis including the 38 mm Length Group**

Table 9-19: 38 mm Length Group – Primary Endpoint Analyses

38 mm Length Group	Resolute (N=223)	Performance Goal	Upper One-Sided 95% CI ¹		P-value ²
12-month TLF	4.5% (10/223)	19.00%	7.5%		< 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).

The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 38 mm lesions.

12-month timeframe includes follow-up window (360 days \pm 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 9-20: 38 mm Length Group - Principal Safety and Effectiveness

	38 mm Length Group (N = 223)	R-US Sub-study (N = 114)	R-Asia Cohort (N = 109)	38 mm Length Group (N = 223)
COMPOSITE SAFETY AND EFFECTIVENESS	Outcomes at 12 Months	Outcomes at 12 Months	Outcomes at 12 Months	Outcomes at 60 Months
TLF	5.4% (12/222)	7.1% (8/113)	3.7% (4/109)	13.8% (30/217)
TVF	6.8% (15/222)	9.7% (11/113)	3.7% (4/109)	17.1% (37/217)
MACE	6.3% (14/222)	8.8% (10/113)	3.7% (4/109)	17.5% (38/217)
EFFECTIVENESS				
Clinically-driven TVR	2.7% (6/222)	4.4% (5/113)	0.9% (1/109)	9.7% (21/217)
TLR	1.4% (3/222)	1.8% (2/113)	0.9% (1/109)	6.0% (13/217)
TLR, PCI	1.4% (3/222)	1.8% (2/113)	0.9% (1/109)	5.5% (12/217)
TLR, CABG	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)	0.5% (1/217)
Non-TL TVR	1.4% (3/222)	2.7% (3/113)	0.0% (0/109)	3.7% (8/217)
Non-TL TVR, PCI	1.4% (3/222)	2.7% (3/113)	0.0% (0/109)	3.2% (7/217)
Non-TL TVR, CABG	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)	0.5% (1/217)
SAFETY				
Total Death	0.9% (2/222)	1.8% (2/113)	0.0% (0/109)	6.5% (14/217)
Cardiac Death	0.9% (2/222)	1.8% (2/113)	0.0% (0/109)	4.1% (9/217)
Non Cardiac Death	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)	2.3% (5/217)
Cardiac Death or TVMI	4.5% (10/222)	5.3% (6/113)	3.7% (4/109)	8.8% (19/217)
TVMI	3.6% (8/222)	3.5% (4/113)	3.7% (4/109)	6.0% (13/217)
Q wave MI	0.9% (2/222)	0.9% (1/113)	0.9% (1/109)	0.9% (2/217)
Non-Q wave MI	2.7% (6/222)	2.7% (3/113)	2.8% (3/109)	5.1% (11/217)
Side Branch Occlusion [†]	5.4% (12/222)	7.1% (8/113)	3.7% (4/109)	5.5% (12/217)
Stent Thrombosis ARC Defined				
Definite/Probable	0.9% (2/222)	0.9% (1/113)	0.9% (1/109)	1.4% (3/217)
Definite	0.5% (1/222)	0.0% (0/113)	0.9% (1/109)	0.5% (1/217)
Probable	0.5% (1/222)	0.9% (1/113)	0.0% (0/109)	0.9% (2/217)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

[†] 5 subjects with side branch occlusion had a TVMI.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-21: 38 mm Length Group – ARC Defined/Probable Stent Thrombosis Through 60 Months

	38 mm Length Group (N = 223)
Stent Thrombosis	1.4% (3/217)
Acute (0-1 day)	0.0% (0/217)
Subacute (2-30 days)	0.9% (2/217)
Late (31-360 days)	0.0% (0/217)
Very Late (361 - 1800 days)	0.5% (1/217)
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).	
60-month timeframe includes follow-up window (1800 days ± 30 days).	
See Table 9-4 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 9-22 shows the Pooled Resolute Analysis including the 38 mm Length Groups. The safety and efficacy data from the 38 mm Length Group and five (5) Resolute studies; Resolute FIM, Resolute US (PEG), Resolute International, Resolute All-Corners and Resolute Japan are presented to 60 Months.

Table 9-22: Pooled Resolute Analysis including the 38 mm Length Groups - Through 60 Months

Pooled Resolute analysis with the 38mm Length Group	(N=5353)
Safety Measures to 12 Months	
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	6.5% (348/5321)
TVF	7.5% (397/5321)
MACE	7.5% (398/5321)
EFFECTIVENESS	
Clinically Driven TVR	4.2% (226/5321)
Clinically Driven TLR	3.2% (169/5321)
SAFETY	
Death	1.9% (100/5321)
Cardiac Death	1.2% (62/5321)
Non Cardiac Death	0.7% (38/5321)
TVMI (Extended Historical Definition)	3.0% (157/5321)
Cardiac Death or Target Vessel MI (TVMI)	3.9% (210/5321)
Stent Thrombosis ARC defined	
Definite/Probable	0.8% (42/5321)
Definite	0.6% (30/5321)
Probable	0.3% (14/5321)
Safety Measures to 36 Months	
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	10.7% (562/5234)
TVF	13.0% (681/5234)
MACE	13.5% (708/5234)
EFFECTIVENESS	

Table 9-22: Pooled Resolute Analysis including the 38 mm Length Groups - Through 60 Months

Pooled Resolute analysis with the 38mm Length Group	(N=5353)
Clinically Driven TVR	7.9% (413/5234)
Clinically Driven TLR	5.3% (276/5234)
SAFETY	
Death	5.4% (284/5234)
Cardiac Death	3.1% (161/5234)
Non Cardiac Death	2.4% (123/5234)
TVMI (Extended Historical Definition)	3.8% (200/5234)
Cardiac Death or Target Vessel MI (TVMI)	6.5% (339/5234)
Stent Thrombosis ARC defined	
Definite/Probable	1.1% (56/5234)
Definite	0.7% (38/5234)
Probable	0.4% (20/5234)
Safety Measures to 60 Months*	
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	14.0% (406/2905)
TVF	18.0% (523/2905)
MACE	19.2% (559/2905)
EFFECTIVENESS	
Clinically Driven TVR	11.3% (327/2905)
Clinically Driven TLR	6.6% (192/2905)
SAFETY	
Death	9.6% (280/2905)
Cardiac Death	4.8% (140/2905)
Non Cardiac Death	4.8% (140/2905)
TVMI (Extended Historical Definition)	4.6% (133/2905)
Cardiac Death or Target Vessel MI (TVMI)	8.7% (253/2905)
Stent Thrombosis ARC defined	
Definite/Probable	1.3% (37/2905)
Definite	0.8% (23/2905)
Probable	0.5% (15/2905)
Notes	
N = The total number of subjects enrolled.	
Numbers are % (Count/Number of Eligible Subjects).	
Subjects are only counted once for each time period.	
The definitions of the outcomes are presented as table notes to Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up- Principal Adverse Events.	
12-month timeframe includes follow-up window (360 days ± 30 days).	
36-month timeframe includes follow-up window (1080 days ± 30 days).	
60-month timeframe includes follow-up window (1800 days ± 30 days).	
* Note: R-Int. follow-up ends at three years and is not included in this analysis.	
See Table 9-4 for the definition of the ARC defined Stent Thrombosis.	

Table 9-23 shows the baseline demographic and clinical characteristics stratified by gender for subjects in the 38 mm Length Group analysis, 47/223 (21.1%) subjects were female and 176/223 (78.9%) were male. Consistent with other DES clinical studies, female patients were older, and there was no other significant difference in baseline demographic and clinical characteristics observed between gender groups.

Table 9-23: RESOLUTE 38 mm Length Group - Baseline Demographic and Lesion Characteristics Male vs. Female

Patient Characteristics	Male (N = 176)	Female (N = 47)	p-value
Age (Years)	60.1±10.7	64.0±10.2	0.028
History of smoking/tobacco use	20.5% (36/176)	12.8% (6/47)	0.469
Prior PCI	25.0% (44/176)	36.2% (17/47)	0.142
Hyperlipidemia	56.3% (99/176)	68.1% (32/47)	0.182
Diabetes Mellitus	36.4% (64/176)	42.6% (20/47)	0.499
Insulin Dependent	9.1% (16/176)	14.9% (7/47)	0.280
Hypertension	72.2% (127/176)	85.1% (40/47)	0.088
Prior MI	32.4% (55/170)	32.6% (15/46)	1.000
Prior CABG	7.4% (13/176)	6.4% (3/47)	1.000
Ejection fraction - Qualitative			0.389
<30%	0.0% (0/144)	0.0% (0/40)	
30-40%	4.2% (6/144)	7.5% (3/40)	
>40%	95.8% (138/144)	92.5% (37/40)	
Lesion Class			0.634
A	1.9% (4/209)	0.0% (0/54)	
B1	8.1% (17/209)	3.7% (2/54)	
B2	9.6% (20/209)	9.3% (5/54)	
C	80.4% (168/209)	87.0% (47/54)	
Moderate/Severe Calcification	32.5% (68/209)	44.4% (24/54)	0.111
Pre procedure RVD (mm)	2.79±0.44	2.75±0.37	0.504
Pre procedure MLD (mm)	0.80±0.36	0.80±0.36	0.912
Pre procedure Diameter Stenosis (%)	71.42±11.49	70.98±12.15	0.805
Lesion Length (mm)	25.16±8.45	25.48±10.27	0.808

The 12 month rate of TLF was 4.0% in males and 10.9% in females (Table 9-24). Although event rates were numerically higher in women, the number of women in the study was small. Further, the RESOLUTE 38 mm Length study was not designed or powered to study the safety or effectiveness of the 38 mm Resolute stent in gender-specific subgroups, so these post hoc analyses are considered hypothesis-generating.

Table 9-24: RESOLUTE 38 mm Length Group - 12 Month Clinical Endpoints by Gender – Principal Safety and Effectiveness

	Male (N = 176)	Female (N = 47)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.0% (7/176)	10.9% (5/46)
TVF	5.1% (9/176)	13.0% (6/46)
MACE	5.1% (9/176)	10.9% (5/46)
EFFECTIVENESS		
Clinically Driven TVR	1.7% (3/176)	6.5% (3/46)
TLR	0.6% (1/176)	4.3% (2/46)
SAFETY		
Total Death	0.6% (1/176)	2.2% (1/46)
Cardiac Death	0.6% (1/176)	2.2% (1/46)
Non-Cardiac Death	0.0% (0/176)	0.0% (0/46)
TVMI	2.8% (5/176)	6.5% (3/46)
Cardiac Death or TVMI	3.4% (6/176)	8.7% (4/46)
Stent Thrombosis defined		
ARC		
Definite/Probable	0.6% (1/176)	2.2% (1/46)
Definite	0.0% (0/176)	2.2% (1/46)
Probable	0.6% (1/176)	0.0% (0/46)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1: Principal Adverse Events from Post-Procedure Through Latest Available Follow-up- Principal Adverse Events.

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

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

9.2 Results of the RESOLUTE AC Clinical Trial

Primary Objective: 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, clinically indicated TLR at 12 months.

The data from the RESOLUTE AC trial were used to support the 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. See **Section 8.1 – Observed Adverse Events**.

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. 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 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.

Demographics and clinical characteristics: Refer to Table 9-25: R-AC – Baseline Characteristics.

Table 9-25: R-AC - Baseline Characteristics

Baseline Characteristics	Resolute (N = 1140 subjects; M = 1661 lesions)	Xience V (N = 1152 subjects; M = 1705 lesions)
Mean Age (years)	64.4	64.2
Male Enrollment	76.67% (873/1140)	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)
* 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).		
The remaining baseline clinical features were well-matched between both arms.		

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

- Table 9-26: R-AC Principal Safety and Effectiveness (All subjects)
- Table 9-27: R-AC Principal Safety and Effectiveness (Complex cohort)
- Table 9-28: R-AC Principal Safety and Effectiveness (Non-Complex cohort)
- Table 9-29: R-AC ARC Defined Definite/Probable Stent Thrombosis through 60 Months (Complex and Non-Complex)

The 12 month and 5 year follow-up rates for the RESOLUTE All Comers study were 99.5% (2280/2292) and 98.8% (2265/2292) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in a randomized study in an all comer population. A limitation was that this trial was not sized to determine the rate of low frequency events with a pre-specified precision.

The published RESOLUTE All-Comers trial results are available in *Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010; 363: 136-46.*

Table 9-26: R-AC Principal Safety and Effectiveness (All subjects)

COMPOSITE SAFETY AND EFFECTIVENESS	All subjects			
	12 Months		60 Months	
	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 1140)	Xience V (N = 1152)
TLF	8.1% (92/1132)	8.5% (97/1142)	17.0% (191/1123)	16.2% (183/1133)
TVF	8.9% (101/1132)	9.7% (111/1142)	20.0% (225/1123)	19.1% (216/1133)
MACE	8.6% (97/1132)	9.8% (112/1142)	21.9% (246/1123)	21.6% (245/1133)
EFFECTIVENESS				
Clinically Driven TVR	4.9% (55/1132)	4.8% (55/1142)	11.4% (128/1123)	10.9% (123/1133)
TLR	3.9% (44/1132)	3.4% (39/1142)	7.8% (88/1123)	7.1% (81/1133)
TLR, PCI	3.4% (38/1132)	2.7% (31/1142)	6.9% (77/1123)	6.0% (68/1133)
TLR, CABG	0.5% (6/1132)	0.8% (9/1142)	1.4% (16/1123)	1.4% (16/1133)
Non-TL TVR	1.9% (21/1132)	2.2% (25/1142)	6.1% (68/1123)	6.1% (69/1133)
Non-TL TVR, PCI	1.5% (17/1132)	1.9% (22/1142)	5.2% (58/1123)	5.2% (59/1133)
Non-TL TVR, CABG	0.4% (4/1132)	0.4% (4/1142)	0.9% (10/1123)	1.0% (11/1133)
SAFETY				
Total Death	1.6% (18/1132)	2.7% (31/1142)	11.0% (123/1123)	10.8% (122/1133)
Cardiac Death	1.3% (15/1132)	1.7% (19/1142)	6.5% (73/1123)	5.7% (65/1133)
Non-Cardiac Death	0.3% (3/1132)	1.1% (12/1142)	4.5% (50/1123)	5.0% (57/1133)
Cardiac Death or TVMI	5.3% (60/1132)	5.5% (63/1142)	11.5% (129/1123)	10.6% (120/1133)
TVMI	4.2% (48/1132)	4.2% (48/1142)	5.7% (64/1123)	5.7% (65/1133)
Q wave MI	0.8% (9/1132)	0.4% (5/1142)	1.3% (15/1123)	0.8% (9/1133)
Non-Q wave MI	3.5% (40/1132)	3.8% (43/1142)	4.6% (52/1123)	4.9% (56/1133)
Stent Thrombosis ARC defined				
Definite/Probable	1.6% (18/1132)	0.7% (8/1142)	2.4% (27/1123)	1.7% (19/1133)
Definite	1.1% (13/1132)	0.3% (3/1142)	1.6% (18/1123)	0.8% (9/1133)
Probable	0.5% (6/1132)	0.4% (5/1142)	0.9% (10/1123)	0.9% (10/1133)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-27: R-AC Principal Safety and Effectiveness (Complex cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Complex cohort			
	12 Months		60 Months	
	Resolute (N = 764)	Xience V (N = 756)	Resolute (N = 764)	Xience V (N = 756)
TLF	8.8% (67/760)	10.0% (75/750)	18.2% (137/751)	18.4% (137/745)
TVF	9.7% (74/760)	11.3% (85/750)	22.1% (166/751)	21.3% (159/745)
MACE	9.1% (69/760)	11.7% (88/750)	22.5% (169/751)	24.6% (183/745)
EFFECTIVENESS				
Clinically Driven TVR	5.5% (42/760)	5.6% (42/750)	13.4% (101/751)	11.7% (87/745)
TLR	4.3% (33/760)	4.1% (31/750)	8.9% (67/751)	8.1% (60/745)
TLR, PCI	3.9% (30/760)	3.2% (24/750)	8.1% (61/751)	6.7% (50/745)
TLR, CABG	0.4% (3/760)	1.1% (8/750)	1.2% (9/751)	1.7% (13/745)
SAFETY				
Total Death	1.4% (11/760)	3.3% (25/750)	10.4% (78/751)	13.2% (98/745)
Cardiac Death	1.3% (10/760)	2.1% (16/750)	6.4% (48/751)	7.4% (55/745)
Non-Cardiac Death	0.1% (1/760)	1.2% (9/750)	4.0% (30/751)	5.8% (43/745)
Cardiac Death or TVMI	5.4% (41/760)	6.4% (48/750)	11.9% (89/751)	12.2% (91/745)
TVMI	4.2% (32/760)	4.7% (35/750)	5.9% (44/751)	6.0% (45/745)
Q wave MI	0.7% (5/760)	0.5% (4/750)	1.3% (10/751)	0.9% (7/745)
Non-Q wave MI	3.7% (28/760)	4.1% (31/750)	4.8% (36/751)	5.1% (38/745)
Stent Thrombosis ARC defined				
Definite/Probable	1.7% (13/759)	0.9% (7/749)	2.5% (19/751)	2.0% (15/745)
Definite	1.2% (9/759)	0.4% (3/749)	1.7% (13/751)	0.9% (7/745)
Probable	0.7% (5/759)	0.5% (4/749)	0.9% (7/751)	1.1% (8/745)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-28: R-AC Principal Safety and Effectiveness (Non-Complex Cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Non-Complex cohort			
	12 Months		60 Months	
	Resolute (N = 376)	Xience V (N = 396)	Resolute (N = 376)	Xience V (N = 396)
TLF	6.7% (25/372)	5.6% (22/392)	14.5% (54/372)	11.9% (46/388)
TVF	7.3% (27/372)	6.6% (26/392)	15.9% (59/372)	14.7% (57/388)
MACE	7.5% (28/372)	6.1% (24/392)	20.7% (77/372)	16.0% (62/388)
EFFECTIVENESS				
Clinically Driven TVR	3.5% (13/372)	3.3% (13/392)	7.3% (27/372)	9.3% (36/388)
TLR	3.0% (11/372)	2.0% (8/392)	5.6% (21/372)	5.4% (21/388)
TLR, PCI	2.2% (8/372)	1.8% (7/392)	4.3% (16/372)	4.6% (18/388)
TLR, CABG	0.8% (3/372)	0.3% (1/392)	1.9% (7/372)	0.8% (3/388)
SAFETY				
Total Death	1.9% (7/372)	1.5% (6/392)	12.1% (45/372)	6.2% (24/388)
Cardiac Death	1.3% (5/372)	0.8% (3/392)	6.7% (25/372)	2.6% (10/388)
Non-Cardiac Death	0.5% (2/372)	0.8% (3/392)	5.4% (20/372)	3.6% (14/388)
Cardiac Death or TVMI	5.1% (19/372)	3.8% (15/392)	10.8% (40/372)	7.5% (29/388)
TVMI	4.3% (16/372)	3.3% (13/392)	5.4% (20/372)	5.2% (20/388)
Q wave MI	1.1% (4/372)	0.3% (1/392)	1.3% (5/372)	0.5% (2/388)
Non-Q wave MI	3.2% (12/372)	3.1% (12/392)	4.3% (16/372)	4.6% (18/388)
Stent Thrombosis ARC defined				
Definite/Probable	1.3%(5/372)	0.3%(1/392)	2.2% (8/372)	1.0% (4/388)
Definite	1.1%(4/372)	0.0%(0/392)	1.3% (5/372)	0.5% (2/388)
Probable	0.3%(1/372)	0.3%(1/392)	0.8% (3/372)	0.5% (2/388)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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 9-29: R-AC ARC Defined Definite/Probable Stent Thrombosis Through 60 Months (All Subjects, and Complex and Non-Complex Subjects)

	All Subjects		Non-Complex		Complex	
	Resolute (N = 1140)	Xiience V (N = 1152)	Resolute (N = 376)	Xiience V (N = 396)	Resolute (N = 764)	Xiience V (N = 756)
Cumulative Stent Thrombosis Through 1-Year	1.6% (18/1132)	0.7% (8/1142)	1.3% (5/372)	0.3% (1/392)	1.7% (13/760)	0.9% (7/750)
Cumulative Stent Thrombosis Through 5-Years	2.4% (27/1123)	1.7% (19/1133)	2.2% (8/372)	1.0% (4/388)	2.5% (19/751)	2.0% (15/745)
Acute (0 - 1 day)	0.4% (5/1123)	0.2% (2/1133)	0.3% (1/372)	0.0% (0/388)	0.5% (4/751)	0.3% (2/745)
Subacute (2 - 30 days)	0.7% (8/1123)	0.4% (4/1133)	0.3% (1/372)	0.3% (1/388)	0.9% (7/751)	0.4% (3/745)
Late (31 - 360 days)	0.6% (7/1123)	0.2% (2/1133)	0.8% (3/372)	0.0% (0/388)	0.5% (4/751)	0.3% (2/745)
Very Late (361 - 1800 days)	0.8% (9/1123)	1.0% (11/1133)	0.8% (3/372)	0.8% (3/388)	0.8% (6/751)	1.1% (8/745)

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)

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 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).

9.3 Results of the RESOLUTE International Study

Primary Objective: 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.

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. 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 9.2 - Results of the RESOLUTE AC Clinical Trial**.

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 6 months and up to 12 months in subjects who were not at a high risk of bleeding.

Demographics and clinical characteristics: 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 ± 12.12 %. The ACC/AHA lesion classification was reported by sites as type B2/C for 57.1% (1798/3147) of the lesions.

Results: These analyses are based on the intent-to-treat population. The 12 month and 3 year follow-up rates for the RESOLUTE International study were 97.7% (2295/2349) and 96.7% (2271/2349) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in an all comer population. A limitation was that this trial was not sized to determine the rate of low frequency events with a pre-specified precision.

The results are presented in the following tables:

- Table 9-30: RESOLUTE International - Principal Safety and Effectiveness
- Table 9-31: RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis Through 36 Months

Table 9-30: RESOLUTE International - Principal Safety and Effectiveness

	(N = 2349)	(N = 2349)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	36 Months
TLF	7.1% (165/2337)	11.4% (261/2284)
TVF	7.7% (180/2337)	12.9% (294/2284)
MACE	8.3% (193/2337)	14.4% (329/2284)
EFFECTIVENESS		
Clinically Driven TVR	4.2% (99/2337)	7.4% (168/2284)
TLR	3.5% (81/2337)	5.7% (130/2284)
TLR, PCI	3.1% (72/2337)	5.2% (118/2284)
TLR, CABG	0.4% (10/2337)	0.6% (14/2284)
Non-TL TVR	1.2% (27/2337)	2.6% (59/2284)
Non-TL TVR, PCI	1.2% (27/2337)	2.5% (56/2284)
Non-TL TVR, CABG	0.0% (0/2337)	0.2% (4/2284)
SAFETY		
Total Death	2.4% (57/2337)	6.1% (139/2284)
Cardiac Death	1.5% (34/2337)	3.6% (82/2284)
Non-Cardiac Death	1.0% (23/2337)	2.5% (57/2284)
Cardiac Death or MI	4.2% (99/2337)	7.0% (161/2284)
TVMI	3.0% (71/2337)	3.9% (89/2284)
Q wave MI	0.5% (12/2337)	0.9% (20/2284)
Non-Q wave MI	2.5% (59/2337)	3.0% (69/2284)
Stent Thrombosis ARC defined		
Definite/Probable	0.9% (20/2337)	1.1% (26/2284)
Definite	0.6% (15/2337)	0.8% (19/2284)
Probable	0.3% (6/2337)	0.4% (8/2284)

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).

36-month timeframe includes follow-up window (1080 days ± 30 days).

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-31: RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis Through 36 Months

	Resolute (N = 2349)
Stent Thrombosis	1.1% (26/2284)
Acute (0 - 1 day)	0.1% (3/2284)
Subacute (2 - 30 days)	0.6% (14/2284)
Late (31 - 360 days)	0.1% (3/2284)
Very Late (361 - 1080 days)	0.3% (6/2284)

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).

36-month timeframe includes follow-up window (1080 days ± 30 days)

See Table 9-4 for the definition of the ARC defined Stent Thrombosis

9.4 Results of the RESOLUTE FIM Clinical Trial

Primary Objective: 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.

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 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 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.

Primary Endpoint: The primary endpoint was in-stent late lumen loss (LL) at 9 months post-procedure as measured by QCA.

Control Group and Statistical Analysis Plan: 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.

Demographics and clinical characteristics: 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 ± 11.37%. The ACC/AHA lesion classification was reported by sites as type B2/C for 81.4% (114/140) of the lesions.

Results: The Resolute stent met the primary non-inferiority endpoint with a 9-month 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_{non-inferiority} < 0.001. The 12 month and 5 year follow-up rates were 99.3% (138/139) and 97.1% (135/139) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that it was a single arm feasibility study.

These analyses are based on the intent-to-treat population. PK results are presented in **Section 6.3** for the **Pharmacokinetics of the Resolute Stent**. The results are presented in the following tables:

- Table 9-32: RESOLUTE FIM - Primary Endpoint Analysis
- Table 9-33: RESOLUTE FIM - Principal Safety and Effectiveness
- Table 9-34: RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis through 60 Months
- Table 9-35: RESOLUTE FIM - Angiographic and IVUS Results

Table 9-32: 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 ± 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 9-33: RESOLUTE FIM - Principal Safety and Effectiveness

	Outcomes at 9 Months (N = 139)	Outcomes at 12 Months (N = 139)	Outcomes at 60 Months (N = 139)
COMPOSITE SAFETY AND EFFECTIVENESS			
TVF	6.5% (9/139)	7.2% (10/139)	13.2% (18/136)
MACE	7.2% (10/139)	8.6% (12/139)	16.2% (22/136)
EFFECTIVENESS			
Clinically Driven TVR	0.0% (0/139)	0.7% (1/139)	5.1% (7/136)
TLR	0.0% (0/139)	0.7% (1/139)	2.9% (4/136)
TLR, PCI	0.0% (0/139)	0.7% (1/139)	2.2% (3/136)
TLR, CABG	0.0% (0/139)	0.0% (0/139)	0.7% (1/136)
Non-TL TVR	0.0% (0/139)	0.0% (0/139)	2.2% (3/136)
Non-TL TVR, PCI	0.0% (0/139)	0.0% (0/139)	2.2% (3/136)
Non-TL TVR, CABG	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
SAFETY			
Total Death	1.4% (2/139)	2.2% (3/139)	6.6% (9/136)
Cardiac Death	0.7% (1/139)	0.7% (1/139)	1.5% (2/136)
Non-Cardiac Death	0.7% (1/139)	1.4% (2/139)	5.1% (7/136)
Cardiac Death or MI	6.5% (9/139)	6.5% (9/139)	8.1% (11/136)
MI	5.8% (8/139)	5.8% (8/139)	6.6% (9/136)
Q wave MI	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
Non-Q wave MI	5.8% (8/139)	5.8% (8/139)	6.6% (9/136)
Stent Thrombosis ARC defined			
Definite/Probable	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
Definite	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)
Probable	0.0% (0/139)	0.0% (0/139)	0.0% (0/136)

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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

**Table 9-34: RESOLUTE FIM - ARC Defined
Definite/Probable Stent Thrombosis
through 60 Months**

	Resolute (N = 139)
Stent Thrombosis	0.0% (0/136)
Acute (0 - 1 day)	0.0% (0/136)
Subacute (2 - 30 days)	0.0% (0/136)
Late (31 - 360 days)	0.0% (0/136)
Very late (361 - 1800 days)	0.0% (0/136)

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).
 60-month time frame includes follow-up window (1800 days ± 30 days).
 See Table 9-4 for the definition of the ARC defined Stent Thrombosis

Table 9-35: 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)
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 Evaluable Lesions) or Mean ± SD (Number of Evaluable Lesions).

Subjects are only counted once for each time period.

9.5 Results of the RESOLUTE Japan Clinical Trial

Primary Objective: 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.

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.

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 8 months post-procedure. 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 subjects who were not at a high risk of bleeding.

Primary Endpoint: The primary endpoint was in-stent late LL at 8 months post-procedure measured by 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 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.

Demographics and clinical characteristics: Baseline demographics and clinical characteristics showed a mean age of 67.7 years with 77.0% (77/100) of subjects 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 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 $69.17 \pm 7.80\%$.

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. The 12 month and 5 year follow-up rates were 100% (100/100) and 96% (96/100) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

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

Table 9-36: RESOLUTE Japan - Primary Endpoint Analysis

Table 9-37: RESOLUTE Japan - Principal Safety and Effectiveness

Table 9-38: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis through 60 Months

Table 9-39: RESOLUTE Japan - Angiographic and IVUS Results

Table 9-36: 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 9-37: RESOLUTE Japan - Principal Safety and Effectiveness

	(N = 100)	(N = 100)
COMPOSITE SAFETY AND EFFECTIVENESS	12 Months	60 Months
TLF	4.0% (4/100)	6.1% (6/98)
TVF	5.0% (5/100)	10.2% (10/98)
MACE	5.0% (5/100)	14.3% (14/98)
EFFECTIVENESS		
Clinically Driven TVR	1.0% (1/100)	5.1% (5/98)
TLR	0.0% (0/100)	1.0% (1/98)
TLR, PCI	0.0% (0/100)	1.0% (1/98)
TLR, CABG	0.0% (0/100)	0.0% (0/98)
Non-TL TVR	1.0% (1/100)	4.1% (4/98)
Non-TL TVR, PCI	1.0% (1/100)	3.1% (3/98)
Non-TL TVR, CABG	0.0% (0/100)	1.0% (1/98)
SAFETY		
Total Death	1.0% (1/100)	7.1% (7/98)
Cardiac Death	0.0% (0/100)	1.0% (1/98)
Non-Cardiac Death	1.0% (1/100)	6.1% (6/98)
Cardiac Death or MI	4.0% (4/100)	5.1% (5/98)
TVMI	4.0% (4/100)	4.1% (4/98)
Q wave MI	0.0% (0/100)	0.0% (0/98)
Non-Q wave MI	4.0% (4/100)	4.1% (4/98)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/100)	0.0% (0/98)
Definite	0.0% (0/100)	0.0% (0/98)
Probable	0.0% (0/100)	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).

60-month timeframe includes follow-up window (1800 days ± 30 days)

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-38: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis through 60 Months

	Resolute (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 - 360 days)	0.0% (0/98)
Very late (361 - 1800 days)	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).

60-month timeframe includes follow-up window (1800 days ± 30 days).

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-39: 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)	3.19 ± 4.53 (99)
% Volume Obstruction	2.33 ± 3.51 (99)
Incomplete Apposition	
Persistent	4.9% (5/103)
Late Acquired	2.9% (3/103)

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.

9.6 Results of the RESOLUTE INTEGRITY US Post Market Study

The RESOLUTE INTEGRITY US Post Market Study is a post approval study of the Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System in the Treatment of De Novo Lesions in Native Coronary Arteries with a Reference Vessel Diameter of 2.25 mm to 4.2 mm.

Primary Objective: The objective of this study is to assess the safety and efficacy of the Resolute Integrity Stent for the treatment of *de novo* lesions in native coronary arteries with a reference vessel diameter (RVD) of 2.25 mm to 4.2 mm in two groups of patients, specifically those patients receiving stents \leq 30 mm in length, referred to as the Primary Enrollment Group (PEG) and those patients who receive extended length stents (34 mm or 38 mm) referred to as the Extended Length (XL) Sub-study.

Design: The RESOLUTE INTEGRITY US Post Market Study is a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects that are treated with the commercially available Medtronic Resolute Integrity Zotarolimus-Eluting Coronary Stent System.

This study enrolled 286 patients with *de novo* lesions in native coronary arteries who met the eligibility criteria and signed the informed consent form to participate in this study of which 230 patients were part of the PEG and 56 patients in the XL Sub-study.

For the PEG, centers were allowed to enroll a maximum of 40 subjects per center until study enrollment has been completed, whichever came first. For the XL Sub study, centers were allowed to enroll a maximum of 16 subjects per center until study enrollment was completed, whichever comes first.

The expected time of participation in the studies for each subject is two years for the PEG and five years for the XL Sub-study.

Patient follow up occurs at: 30 days \pm 5 days (Contact); 6 months \pm 14 days (Contact); 12 months \pm 30 days (Clinic Visit with 12-lead ECG); 24 months \pm 30 days (Contact). The XL Sub-study has additional visits at 3-5 years \pm 30 days (Contact).

Primary Endpoint: The primary endpoint for this study was composite rate of cardiac death and target vessel myocardial infarction (MI) at 12 months.

Control Group and Statistical Analysis Plan: The primary analysis sample was based on intent-to-treat (ITT): For this study, all subjects who sign the written informed consent and are enrolled in the study will be counted in the ITT set, which will be the primary analysis set.

Demographics and Clinical Characteristics for the RESOLUTE Integrity-US PEG: Baseline demographics and clinical characteristics showed a mean age of 64.4 years with 69.6% (160/230) of subjects being males. Of the subjects enrolled, 42.2% (97/230) had diabetes mellitus, 18.3% (42/230) were current smokers, 24.4% (55/225) had prior MI, 35.7% (82/230) had prior PCI, 86.5% (199/230) had hypertension, and 82.6% (190/230) reported hyperlipidemia. Baseline lesion characteristics include 40.9% (94/230) LAD lesions, a mean lesion length of 13.03 \pm 5.76 mm, 82.9% (200/241) ACC/AHA type B2/C lesions and 36.5% (88/241) lesions involving a bifurcation. The mean RVD was 2.60 \pm 0.45 mm and the percentage diameter stenosis was 66.84 \pm 10.37%.

Results for the RESOLUTE Integrity-US PEG: These analyses are based on the intent-to-treat population.

The results specifically for the RI-US PEG are presented in the following tables:

Table 9-40 RESOLUTE Integrity US (PEG) - Primary Endpoint Analysis

Table 9-41: RESOLUTE Integrity US (PEG) - Principal Safety and Effectiveness

Table 9-42: RESOLUTE Integrity US (PEG) - ARC Defined Definite/Probable Stent Thrombosis through 24 Months

Table 9-40:RESOLUTE Integrity US (PEG) - Primary Endpoint Analysis

	Resolute Integrity US (PEG) (N=230)	95% Confidence Interval ¹
Primary Endpoint - Cardiac Death/TVMI at 12-month- ITT set	3.5% (8/226)	[1.5%, 6.9%]

¹ The two-sided 95% CI is calculated by binomial (exact) distribution.

Table 9-41: RESOLUTE Integrity US (PEG) - Principal Safety and Effectiveness

Clinical Outcomes	RESOLUTE INTEGRITY US (PEG) (N=230 Patients) (N=251 Lesions) (m/n) ¹	
	Outcomes at 12 Months	Outcomes at 24 Months
Target Lesion Failure (TLF)	4.9% (11/226)	9.1% (20/219)
Target Vessel Failure (TVF)	7.1% (16/226)	12.3% (27/219)
MACE	5.8% (13/226)	11.0% (24/219)
Cardiac Death or Target Vessel MI (TVMI)	3.5% (8/226)	5.9% (13/219)
Death	1.8% (4/226)	2.7% (6/219)
Cardiac Death	1.3% (3/226)	1.8% (4/219)
Non Cardiac Death	0.4% (1/226)	0.9% (2/219)
TVMI (Extended historical definition)	2.2% (5/226)	4.1% (9/219)
Clinically Driven TLR	2.2% (5/226)	5.0% (11/219)
Clinically Driven TVR	4.4% (10/226)	8.2% (18/219)
Stent Thrombosis (ARC) Definite/Probable	0.9% (2/220)	1.8% (4/219)
Early Thrombosis (<=30 days)	0.9% (2/226)	0.9% (2/219)
Late Thrombosis (31-360 days)	0.0% (0/226)	0.0% (0/219)
Very Late Thrombosis (361-720 days)	N/A	0.9% (2/219)
Effectiveness Measures		
Lesion Success (Definition 1) ²	100.0% (245/245)	
Lesion Success (Definition 2) ³	99.2% (243/245)	
Device Success (Definition 1) ⁴	100.0% (245/245)	
Device Success (Definition 2) ⁵	99.2% (243/245)	
Procedure Success (Definition 1) ⁶	98.2% (223/227)	
Procedure Success (Definition 2) ⁷	97.4% (221/227)	
Device Specific Procedure Success (Definition 1) ⁸	98.2% (223/227)	
Device Specific Procedure Success (Definition 2) ⁹	97.4% (221/227)	

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

² The attainment of <50% residual stenosis of the target lesion using any percutaneous method.

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

⁴ The attainment of <50% residual stenosis of the target lesion using only the assigned device.

⁵ The attainment of < 30% residual stenosis by OCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only.

⁶ The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.

⁷ The attainment of < 30% residual stenosis by OCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.

⁸ The attainment of <50% residual stenosis of the target lesion using only the assigned device and no in-hospital MACE.

⁹ The attainment of < 30% residual stenosis by OCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only, and no in-hospital MACE.

Table 9-42: RESOLUTE Integrity US (PEG) - ARC Defined Definite/Probable Stent Thrombosis through 24 Months

	Resolute Integrity (N = 230)
Stent Thrombosis	1.8% (4/219)
Acute (0 - 1 day)	0.0% (0/219)
Subacute (2 - 30 days)	0.9% (2/219)
Late (31 - 360 days)	0.0% (0/219)
Very Late Thrombosis (361-720 days)	0.9% (2/219)

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).
 24-month time frame includes follow-up window (720 days ± 30 days).
 See Table 9-4 for the definition of the ARC defined Stent Thrombosis

The 12 month and 24 month follow-up rates for the RESOLUTE Integrity US Post Market Study PEG were 94.3% (217/230) and 94.8% (218/230) respectively.

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

Results for the RESOLUTE Integrity US XL Sub-study: These analyses are based on the intent-to-treat population.

The results specifically for the RESOLUTE Integrity US XL Sub-study are presented in the following tables:

Table 9-43: RESOLUTE Integrity US (XL Sub-study) - Primary Endpoint Analysis

Table 9-44: RESOLUTE Integrity US (XL Sub-study) - Principal Safety and Effectiveness

Table 9-45: RESOLUTE Integrity US (XL Sub-study) - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 9-43: RESOLUTE Integrity US (XL Sub-study) - Primary Endpoint Analysis

	Resolute Integrity US (XL Sub-study) (N=56)	95% Confidence Interval ¹
Primary Endpoint - Cardiac Death/TVMI at 12-month- ITT set	7.4% (4/54)	[2.1%, 17.9%]

¹ The two-sided 95% CI is calculated by binomial (exact) distribution.

Table 9-44: RESOLUTE Integrity US (XL Sub-study) - Principal Safety and Effectiveness

	RESOLUTE INTEGRITY US (XL Sub-study) (N=56 Patients) (N=69 Lesions) (m/n) ¹
Clinical Outcomes	Outcomes at 12 Months
Target Lesion Failure (TLF)	7.4% (4/54)
Target Vessel Failure (TVF)	7.4% (4/54)

Table 9-44: RESOLUTE Integrity US (XL Sub-study) - Principal Safety and Effectiveness	
	RESOLUTE INTEGRITY US (XL Sub-study) (N=56 Patients) (N=69 Lesions) (m/n)¹
Clinical Outcomes	Outcomes at 12 Months
MACE	9.3% (5/54)
Cardiac Death or Target Vessel MI (TVMI)	7.4% (4/54)
Death	1.9% (1/54)
Cardiac Death	1.9% (1/54)
Non Cardiac Death	0.0% (0/54)
TVMI (Extended historical definition)	5.6% (3/54)
Clinically Driven TLR	1.9% (1/54)
Clinically Driven TVR	1.9% (1/54)
Stent Thrombosis (ARC) Definite/Probable	1.9% (1/54)
Early Thrombosis (<=30 days)	1.9% (1/54)
Late Thrombosis (31-360 days)	0.0% (0/54)
Effectiveness Measures	
Lesion Success (Definition 1) ²	100.0% (67/67)
Lesion Success (Definition 2) ³	98.6% (68/69)
Device Success (Definition 1) ⁴	97.0% (65/67)
Device Success (Definition 2) ⁵	95.7% (66/69)
Procedure Success (Definition 1) ⁶	98.2% (55/56)
Procedure Success (Definition 2) ⁷	96.4% (54/56)
Device Specific Procedure Success (Definition 1) ⁸	94.6% (53/56)
Device Specific Procedure Success (Definition 2) ⁹	92.9% (52/56)
¹ Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage (%) was calculated as 100 x (m/n) ² The attainment of <50% residual stenosis of the target lesion using any percutaneous method. ³ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method. ⁴ The attainment of <50% residual stenosis of the target lesion using only the assigned device. ⁵ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only. ⁶ The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE. ⁷ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay. ⁸ The attainment of <50% residual stenosis of the target lesion using only the assigned device and no in-hospital MACE. ⁹ The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only, and no in-hospital MACE.	

Table 9-45: RESOLUTE Integrity US (XL Sub-study) - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	Resolute Integrity (N = 56)
Stent Thrombosis	1.9% (1/54)
Acute (0 - 1 day)	0.0% (0/54)
Subacute (2 - 30 days)	1.9% (1/54)

Table 9-45: RESOLUTE Integrity US (XL Sub-study) - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

	Resolute Integrity (N = 56)
Late (31 – 360 days)	0.0% (0/54)

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 9.4 for the definition of the ARC defined Stent Thrombosis

The 12 month follow-up rate for the RESOLUTE Integrity US Post Market Study XL Sub-study was 96.4% (54/56).

Strengths of this analysis include the collection and presentation of both short and long term outcomes demonstrating safety and effectiveness in the intended population. A limitation was that the patient and lesion characteristics excluded many complex subjects.

9.7 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.

Primary Objective: 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 diabetes mellitus cohort:

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

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 FIM 2.7% (24/878).

Subjects from the 38 mm Length sub-study are not included in this Resolute Pooled Analysis of Subjects with Diabetes Mellitus. Additional information is provided in **Section 9.7.1** for the Resolute US 38 mm Length Group for subjects with Diabetes Mellitus.

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.

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 stent 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 the following clinical or lesion characteristics were excluded: total lesion length per vessel > 27 mm, > 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 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. 28.5% (250/878) of the subjects were insulin dependent diabetics. Of the subjects included in this analysis, 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 9-46: RESOLUTE Diabetes Mellitus Cohort - Primary Endpoint Analysis
- Table 9-47: 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
- Table 9-48: RESOLUTE Diabetes Mellitus Cohort - ARC Defined Definite/Probable Stent Thrombosis Events through 12 Months

Table 9-46: 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 timeframe includes follow-up window (360 days ± 30 days).

¹ One-sided confidence interval using exact method.

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

Table 9-47: 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).

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-48: 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 9-4 for the definition of the ARC defined Stent Thrombosis.

9.7.1 Subjects with Diabetes Mellitus in the RESOLUTE 38 mm Length Stent Sub-study

Additional information is provided in Table 9-49 for the RESOLUTE US 38 mm Length Group in subjects with Diabetes Mellitus.

Table 9-49: RESOLUTE 38 mm Length Group: All 38 mm Subjects, Insulin-Dependent DM Subjects (IDDM), Non-Insulin Dependent DM Subjects (Non-IDDM), and Non-DM Subjects – Principal Safety and Effectiveness through 12 Months

	All Diabetic 38 mm Length Group Subjects (N = 84 Patients)	38 mm Length Group IDDM (N = 23 Patients)	38 mm Length Group – Non-IDDM (N = 61 Patients)	38 mm Length Group – Non-DM (N = 139 Patients)
COMPOSITE SAFETY AND EFFECTIVENESS				
TLF	6.0% (5/84)	4.3% (1/23)	6.6% (4/61)	5.1% (7/138)
TVF	7.1% (6/84)	4.3% (1/23)	8.2% (5/61)	6.5% (9/138)
MACE	8.3% (7/84)	4.3% (1/23)	9.8% (6/61)	5.1% (7/138)
EFFECTIVENESS				
Clinically-driven TVR	3.6% (3/84)	0.0% (0/23)	4.9% (3/61)	2.2% (3/138)
TLR	2.4% (2/84)	0.0% (0/23)	3.3% (2/61)	0.7% (1/138)
SAFETY				
Total Death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Cardiac Death	1.2% (1/84)	0.0% (0/23)	1.6% (1/61)	0.7% (1/138)
Non Cardiac Death	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)
Cardiac Death or TVMI	3.6% (3/84)	4.3% (1/23)	3.3% (2/61)	5.1% (7/138)
TVMI	2.4% (2/84)	4.3% (1/23)	1.6% (1/61)	4.3% (6/138)
Stent Thrombosis ARC defined				
Stent Thrombosis (ARC def/prob)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Early (<= 30 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	1.4% (2/138)
Late (> 30 and <=360 days)	0.0% (0/84)	0.0% (0/23)	0.0% (0/61)	0.0% (0/138)

9.8 Subjects with Chronic Total Occlusion

The PERSPECTIVE Study – RESOLUTE CTO Cohort

The PERSPECTIVE Study included a retrospective and a prospective study arm. Both arms of this study enrolled approximately 250 patients at a single center experienced in CTO procedures. The prospective arm essentially comprised a separate substudy designed to evaluate procedural and 1-year clinical outcomes among consecutive patients undergoing attempted percutaneous Chronic Total Occlusion (CTO) revascularization. The prospective arm of the PERSPECTIVE study included a pre-specified subgroup analysis of patients treated with the Resolute family of drug eluting stents (all were Resolute Integrity).

Primary Objective: To assess the safety and effectiveness of the Resolute Zotarolimus-eluting Coronary Stent System (Resolute ZES) for the treatment of chronic total occlusions.

Population: The population consisted of prospectively enrolled subjects undergoing attempted percutaneous CTO revascularization and treated with the Resolute ZES.

Design: The PERSPECTIVE Study (Prospective Arm/Prespecified Resolute ZES for CTO Analysis) was a single-center, investigator-initiated, observational study which prospectively enrolled approximately 250 subjects undergoing attempted CTO. Assessment of use of Resolute ZES stents in CTO revascularization was based on prospectively enrolled CTO patients compared to a pre-specified performance goal.

Comment [KA1]: Changed font from Times to Arial

An estimated MACE rate was derived based on a weighted average of the reported rates for drug-eluting stents from the PRISION II⁶¹ and EXPERT CTO⁷² studies. Due to difference in the definition of myocardial infarction used in the PRISION II study, an adjustment for the MACE rate was made to approximate the MACE rate if the ARC definition of myocardial infarction had been applied. The weighted average produced an estimated MACE rate of 16.6% using the ARC definition of MI. The performance goal (PG) for the pre-specified RESOLUTE CTO Cohort analysis was 25.2% based on the estimated MACE rate of 16.6% and a one-sided 95% CI.

Comment [KA2]: Updated formatting to superscript and update reference numbers; Deleted the "T"; The references are added as footnotes

Comment [WK3]: Update suggested via email

Comment [CJP4]: Accepted.

Demographics: In the RESOLUTE CTO Cohort of the PERSPECTIVE Study, the mean age was 63.4 ± 9.5, 79.8% (146/183) were male, 98.4% (180/183) reported dyslipidemia, 88.5% (162/183) had hypertension, 18.0% (31/172) were current smokers, 35.5% (65/183) were diabetic including 12.6% (23/182) reported as insulin dependent, 33.3% (61/183) had a prior MI, and 80.9% (140/173) were classified as having stable angina.

Primary Endpoint: Major Adverse Cardiac Events (MACE) at one year; a composite of death, myocardial infarction (MI) (ARC defined), and clinically-driven target lesion revascularization (TLR).

Results: The observed MACE rate at one year for the RESOLUTE CTO Cohort was 18.2% (33/181) for the ITT population. The ITT population met the primary endpoint. The upper limit of the 95% confidence interval was 23.6% which is lower than the pre-specified performance goal (25.2%). A post hoc gender subgroup analysis of the primary endpoint resulted in MACE rates at one year of 18.8% (27/144) in male subjects and 16.2% (6/37) in female subjects.

The PERSPECTIVE Study results are presented in Table 9-50, Table 9-51, and Table 9-52

Table 9-50: Primary Endpoint Analysis – MACE at 12 Months (ITT and PP)

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

⁶ Suttrop MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISION II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation* 2006; 114(9): 921 – 928.

⁷ Kandzari DE, Kini AS, Karpaliotis D, et al. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results From the EXPERT CTO Multicenter Trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions). *J Am Coll Cardiol Intv* 2015; 8(6): 761 – 769.

Table 9-51: Principal Safety and Effectiveness Results

Safety and Effectiveness Measures	RESOLUTE CTO cohort (N=183 Subjects) %(m/n)
Safety Measures (In-hospital)	
TLF	15.3% (28/183)
TVF	15.3% (28/183)
MACE	15.3% (28/183)
Cardiac Death or MI	15.3% (28/183)
Death or MI	15.3% (28/183)
Death	1.1% (2/183)
Cardiac Death	1.1% (2/183)
Non-Cardiac Death	0.0% (0/183)
MI	14.8% (27/183)
TLR	0.0% (0/183)
TVR	0.0% (0/183)
Safety Measures (to 6 Months/183 days)	
TLF	17.5% (32/183)
TVF	17.5% (32/183)
MACE	17.5% (32/183)
Cardiac Death or MI	17.5% (32/183)
Death or MI	17.5% (32/183)
Death	2.7% (5/183)
Cardiac Death	2.2% (4/183)
Non-Cardiac Death	0.5% (1/183)
MI	15.8% (29/183)
TLR	0.5% (1/183)
TVR	0.5% (1/183)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.6% (3/183)
Stent Thrombosis ARC Definite/Probable	0.6% (1/183)
Stent Thrombosis ARC Possible	1.1% (2/183)
Early Stent Thrombosis (0 to 30 days)	0.6% (1/183)
Definite	0.6% (1/183)
Probable	0.0% (0/183)
Possible	0.0% (0/183)
Late Stent Thrombosis (31 days – 6 months)	1.1% (2/183)
Definite	0.0% (0/183)
Probable	0.0% (0/183)
Possible	1.1% (2/183)
Safety Measures (to 1 year/365 days)	
TLF	18.2% (33/181)
TVF	18.2% (33/181)
MACE	18.2% (33/181)
Cardiac Death or MI	17.7% (32/181)
Death or MI	17.7% (32/181)
Death	2.8% (5/181)
Cardiac Death	2.2% (4/181)
Non-Cardiac Death	0.6% (1/181)
MI	16.0% (29/181)
TLR	1.1% (2/181)
TVR	1.1% (2/181)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.7% (3/181)
Stent Thrombosis ARC Definite/Probable	0.6% (1/181)

Table 9-51: Principal Safety and Effectiveness Results

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

¹CTO procedural success as defined by achievement of <50% residual stenosis with ≥TIMI 2 antegrade flow

²Successful guidewire crossing with placement in distal true lumen of CTO target lesion

Table 9-52: RESOLUTE CTO Cohort – Primary Endpoint Analysis by Gender

Primary Endpoint	Male Subjects RESOLUTE CTO cohort (N=146 Subjects) % (m/n)	Male-Female Subjects RESOLUTE CTO cohort (N=37 Subjects) % (m/n)
MACE at 12 months	18.8% (27/144)	16.2% (6/37)

Global RESOLUTE Clinical Program – RESOLUTE Pooled CTO

Population: In order to provide additional support for the performance of the Resolute family of stents in the treatment of CTOs, a retrospective, pooled analysis was performed which was comprised of pooled CTO patients from the Global RESOLUTE Clinical Program.

The following Global RESOLUTE Clinical Trials contributed subjects to the CTO cohort:

- RESOLUTE International
The RESOLUTE International Study (R-Int) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real world subject population. A total 2349 subjects were enrolled into the study. Subjects were followed for 3 years post-procedure. A total of 186 subjects from the R-Int study were included in the RESOLUTE Pooled CTO analysis.
- RESOLUTE China Randomized Controlled Trial
The RESOLUTE China Randomized Controlled Trial (R-China RCT) was a prospective, multi-center, randomized, open-label study designed to assess the non-inferiority of the Resolute stent compared to the Taxus Liberte stent for in-stent late lumen loss. A total of 198 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 15 subjects from the R-China RCT study were included in the RESOLUTE Pooled CTO analysis.
- RESOLUTE China Registry
The RESOLUTE China Registry (R-China Registry) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real-world patient population requiring stent implantation. A total of 1800 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 157 subjects from the R-China Registry were included in the RESOLUTE Pooled CTO Analysis.

Design: The Resolute stent performance for the treatment of CTO lesions was analyzed from data collected in the R-Int, R-China RCT, and R-China Registry studies. The results pooled datasets from the 5-year data of R-China RCT, 4-year data of R-China Registry, and 3-year data from R-Int. In total, 358 subjects were evaluable for this CTO subset.

Demographics: The average age in the RESOLUTE Pooled CTO subset (n=358) was 60.4 ± 11.3 years and 84.4% (302/358) were male. For this population, 37.7% (133/353) experienced a prior MI, 65.1% (233/358) had hypertension, 50.3% (180/358) had hyperlipidemia and 26.5% (95/358) had diabetes.

Global RESOLUTE Clinical Program results are presented in the following table:

Table 9-53: RESOLUTE Pooled CTO Analysis Safety and Effectiveness Results

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n) ^a
Effectiveness Measures	
Lesion Success ⁶	100.0% (526/526)
Device Success ⁷	94.1% (496/527)
Procedure Success ⁸	97.5% (348/357)
1 Year	
TLF ¹	4.5% (16/352)
TVF ²	4.8% (17/352)
MACE ³	5.7% (20/352)
Composite Endpoint ⁴	12.2% (43/352)
Cardiac Death or TVMI	3.1% (11/352)
Death or TVMI	4.0% (14/352)
Death	1.7% (6/352)
Cardiac Death	0.9% (3/352)
Non Cardiac Death	0.9% (3/352)
TVMI (Extended historical definition)	2.3% (8/352)
Clinically Driven TLR	2.0% (7/352)
Clinically Driven TVR	2.3% (8/352)
Stent Thrombosis (ARC) Definite/Probable	0.6% (2/352)
Early Thrombosis(<=30 days)	0.3% (1/352)
Late Thrombosis(>30 and <=360 days)	0.3% (1/352)
Significant Bleeding Complications ⁵	1.1% (4/352)
Stroke	0.9% (3/352)
3 Years	
TLF ¹	8.9% (31/347)
TVF ²	10.1% (35/347)
MACE ³	10.1% (35/347)
Composite Endpoint ⁴	18.4% (64/347)
Cardiac Death or TVMI	6.6% (23/347)
Death or TVMI	7.8% (27/347)
Death	5.5% (19/347)
Cardiac Death	4.3% (15/347)
Non Cardiac Death	1.2% (4/347)
TVMI (Extended historical definition)	3.2% (11/347)
Clinically Driven TLR	3.2% (11/347)
Clinically Driven TVR	4.3% (15/347)
Stent Thrombosis (ARC) Definite/Probable	1.2% (4/347)
Early Thrombosis(<=30 days)	0.3% (1/347)
Late Thrombosis(>30 and <=360 days)	0.3% (1/347)
Very Late Thrombosis(>360 days)	0.9% (3/347)
Significant Bleeding Complications ⁵	1.2% (4/347)
Stroke	1.7% (6/347)

Table 9-53: RESOLUTE Pooled CTO Analysis Safety and Effectiveness Results

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n) ^a
1. Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. 2. Cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization. 3. Death, myocardial infarction, (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically driven/clinically indicated) by percutaneous or surgical methods. 4. The combined clinical outcome of (all cause) mortality, Myocardial Infarction (Q-wave and non Q-wave), or (any) revascularization. 5. Bleeding complication is defined as a procedure related hemorrhagic event that requires a transfusion or surgical repair. These may include a hematoma requiring treatment of retroperitoneal bleed. Significant Bleeding complication is defined as the bleeding complication that has at least one of the following scenarios: <ul style="list-style-type: none"> • Bleedings that led to an interruption of anti-platelet medication; • Bleedings that require transfusion; • Intracerebral bleedings; or • Bleedings that resulted in substantial hemodynamic compromise requiring treatment 6. The attainment of <50% residual stenosis of the target lesion using any percutaneous method. 7. The attainment of <50% residual stenosis of the target lesion using only the assigned device. 8. The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE. 9. Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage (%) was calculated as $100 \times (m/n)$ Extended historical definition of MI is used for all the composite endpoints.	

9.9 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, a subject-level pooled analysis was conducted. Table 9-54 below provides the total number of subjects included in the analyses.

Table 9-54: Subjects Included in the Analyses by Clinical Study

	All Subjects	On-label
RESOLUTE FIM	139	139
RESOLUTE All-Comers – Resolute	1140	376
RESOLUTE International	2349	763
RESOLUTE US	1402	1402
RESOLUTE Japan	100	100
Pooled Resolute Dataset	5130	2780

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis presented here.

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 (ISR) target lesion, 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 of > 2.5 mg/dl, a lesion length > 27 mm, 2 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 9-55: Resolute Pooled Analysis - Principal Safety and Effectiveness
- Table 9-56: Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis through 60 Months

Table 9-55: Resolute Pooled Analysis - Principal Safety and Effectiveness through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
Outcomes at 12 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	6.6% (336/5098)	5.4% (150/2759)
TVF	7.5% (382/5098)	6.6% (181/2759)
MACE	7.5% (384/5098)	6.3% (174/2759)
EFFECTIVENESS		
Clinically Driven TVR	4.3% (220/5098)	3.7% (103/2759)
Clinically Driven TLR	3.3% (166/5098)	2.5% (69/2759)
SAFETY		
Total Death	1.9% (98/5098)	1.6% (44/2759)
Cardiac Death	1.2% (60/5098)	0.9% (26/2759)
Non-Cardiac Death	0.7% (38/5098)	0.7% (18/2759)
TVMI	2.9% (149/5098)	2.4% (66/2759)
Cardiac Death or TVMI	3.9% (200/5098)	3.3% (90/2759)
Stent Thrombosis ARC defined		
Definite/Probable	0.8% (40/5098)	0.3% (9/2759)
Definite	0.6% (29/5098)	0.2% (6/2759)
Probable	0.3% (13/5098)	0.1% (3/2759)
Outcomes at 36 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	10.8% (539/5012)	9.2% (249/2709)
TVF	13.0% (652/5012)	12.0% (324/2709)
MACE	13.5% (679/5012)	12.0% (325/2709)
EFFECTIVENESS		
Clinically Driven TVR	7.9% (397/5012)	7.5% (204/2709)
Clinically Driven TLR	5.3% (267/5012)	4.4% (119/2709)
SAFETY		
Total Death	5.5% (275/5012)	5.0% (135/2709)
Cardiac Death	3.1% (156/5012)	2.6% (70/2709)
Non-Cardiac Death	2.4% (119/5012)	2.4% (65/2709)
TVMI	3.8% (188/5012)	3.1% (84/2709)
Cardiac Death or TVMI	6.5% (324/5012)	5.4% (145/2709)
Stent Thrombosis ARC defined		
Definite/Probable	1.1% (54/5012)	0.5% (13/2709)

Table 9-55: Resolute Pooled Analysis - Principal Safety and Effectiveness through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
Definite	0.7% (37/5012)	0.3% (7/2709)
Probable	0.4% (19/5012)	0.2% (6/2709)
Outcomes at 60 Months*		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	14.0% (376/2688)	12.3% (239/1937)
TVF	18.1% (486/2688)	16.5% (320/1937)
MACE	19.4% (521/2688)	18.2% (352/1937)
EFFECTIVENESS		
Clinically Driven TVR	11.4% (306/2688)	10.6% (205/1937)
Clinically Driven TLR	6.7% (179/2688)	5.8% (112/1937)
SAFETY		
Total Death	9.9% (266/2688)	9.7% (188/1937)
Cardiac Death	4.9% (131/2688)	4.3% (83/1937)
Non-Cardiac Death	5.0% (135/2688)	5.4% (105/1937)
TVMI	4.5% (120/2688)	3.9% (76/1937)
Cardiac Death or TVMI	8.7% (234/2688)	7.5% (145/1937)
Stent Thrombosis ARC defined		
Definite/Probable	1.3% (34/2688)	0.8% (15/1937)
Definite	0.8% (22/2688)	0.5% (9/1937)
Probable	0.5% (13/2688)	0.3% (6/1937)

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).

36-month timeframe includes follow-up window (1080 days ± 30days).

60-month timeframe includes follow-up window (1800 days ± 30days)

* Note: R-Int. follow-up ends at three years and is not included in this analysis.

The definitions of the outcomes are presented as table notes to Table 8-1 - Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

Table 9-56: Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	All Subjects* (N = 2781)	On-label* (N = 2017)
Stent Thrombosis	1.3% (34/2688)	0.8% (15/1937)
Early (0 - 30 days)	0.5% (13/2688)	0.2% (3/1937)
Late (31 - 360 days)	0.3% (8/2688)	0.2% (4/1937)
Very Late (361 - 1800 days)	0.5% (14/2688)	0.4% (8/1937)

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 \pm 30 days).
60-month timeframe includes follow-up window (1800 days \pm 30 days).
* Note: R-Int. follow-up ends at three years and is not included in this analysis.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis.

9.9.1 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).⁸ 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 pathophysiology,⁹ 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 coronary arteries and increased prevalence of baseline comorbidities including advanced age, diabetes, hypertension, and peripheral vascular disease.

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis.

Table 9-57 describes the baseline and demographic characteristics by gender for subjects in the pooled on-label analysis. 784/2780 (28.2%) subjects were female and 1996/2780 (71.8%) were male. Female patients at baseline were older, had higher rates of diabetes and hypertension, and had smaller reference vessel diameters (RVD).

⁸ 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.

⁹ 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.

Table 9-57: Baseline Characteristics of Male vs. Female for Pooled On-Label Resolute Patients

Patient Characteristics	Male N = 1996	Female N = 784	p-value
Age(years)	62.9±10.5 (1996)	67.1±10.6 (784)	<.001
History of Smoking/Tobacco use	64.1% (1280/1996)	45.5% (357/784)	<.001
Prior PCI	32.4% (646/1996)	28.1% (220/784)	0.029
Hyperlipidemia	78.6% (1568/1996)	80.9% (634/784)	0.194
Diabetes Mellitus	29.2% (582/1996)	37.6% (295/784)	<.001
Insulin Dependent	7.0% (140/1996)	13.9% (109/784)	<.001
History of Hypertension	75.1% (1499/1996)	84.3% (661/784)	<.001
Prior MI	28.1% (556/1977)	18.3% (141/772)	<.001
Prior CABG	9.4% (187/1996)	5.7% (45/784)	0.002
Ejection Fraction (%)			0.059
< 30%	0.1% (1/1463)	0.2% (1/593)	
30 - 40%	6.9% (101/1463)	4.6% (27/593)	
> 40%	93.0% (1361/1463)	95.3% (565/593)	
Lesion Class ACC/AHA			0.133
A	7.8% (172/2219)	9.5% (81/857)	
B1	25.8% (573/2219)	27.5% (236/857)	
B2	32.0% (710/2219)	29.8% (255/857)	
C	34.4% (764/2219)	33.3% (285/857)	
Moderate/Severe Calcification	39.1% (867/2216)	39.2% (335/855)	1.000
Pre procedure RVD (mm)	2.7±0.5 (2201)	2.6±0.5 (855)	<.001
Pre procedure MLD (mm)	0.7±0.4 (2212)	0.8±0.4 (856)	0.025
Pre procedure Diameter Stenosis (%)	73.0±13.8 (2212)	70.5±13.5 (856)	<.001
Lesion Length (mm)	13.8±5.8 (2201)	12.9±5.7 (855)	<.001

The pooled Resolute stent on-label use data were evaluated retrospectively for gender-based clinical outcomes. Table 9-58 shows a *post-hoc* analysis of the principal 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. The event rates were numerically higher in women (except for non-cardiac death) at 12 months; although after 60 months are evenly distributed among the two groups. These results suggest that the safety and effectiveness profile of the Resolute stent is generalizable to both males and females.

Table 9-58: Resolute Pooled On-Label Gender (Male vs. Female) – Principal Safety and Effectiveness Through 60 Months

	Male (N = 1996)	Female (N = 784)
Safety Outcomes (to 12 Months)		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	4.9% (97/1983)	6.8% (53/776)
TVF	5.8% (115/1983)	8.5% (66/776)
MACE	6.0% (118/1983)	7.2% (56/776)
EFFECTIVENESS		
Clinically Driven TVR	3.3% (66/1983)	4.8% (37/776)
Clinically Driven TLR	2.3% (46/1983)	3.0% (23/776)
SAFETY		
Death	1.5% (30/1983)	1.8% (14/776)
Cardiac Death	0.8% (15/1983)	1.4% (11/776)
Non Cardiac Death	0.8% (15/1983)	0.4% (3/776)
TVMI (Extended Historical Definition)	2.1% (41/1983)	3.2% (25/776)
Cardiac Death or Target Vessel MI (TVMI)	2.8% (55/1983)	4.5% (35/776)
Stent Thrombosis ARC defined		
Definite/Probable	0.3% (5/1983)	0.5% (4/776)
Definite	0.2% (4/1983)	0.3% (2/776)
Probable	0.1% (1/1983)	0.3% (2/776)
Outcomes to 36 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	8.8% (172/1949)	10.1% (77/760)
TVF	11.4% (222/1949)	13.4% (102/760)
MACE	11.8% (230/1949)	12.5% (95/760)
EFFECTIVENESS		
Clinically Driven TVR	7.3% (142/1949)	8.2% (62/760)
Clinically Driven TLR	4.4% (86/1949)	4.3% (33/760)
SAFETY		
Death	5.0% (98/1949)	4.9% (37/760)
Cardiac Death	2.5% (48/1949)	2.9% (22/760)
Non Cardiac Death	2.6% (50/1949)	2.0% (15/760)
TVMI (Extended Historical Definition)	2.6% (51/1949)	4.3% (33/760)
Cardiac Death or Target Vessel MI (TVMI)	4.8% (94/1949)	6.7% (51/760)
Stent Thrombosis ARC defined		
Definite/Probable	0.4% (7/1949)	0.8% (6/760)
Definite	0.3% (5/1949)	0.3% (2/760)
Probable	0.1% (2/1949)	0.5% (4/760)
Outcomes to 60 Months*		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	12.4% (169/1363)	12.2% (70/574)
TVF	16.6% (226/1363)	16.4% (94/574)
MACE	18.3% (249/1363)	17.9% (103/574)
EFFECTIVENESS		
Clinically Driven TVR	10.6% (144/1363)	10.6% (61/574)
Clinically Driven TLR	5.9% (80/1363)	5.6% (32/574)
SAFETY		
Death	9.8% (133/1363)	9.6% (55/574)
Cardiac Death	4.3% (58/1363)	4.4% (25/574)
Non Cardiac Death	5.5% (75/1363)	5.2% (30/574)
TVMI (Extended Historical Definition)	3.6% (49/1363)	4.7% (27/574)
Cardiac Death or Target Vessel MI (TVMI)	7.3% (99/1363)	8.0% (46/574)
Stent Thrombosis ARC defined		
Definite/Probable	0.7% (9/1363)	1.0% (6/574)
Definite	0.4% (6/1363)	0.5% (3/574)

Table 9-58: Resolute Pooled On-Label Gender (Male vs. Female) – Principal Safety and Effectiveness Through 60 Months

	Male (N = 1996)	Female (N = 784)
Probable	0.2% (3/1363)	0.5% (3/574)

Notes

N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

The definitions of the outcomes are presented as table notes to Table 8-1- Principal Adverse Events.

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

36-month timeframe includes follow-up window (1080 days ± 30 days).

60-month timeframe includes follow-up window (1800 days ± 30 days).

* Note: R-Int. follow-up ends at three years and is not included in this analysis. See Table 9-4 for the definition of the ARC defined Stent Thrombosis

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis.

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

9.9.2 Subset Analyses from the Resolute Pooled Dataset

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 studies, 33% of enrolled subjects who 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 tables below (Table 9-59, Table 9-60, Table 9-61).

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 9-59: 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 ≥ 27 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 9-60: 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 9-61: 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)
TVMI	5.9% (41/690)	2.4% (12/497)	7.1% (4/56)	5.3% (7/133)	2.4% (19/788)
Cardiac Death or TVMI	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).

The definitions of the outcomes are presented as table notes to Table 8-1 - Principal Adverse Events.

See Table 9-4 for the definition of the ARC defined Stent Thrombosis

¹ Total Occlusion is defined as pre procedure TIMI = 0.

² Renal Insufficiency is defined as serum creatinine > 2.5 mg/dl.

Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis

10 PATIENT SELECTION AND TREATMENT

See also **Section 5.5 Use in Special Population**. The risks and benefits described above should be carefully considered for each patient before use of the Resolute Integrity Stent System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anti-thrombotic therapy. In the clinical studies reviewed to support the approval of the Resolute Integrity Stent System, subjects were prescribed DAPT for at least 6 months post-procedure, and most patients who were not at a high risk of bleeding used DAPT for at least 12 months.

Post-Resolute Integrity Stent implantation, aspirin should be continued indefinitely, and a P2Y12 platelet inhibitor should be given for at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS). A longer duration of DAPT may be considered in patients who have tolerated DAPT without a bleeding complication and who are not at a high bleeding risk. In patients who are at a high risk of bleeding, or who develop significant bleeding during DAPT treatment, a shorter DAPT duration may be reasonable (see **Section 5.1 - Pre- and Post-**

Procedure Antiplatelet Regimen). However, definitive evidence supporting the safety of short DAPT duration has not been established in prospective clinical studies. The safety and effectiveness of the Resolute Integrity stent have not been evaluated in patients at high bleeding risk.

11 PATIENT COUNSELING INFORMATION

Physicians should consider the following in counseling the patient about this product:

- Discuss the risks associated with stent placement
- Discuss the risks associated with a zotarolimus-eluting stent implant
- Discuss the risk/benefit issues for the particular patient
- Discuss alteration to current lifestyle immediately following the procedure and over the long term
- Discuss the risks of early discontinuation of the antiplatelet therapy

The following patient materials will be provided to physicians to educate their patients about the options available for treating coronary artery disease and provide contact information to the patient after their stent implant procedure:

- A Patient Guide which includes information on the Resolute Integrity Zotarolimus-Eluting Coronary Stent System, coronary artery disease, and the stent implantation procedure.
- A Stent Patient Implant Card that includes patient information, stent implant information and MRI guidelines. All patients should be instructed to keep this card in their possession at all times for procedure/stent identification.

12 HOW SUPPLIED

STERILE: This product is sterilized with ethylene oxide (EO) and is nonpyrogenic. Do not use if the package is opened or damaged. Do not resterilize. If the product or package is opened or damaged, return to Medtronic Returned Goods. Contact your local Medtronic, Inc. Representative for return information.

CONTENTS: Package contains one (1) Resolute Integrity Zotarolimus-Eluting Coronary Stent mounted on an Over the Wire (OTW) stent delivery system.

STORAGE: Store in the original container. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Use by the "Use By" date noted on the package.

DISPOSAL INSTRUCTIONS: After use, dispose of product and packaging in accordance with hospital, administrative and/ or local government policy.

13 DIRECTIONS FOR USE

13.1 Access to Package Holding Sterile Stent Delivery System

Remove the stent delivery system from the package. Special care must be taken not to handle the stent or in any way disrupt its placement on the balloon. This is most important during catheter removal from packaging, placement over guidewire, and advancement through the rotating hemostatic valve and guiding catheter hub. Excessive manipulation, e.g., rolling the mounted stent, may cause dislodgement of the stent from the delivery balloon.

13.2 Inspection Prior to Use

Before opening the product, carefully inspect the stent delivery system package, and check for damage to the sterile barrier. Do not use after the "Use By" date. If the sterile package is intact, carefully remove the system from the package and inspect it for bends, kinks, and other damage. Do not use the product if any damage to the packaging or system is noted.

A protective sheath covers the stent mounted on the balloon. After removal of the sheath, visually inspect the stent to ensure that it has not been damaged or displaced from its original position (between proximal and distal marker bands) on the balloon.

13.3 Materials Required

Quantity	Material
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N/A	Guide catheter [\geq 5 F (1.42 mm, 0.056 inch) inner diameter]
2-3	20 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [\leq 0.014 inch (0.36 mm) outer diameter]
1	Rotating hemostatic valve
N/A	Contrast medium diluted 1:1 with heparinized normal saline
1	Inflation device
1	Stopcock (3-way minimum)
1	Torque device
N/A	Appropriate anticoagulation and antiplatelet drugs

13.4 Preparation Precaution

- DO NOT use product if the protective sheath is not present or the stent is damaged/displaced.
- AVOID manipulation of the stent during flushing of the guidewire lumen, as this may disrupt the placement of the stent on the balloon.
- DO NOT apply positive pressure to the balloon during the delivery system preparation.

13.4.1 Guidewire Lumen Flush

Flush the stent system guidewire lumen with heparinized normal saline until the fluid exits the distal tip.

13.4.2 Delivery System Preparation

Step	Action
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- | | |
|-----|--|
| 1. | Prepare the guide catheter and guidewire according to the manufacturer's instructions. |
| 2. | Remove the stent delivery system from the package. |
| 3. | Remove protective sheath covering from the stent/balloon. Removing the protective sheath will also remove the stylette. |
| 4. | Inspect the stent to assure it has not been damaged or displaced from its original position on the balloon. Verify that the stent is positioned between the proximal and distal balloon markers. Verify that there is no visible damage to the stent or the balloon.
Note: Should there be movement of or damage to the stent, do not use. |
| 5. | Flush Stent Delivery System guidewire lumen with heparinized normal saline in routine manner. |
| 6. | Fill a 20 cc syringe with 5 cc of contrast/heparinized normal saline mixture (1:1). |
| 7. | Attach to delivery system and apply negative pressure for 20 - 30 seconds. |
| 8. | Slowly release pressure to allow negative pressure to draw mixture into balloon lumen. |
| 9. | Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen. |
| 10. | Prepare inflation device in standard manner and purge to remove all air from syringe and tubing. |
| 11. | Attach inflation device to catheter directly ensuring no bubbles remain at connection. |
| 12. | Leave on ambient pressure (neutral position). |

Note: Do not apply negative pressure on inflation device after balloon preparation and prior to delivering the stent.

13.5 Delivery Procedure

Step	Action
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|----|--|
| 1. | Prepare the vascular access site according to standard practice. |
| 2. | Pre-dilate the lesion with a PTCA catheter. Pre-dilatation must be performed using a balloon with the following three characteristics: <ul style="list-style-type: none">• A diameter at least 0.5 mm smaller than the treatment stent.• A length equal to or shorter than the lesion length to be dilated.• A length shorter than the stent to be implanted. |
| 3. | Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible.
Note: If resistance is encountered, do not force passage. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine. |
| 4. | Ensure guide catheter stability before advancing the Resolute Integrity System into the coronary artery. Carefully advance the Resolute Integrity System into the hub of the guide catheter. |
| 5. | Advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Precautions – 5 Stent/System Removal Precautions). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel. |
| 6. | Sufficiently tighten the rotating hemostatic valve. Stent is now ready to be deployed. |

Note: Should unusual resistance be felt at any time during either lesion access or removal of the stent delivery system before stent implantation, do not force passage. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. See **Precautions – 5 Stent/System Removal Precautions** for specific stent delivery system removal instructions. In the event the stent is not deployed, contact your local Medtronic, Inc. representative for return information and avoid handling stent with bare hands.

13.6 Deployment Procedure

Step	Action
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- | | |
|----|---|
| 1. | Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning. |
| 2. | Maintain inflation pressure for 15 - 30 seconds for full expansion of the stent. |
| 3. | Do not exceed Rated Burst Pressure (RBP). The RBP is 16atm for the 2.25 mm – 3.5 mm stent diameters and 15atm for the 4.0 mm stent diameter. The Resolute Integrity stents should not be expanded to a diameter beyond the maximum labeled diameter listed on the label. Do not dilate the 2.25 mm - 2.75 mm stents to greater than 3.50 mm. Do not dilate the 3.0 mm - 4.0 mm stents to greater than 4.75 mm. |
| 4. | Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall. |

13.7 Removal Procedures

Step	Action
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|----|--|
| 1. | Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 30 seconds, for full balloon deflation. Longer stents may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast within the balloon. |
| 2. | Open the hemostatic valve to allow removal of the delivery system. |
| 3. | Maintain position of guide catheter and guidewire. Very slowly, withdraw the balloon from the stent, maintaining negative pressure, allowing movement of the myocardium to gently dislodge the balloon from the stent. |
| 4. | After removal of the delivery system, tighten the hemostatic valve. |
| 5. | Repeat angiography and visually assess the vessel and the stent for proper expansion. |

13.8 *In-vitro* Information:

Table 13-1: Inflation Pressure Recommendations

Pressure		Nominal and Rated Burst Pressure*	Stent Nominal Inner Diameter (mm)**					
ATM	kPa		2.25	2.5	2.75	3.0	3.5	4.0
6	608		2.20	2.45	2.70	2.90	3.30	3.75
7	709		2.20	2.45	2.70	2.95	3.35	3.80
8	811		2.25	2.50	2.75	3.00	3.40	3.90
9	912	Nominal	2.30	2.55	2.80	3.05	3.50	3.95
10	1013		2.30	2.60	2.85	3.10	3.55	4.05
11	1115		2.35	2.60	2.90	3.15	3.60	4.10
12	1216		2.40	2.65	2.95	3.20	3.65	4.15
13	1317		2.40	2.70	3.00	3.20	3.70	4.20
14	1419		2.45	2.70	3.05	3.25	3.75	4.25
15	1520	RBP for 4.0 mm	2.50	2.75	3.10	3.30	3.80	4.30
16	1621	RBP*	2.55	2.80	3.15	3.35	3.85	4.35
17	1723		2.60	2.80	3.20	3.40	3.90	4.40
18	1824		2.60	2.85	3.25	3.45	3.95	4.45
19	1925			2.90	3.30	3.50	4.00	4.50
20	2027			2.95	3.40	3.55	4.05	

*Do not exceed the rated burst pressure (RBP). The RBP for 4.0 mm diameter is 15 ATM.

** The shaded cells at pressures 19 ATM and 20 ATM signify that 99% of the balloons did not pass at the listed pressure beyond RBP with 95% confidence.

13.9 Further Dilatation of Stented Segment

The stent delivery balloon may not be used for post-dilatation. Post-dilatation may be performed at the physician’s discretion with appropriately sized (length and diameter) balloons to ensure that the stent is in full contact with the vessel wall. To achieve this, a balloon to artery ratio of 1.0 to 1.1:1.0 should be used to leave a residual diameter stenosis of near 0% (with a recommended maximum of no greater than 10%). Whenever possible, avoid the use of grossly oversized balloons (balloon:artery ratio >1.2).

Precaution: Do not dilate the stent beyond the following limits:

Nominal Stent Diameter	Dilatation Limits
2.25 mm	3.50 mm
2.50 mm	3.50 mm
2.75 mm	3.50 mm
3.00 mm	4.75 mm
3.50 mm	4.75 mm
4.00 mm	4.75 mm

All efforts should be taken to assure that the stent is not under dilated. If the deployed stent size is still inadequate with respect to vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. This further expansion should be performed using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guidewire to avoid dislodging or displacing the stent. The balloon should be centered within the stent and should not extend outside of the stented region. **The Resolute Integrity stents should not be expanded to a diameter beyond the maximum labeled diameter listed on the label. Do not dilate the 2.25 mm - 2.75 mm stents to greater than 3.50 mm. Do not dilate the 3.0 mm - 4.0 mm stents to greater than 4.75 mm.**

14 REUSE PRECAUTION STATEMENT

For single use only.

Do not Resterilize or Reuse.

DISCLAIMER OF WARRANTY

NOTE: ALTHOUGH THE MEDTRONIC RESOLUTE INTEGRITY ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM, HEREAFTER REFERRED TO AS "PRODUCT," HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, MEDTRONIC, INC., MEDTRONIC VASCULAR, INC. AND THEIR AFFILIATES (COLLECTIVELY, "MEDTRONIC") HAVE NO CONTROL OVER CONDITIONS UNDER WHICH THIS PRODUCT IS USED. MEDTRONIC, THEREFORE, DISCLAIMS ALL WARRANTIES, BOTH EXPRESSED AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. MEDTRONIC SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT OR OTHERWISE. NO PERSON HAS ANY AUTHORITY TO BIND MEDTRONIC TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.

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M724129B001 Rev 1J

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