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.

Table of Contents

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.

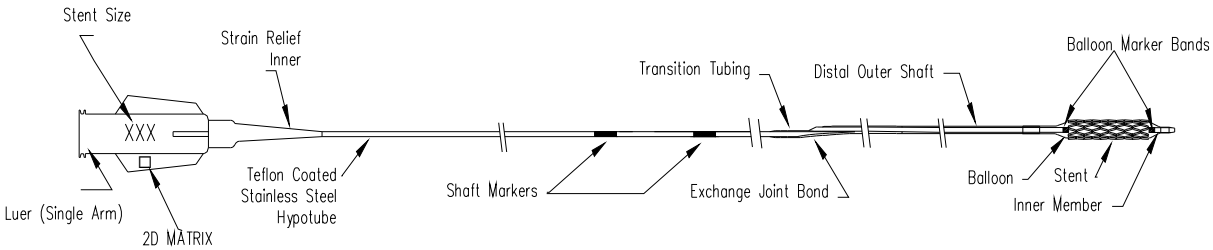


Figure 1-1: MicroTrac RX Delivery System (with Stent)

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**:

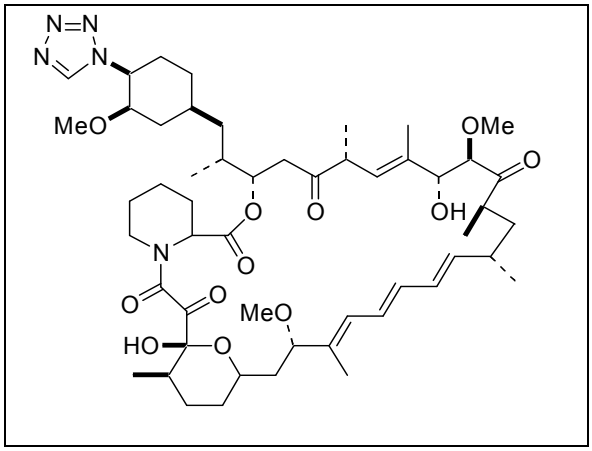


Figure 1-2: Zotarolimus Chemical Structure

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 $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

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

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**:

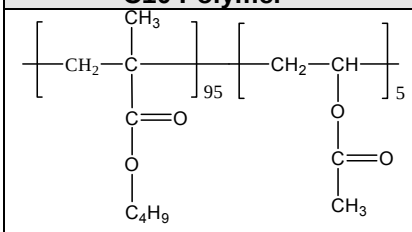
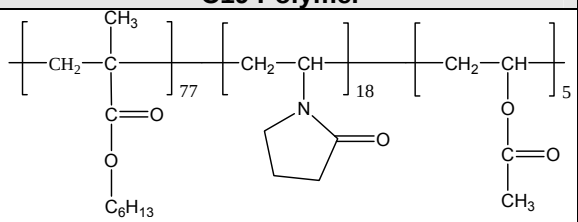
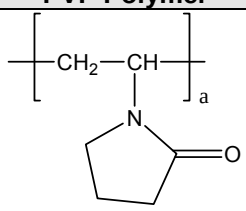
C10 Polymer	C19 Polymer	PVP Polymer
		

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
RSINT27530UX	2.75	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)
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 ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.25 mm to 4.2 mm.

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.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- 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 9.7 – Pooled Results of the Global RESOLUTE Clinical Trial Program** 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. 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, 95.2% and 93.3% of the patients remained on dual antiplatelet therapy at 6 months and 12 months, respectively. In the RESOLUTE AC Clinical Trial, 93.1%, 84.1% and 18.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 24 months, respectively. In the RESOLUTE International Study, 95.6%, and 91.3% of the patients remained on dual antiplatelet therapy at 6 months and 12 months, respectively. In the RESOLUTE FIM Clinical Trial, 79.1%, 58.1% and 35.4% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 48 months, respectively. In the RESOLUTE Japan Clinical Trial, 99.0%, and 94.9% of the patients remained on dual antiplatelet therapy at 6 months and 12 months, respectively. In the RESOLUTE 38 mm Length Group, 91.4%, and 89.5% of the patients remained on dual antiplatelet therapy at 6 months and 12 months, respectively. See **Section 9 - Clinical Studies** for more information.

5.1.1 Oral Antiplatelet Therapy

The optimal duration of dual antiplatelet therapy following DES implantation is unknown, and DES thrombosis may still occur despite continued therapy. Continuation of combination treatment with aspirin and a P2Y12 platelet inhibitor after percutaneous coronary intervention (PCI) appears to reduce major adverse cardiac events. On the basis of randomized clinical trial protocols, and expert consensus opinion, aspirin 81 mg daily should be given indefinitely after PCI. Likewise, a P2Y12 platelet inhibitor should be given daily for at least 12 months in patients who are not at high risk of bleeding.

It is very important that the patient is compliant with the post-procedural antiplatelet recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of stent thrombosis, MI or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation of antiplatelet therapy, the interventional cardiologist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with early discontinuation of antiplatelet therapy. 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 physicians, the antiplatelet therapy should be restarted as soon as possible.

For full oral antiplatelet guidelines, please refer to the following website:

http://content.onlinejacc.org/cgi/content/full/j.jacc.2011.08.007v1

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 9.7.1 – 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 2.25-3.5mm 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 in 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 $AUC_{0\text{-}inf}$ 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.

1.5T
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, the 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 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 ± 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
$AUC_{0\text{-last}}$	(ng•h/mL)	15.08	16.04 ± 4.74	35.89 ± 12.79	31.19 ± 17.69
$AUC_{0\text{-inf}}$[$]	(ng•h/mL)	41.89	39.09 ± 11.77	52.41 ± 12.57	80.12 ± 51.00
β[$]	(1/h)	0.003	0.004 ± 0.001	0.004 ± 0.001	0.003 ± 0.002
$t_{½}$[‡,#]	(h)	263.4	195.5 ± 74.4	167.4 ± 29.7	208.3 ± 144.4
CL/F[$]	(L/h)	3.06	5.23 ± 2.55	4.80 ± 1.11	5.14 ± 3.55
Vd_{β}/F[$]	(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
$AUC_{0\text{-last}}$	Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration	‡	Harmonic mean ± pseudo-standard deviation
$AUC_{0\text{-inf}}$	AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).	#	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
$t_{½}$	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 ($AUC_{0\text{-last}}$) and AUC from time 0 to infinity($AUC_{0\text{-inf}}$). 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 ≥ 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 and 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 embryolethality. 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

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 profile of the Resolute stent**).

The RESOLUTE Japan Clinical Trial is a prospective, multi-center, non-randomized, single-arm trial. A total of 100 subjects were enrolled at 14 investigational sites in Japan. The primary endpoint was in-stent late lumen loss (LL) at 8 months post-procedure as measured by QCA. Post-procedure, subjects were to receive aspirin indefinitely and clopidogrel/ticlopidine for a minimum of 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 of the RESOLUTE clinical trials utilized an independent Clinical Events Committee (CEC) for adjudication of the clinical events. The definitions of clinical events were consistent across the clinical trials, and the event adjudication process was harmonized to ensure consistency and comparability of the data. All clinical trials had oversight by a Data and Safety Monitoring Board (DSMB). All trials had data monitored for verification and accuracy. Independent Angiographic Core Labs were utilized for angiographic and IVUS endpoints.

Table 7-1 summarizes the clinical trial designs for the Global RESOLUTE Clinical Trial Program.

Table 7-1: Clinical Trial Comparisons

	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan	RESOLUTE Asia 38 mm Cohort
Study Type	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial*	▪ Prospective ▪ Multi-center ▪ Randomized (1:1 Resolute vs. Xience V) ▪ Two-arm, non-inferiority trial ▪ Real World subject population	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Observational study ▪ Real World subject population	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial ▪ PK Assessment	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Single-arm ▪ Historical controlled trial	▪ Prospective ▪ Multi-center ▪ Non-randomized
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
Lesion Criteria	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤27 mm for the Primary Enrollment Group, ≤35 mm for the 38 mm Length Group ▪ Target vessel with RVD between 2.25 mm to 4.2 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 mm to 4.0 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 mm to 4.0 mm	▪ Single *de novo* lesion ▪ Lesion length from 14 to 27 mm ▪ Target vessel with RVD between 2.5 mm and 3.5 mm	▪ Single or two *de novo* lesions located in separate coronary arteries ▪ Lesion(s) length ≤27 mm ▪ Target vessel with RVD between 2.5 mm to 3.5 mm	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤35 mm ▪ Target vessel with RVD between 3.0 mm to 4.0 mm ▪ Patients may have received treatment of up to two lesions second lesion RVD 2.25 mm to 4.2 mm), if the lesions were located in separate target vessels.

Table 7-1: Clinical Trial Comparisons

	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan	RESOLUTE Asia 38 mm Cohort
Stent Sizes (Resolute)	Stent diameter: 2.25 mm – 4.0 mm Stent length: 8 mm – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 mm – 4.0 mm Stent length: 8 mm – 30 mm	Stent diameter: 2.25 mm – 4.0 mm Stent length: 8 mm – 38 mm	Stent diameter: 2.5 mm – 3.5 mm Stent length: 8 mm – 30 mm	Stent diameter: 2.5 mm – 3.5 mm Stent length: 8 mm – 30 mm	Stent diameter: 3.0 mm – 4.0 mm Stent Length: 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
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
Follow-up	2.25-3.5 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**
Status	12-month follow-up is complete. 551 subjects qualified for 18-month follow-up	24-month follow-up is complete	12-month follow-up is complete	48-month follow-up complete	12-month follow-up is complete	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.
** RESOLUTE Asia patients were consented for 5 years. At 3 years if the event rates are demonstrated to plateau or decrease as compared to the rates in the prior years, the steering Committee and Sponsor may consider stopping further follow-ups.
[1] The term 'AC' refers to All-Comers.
[2] The term 'Int' refers to International.
[3] The term 'FIM' refers to First-In-Man.

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. 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. 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 (N = 1402)	Resolute (N = 1140)	Xience V (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)
In-Hospital							
TLF[2]	1.4% (19/1402)	3.7% (42/1140)	4.5% (52/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)
TVF[3]	1.4% (19/1402)	3.8% (43/1140)	4.7% (54/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)
MACE[4]	1.4% (19/1402)	3.8% (43/1140)	4.9% (56/1152)	2.7% (63/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)
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)
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)
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)
TVMI[5]	1.2% (17/1402)	3.1% (35/1140)	3.6% (42/1152)	2.2% (51/2349)	4.3% (6/139)	2.0% (2/100)	3.1% (7/223)
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)
Non-Q Wave MI	1.1% (16/1402)	2.8% (32/1140)	3.2% (37/1152)	1.8% (43/2349)	4.3% (6/139)	2.0% (2/100)	2.7% (6/223)
Cardiac Death or TVMI[6]	1.2% (17/1402)	3.2% (36/1140)	4.0% (46/1152)	2.4% (56/2349)	4.3% (6/139)	2.0% (2/100)	3.6% ((8/223)
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)
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)
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)
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)
30 Days							
MACE	1.4% (20/1398)	4.4% (50/1132)	5.2% (60/1144)	3.3% (78/2344)	4.3% (6/139)	3.0% (3/100)	4.5% (10/223)
12 Months							
TLF	4.7% (65/1376)	8.1% (92/1130)	8.5% (97/1138)	7.0% (162/2299)	7.2% (10/139)	4.0% (4/100)	5.4% (12/222)
TVF	6.3% (86/1376)	8.9% (101/1130)	9.8% (111/1138)	7.7% (177/2299)	7.2% (10/139)	5.0% (5/100)	6.8% (15/222)
MACE	5.5% (76/1376)	8.6% (97/1130)	9.8% (112/1138)	8.2% (188/2299)	8.6% (12/139)	5.0% (5/100)	6.3% (14/222)
Total Death	1.3% (18/1376)	1.6% (18/1130)	2.7% (31/1138)	2.4% (56/2299)	2.2% (3/139)	1.0% (1/100)	0.9% (2/222)
Cardiac Death	0.7% (9/1376)	1.3% (15/1130)	1.7% (19/1138)	1.4% (33/2299)	0.7% (1/139)	0.0% (0/100)	0.9% (2/222)
Non-Cardiac Death	0.7% (9/1376)	0.3% (3/1130)	1.1% (12/1138)	1.0% (23/2299)	1.4% (2/139)	1.0% (1/100)	0.0% (0/222)
TVMI	1.4% (19/1376)	4.2% (48/1130)	4.2% (48/1138)	3.1% (71/2299)	5.8% (8/139)	4.0% (4/100)	3.6% (8/222)
Q wave MI	0.1% (2/1376)	0.8% (9/1130)	0.4% (5/1138)	0.5% (12/2299)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)
Non-Q Wave MI	1.2% (17/1376)	3.5% (40/1130)	3.8% (43/1138)	2.6% (59/2299)	5.8% (8/139)	4.0% (4/100)	2.7% (6/222)
Cardiac Death or TVMI	2.0% (28/1376)	5.3% (60/1130)	5.5.% (63/1138)	4.3% (98/2299)	6.5% (9/139)	4.0% (4/100)	4.5% (10/222)
Clinically Driven TVR	4.6% (63/1376)	4.9% (55/1130)	4.8% (55/1138)	4.2% (97/2299)	0.7% (1/139)	1.0% (1/100)	2.7% (6/222)
TLR	2.8% (39/1376)	3.9% (44/1130)	3.4% (39/1138)	3.4% (79/2299)	0.7% (1/139)	0.0% (0/100)	1.4% (3/222)
Non-TL TVR	2.2% (30/1376)	1.9% (21/1130)	2.2% (25/1138)	1.1% (26/2299)	0.0% (0/139)	1.0% (1/100)	1.4% (3/222)
ARC Def/Prob ST[9]	0.1% (2/1376)	1.6% (18/1130)	0.7% (8/1138)	0.9% (20/2299)	0.0% (0/139)	0.0% (0/100)	0. 9%（2/222）
Latest Follow-up	**18 Months N = 551[10]**	**24 Months**			**48 Months**		
TLF	6.8% (37/545)	11.2% (126/1121)	10.7% (121/1128)		8.7% (12/138)		
TVF	8.6% (47/545)	12.6% (141/1121)	12.2% (138/1128)		10.1% (14/138)		
MACE	8.3% (45/545)	12.5% (140/1121)	12.9% (146/1128)		13.8% (19/138)		

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
Total Death	2.4% (13/545)	3.2% (36/1121)	4.0% (45/1128)		5.8% (8/138)		
Cardiac Death	0.9% (5/545)	2.6% (29/1121)	2.2% (25/1128)		0.7% (1/138)		
Non-Cardiac Death	1.5% (8/545)	0.6% (7/1121)	1.8% (20/1128)		5.1% (7/138)		
TVMI	1.5% (8/545)	4.7% (53/1121)	4.5% (51/1128)		5.8% (8/138)		
Q wave MI	0.2% (1/545)	1.0% (11/1121)	0.5% (6/1128)		0.0% (0/138)		
Non-Q Wave MI	1.3% (7/545)	3.8% (43/1121)	4.0% (45/1128)		5.8% (8/138)		
Cardiac Death or TVMI	2.4% (13/545)	7.0% (78/1121)	6.3% (71/1128)		6.5% (9/138)		
Clinically Driven TVR	6.6% (36/545)	7.3% (82/1121)	6.9% (78/1128)		3.6% (5/138)		
TLR	4.4% (24/545)	5.7% (64/1121)	5.1% (58/1128)		2.2% (3/138)		
Non-TL TVR	2.9% (16/545)	3.1% (35/1121)	3.2% (36/1128)		1.4% (2/138)		
ARC Def/Prob ST	0.4% (2/545)	1.9% (21/1121)	1.0% (11/1128)		0.0% (0/138)		

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).
18-month timeframe includes follow-up window (540 days ± 30 days).
24-month timeframe includes follow-up window (720 days ± 30 days).
48-month timeframe includes follow-up window (1440 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.

[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.

[10] N = 551 subjects with 18-month data currently available.

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 ≥ 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 Group[1]

Error! Reference source not found. 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.

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

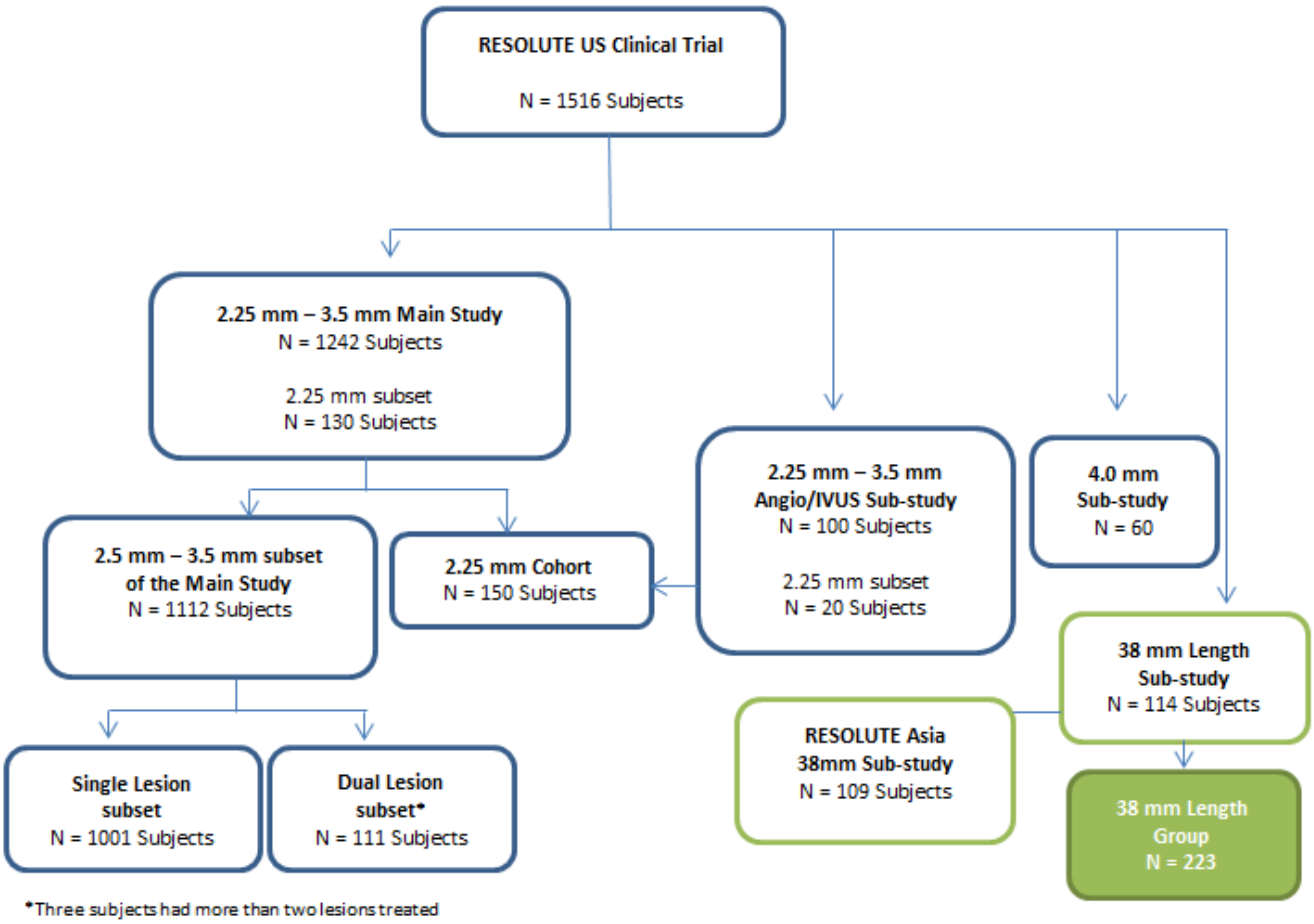


Figure 9-1: Study Designation of RESOLUTE US Clinical Trial

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 ± 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 3.7% (36/982) in comparison to the Endeavor stent historical control rate of 6.5% (70/1076), $P_{non\text{-}inferiority}<0.001$.

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 12 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	3.7% (36/982)	6.5% (70/1076)	-2.8%	-1.3%	<0.001

Notes
N = The total number of subjects enrolled.
TLF = Target lesion failure
Subjects are only counted once for each time period.
The numbers are % (Count/Number of Eligible Subjects) or least squares mean ± standard error.
The primary endpoint analysis for the 2.5 mm – 3.5 mm subset of the Main Study only includes subjects with a single lesion.
12-month timeframe includes follow-up window (360 days ± 30 days).
[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	3.7% (36/982)	6.5% (70/1076)
TVF	5.1% (50/982)	8.3% (89/1076)
MACE	4.3% (42/982)	7.0% (75/1076)
EFFECTIVENESS		
Clinically Driven TVR	3.7% (36/982)	6.0% (65/1076)
TLR	2.0% (20/982)	4.0% (43/1076)
TLR, PCI	1.7% (17/982)	3.7% (40/1076)
TLR, CABG	0.3% (3/982)	0.5% (5/1076)
Non-TL TVR	1.8% (18/982)	2.5% (27/1076)
Non-TL TVR, PCI	1.5% (15/982)	2.1% (23/1076)
Non-TL TVR, CABG	0.3% (3/982)	0.5% (5/1076)
SAFETY		
Total Death	0.9% (9/982)	1.3% (14/1076)
Cardiac Death	0.4% (4/982)	0.8% (9/1076)
Non-Cardiac Death	0.5% (5/982)	0.5% (5/1076)
Cardiac Death or TVMI	1.7% (17/982)	3.2% (34/1076)
TVMI	1.3% (13/982)	2.4% (26/1076)
Q wave MI	0.2% (2/982)	0.3% (3/1076)
Non-Q wave MI	1.2% (12/982)	2.1% (23/1076)
Stent Thrombosis ARC defined		
Definite/Probable	0.0% (0/982)	0.7% (7/1076)
Definite	0.0% (0/982)	0.5% (5/1076)
Probable	0.0% (0/982)	0.2% (2/1076)
ACUTE SUCCESS		
Procedure Success	98.6% (981/995)	97.6% (1060/1086)

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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

Outcomes at 12 Months	2.5 mm - 3.5 mm subset of the Main Study (N = 1112)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	3.8% (42/1093)
TVF	5.3% (58/1093)
MACE	4.6% (50/1093)
EFFECTIVENESS	
Clinically Driven TVR	3.8% (42/1093)
TLR	2.2% (24/1093)
TLR, PCI	1.9% (21/1093)
TLR, CABG	0.3% (3/1093)
Non-TL TVR	1.9% (21/1093)
Non-TL TVR, PCI	1.6% (17/1093)
Non-TL TVR, CABG	0.4% (4/1093)
SAFETY	
Total Death	0.9% (10/1093)
Cardiac Death	0.4% (4/1093)
Non-Cardiac Death	0.5% (6/1093)
Cardiac Death or TVMI	1.7% (19/1093)
TVMI	1.4% (15/1093)
Q wave MI	0.2% (2/1093)
Non-Q wave MI	1.2% (13/1093)
Stent Thrombosis ARC defined	
Definite/Probable	0.0% (0/1093)
Definite	0.0% (0/1093)
Probable	0.0% (0/1093)

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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.

Table 9-4: RESOLUTE US 2.5-3.5 mm Subset of the Main Study - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

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

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

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

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

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

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

Table 9-5: RESOLUTE US 2.5 - 3.5 mm Subset of the Main Study Clinical Results – Single versus Dual Lesion Subjects

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

Notes

* 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).

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 65.3% (98/150) being males. 34.0% (49/144) had a prior history of MI, 42.0% (63/150) had a prior history of PCI, and 15.3% (23/150) had 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 ± 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% (7/146) and an upper one-sided 95% CI of 8.8%. (P-value <0.001).

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

- **Table 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 12 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% (7/146)	20%	8.8%	<0.001

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
The numbers are % (Count/Number of Eligible Subjects) or least squares mean ± standard error.
The primary endpoint analysis utilized a randomly selected lesion from subjects who had treatment of dual 2.25mm lesions.
12-month timeframe includes follow-up window (360 days ± 30 days).
[1] One-sided confidence interval using normal approximation.
[2] One sided p-value test using asymptotic test statistic, to be compared at a 0.05 significance level.

Table 9-7: RESOLUTE US 2.25mm Cohort – Principal Safety and Effectiveness

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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.

Table 9-8: RESOLUTE US 2.25mm Cohort - ARC Defined Definite/Probable Stent Thrombosis Through 12 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)

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
12-month timeframe includes follow-up window (360 days ± 30 days).
See **Table 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 ± 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 $P_{non\text{-}inferiority}<0.001$.

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 12 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.
[1] The CI and P-values are adjusted to propensity score, based on lesion length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society Angina Class as the independent variables.
[2] One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16mm, to be compared at a 0.05 significance level.

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

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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.

Table 9-11: RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months.

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
12-month timeframe includes follow-up window (360 days ± 30 days).
See **Table 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 ± 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, $P_{superiority}<0.001$.

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 12 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 4.0mm lesions

[1] The CI and P-values are adjusted to propensity score, based on lesion length, baseline RVD, age, sex, diabetes, history of MI and worst Canadian Cardiovascular Society Angina Class as the independent variables.

[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

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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.

Table 9-15: RESOLUTE US 4.0mm Sub-study - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
12-month timeframe includes follow-up window (360 days ± 30 days).
See **Table 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, 444/1402 (31.7%) subjects were female and 958/1402 (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=958)	Female (N=444)	p-value
Age (Years)	63.2 ± 10.5	66.2 ± 10.8	< 0.001
History of smoking/tobacco use	66.9% (641/958)	52.9% (235/444)	< 0.001
Prior PCI	34.1% (327/958)	29.5% (131/444)	0.087
Hyperlipidemia	88.5% (848/958)	86.0% (382/444)	0.190
Diabetes Mellitus	31.3% (300/958)	41.0% (182/444)	< 0.001
Insulin Dependent	7.2% (69/958)	14.9% (66/444)	< 0.001
Hypertension	82.3% (788/958)	88.3% (392/444)	0.004
Prior MI	24.6% (232/944)	15.2% (66/435)	< 0.001
Prior CABG	10.6% (102/958)	5.0% (22/444)	< 0.001
Ejection fraction - Qualitative			0.059
<30%	0.1% (1/824)	0.3% (1/385)	
30-40%	6.7% (55/824)	3.4% (13/385)	
>40%	93.2% (768/824)	96.4% (371/385)	
Lesion Class			0.019
A	5.5% (60/1083)	7.7% (37/483)	
B1	17.1% (185/1083)	22.2% (107/483)	
B2	30.8% (334/1083)	27.5% (133/483)	
C	46.5% (504/1083)	42.7% (206/483)	
Moderate/Severe Calcification	25.9% (281/1083)	29.0% (140/483)	0.217
Pre procedure RVD	2.621 ± 0.480	2.528 ± 0.435	< 0.001
Pre procedure MLD	0.754 ± 0.354	0.792 ± 0.339	0.048
Pre procedure Diameter Stenosis	71.4 ± 11.6	68.9 ± 11.2	< 0.001
Lesion Length	13.271 ± 5.892	12.603 ± 5.840	0.038

The 12 month rate of TLF was 4.4% in males and 5.3% in females **(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 - 12 Month Clinical Endpoints by Gender – Principal Safety and Effectiveness

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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

See **Section 9.7.1 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 ≤ 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±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% (10/222) with an upper one-sided 95% CI of 7.5%, which met the performance goal of 19%, (P-value <0.001).

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
- **Table 9-21:** 38 mm Length Group – ARC Defined/Probable Stent Thrombosis Through 12 Months.

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% (10/222)	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 ± 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

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

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 Error! Reference source not found.- Principal Adverse Events.
12-month timeframe includes follow-up window (360 days ± 30 days).
† 5 subjects with side branch occlusion had a TVMI
See Error! Reference source not found. for the definition of the ARC defined Stent Thrombosis.

Table 9-21: 38 mm Length Group – ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

	38 mm Length Group (N = 223)	R-US Sub-study (N = 114)	R-Asia Cohort (N = 109)
Stent Thrombosis	0.9% (2/222)	0.9% (1/113)	0.9% (1/109)
Acute (0-1 day)	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)
Subacute (2-30 days)	0.9% (2/222)	0.9% (1/113)	0.9% (1/109)
Late (31-360 days)	0.0% (0/222)	0.0% (0/113)	0.0% (0/109)

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
12-month timeframe includes follow-up window (360 days ± 30 days).
See **Table 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 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 9-22: 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 9-18)**. 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 9-23: 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 ARC defined		
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 9-24 for R-AC Baseline Characteristics.

Table 9-24: R-AC - Baseline Characteristics

Baseline Characteristics	Resolute (N=1140 subjects; N=1661 lesions)	Xience V (N=1152 subjects; N=1705 lesions)
Mean Age (years)	64.4	64.2
Male Enrollment	76.7% (874/1140)	77.2% (889/1152)
Hx of prior PCI	31.8% (363/1140)	32.1% (370/1152)
Hx of prior MI	28.8% (323/1122)	30.4% (341/1120)
Hx of Diabetes	23.5% (268/1140)	23.4% (270/1152)
Multi-vessel disease	58.4% (666/1140)	59.2% (682/1152)
Type B2/C lesions	77.5% (1268/1636)	74.7% (1251/1673)
Syntax Score	14.8 ± 9.3	14.6 ± 9.2
Complex*	67% (764/1140)	65.6% (756/1152)

* 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 9-25:** R-AC Principal Safety and Effectiveness (All subjects)
- **Table 9-26:** R-AC Principal Safety and Effectiveness (Complex cohort)
- **Table 9-27:** R-AC Principal Safety and Effectiveness (Non-Complex cohort)
- **Table 9-28:** R-AC ARC Defined Definite/Probable Stent Thrombosis through 24 Months (Complex and Non-Complex)

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 9-25 R-AC Principal Safety and Effectiveness (All subjects)

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
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)
24-month timeframe includes follow-up window (720 days ± 30 days).
See **Table 9-4** for the definition of the ARC defined Stent Thrombosis.

Table 9-26 R-AC Principal Safety and Effectiveness (Complex cohort)

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
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)
24-month timeframe includes follow-up window (720 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 9-27: R-AC Principal Safety and Effectiveness (Non-Complex cohort)

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
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)
24-month timeframe includes follow-up window (720 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 ARC Defined Definite/Probable Stent Thrombosis Through 24 Months (All Subjects, and Complex and Non-Complex Subjects)

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

Notes

N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
12-month timeframe includes follow-up window (360± 30 days)
24-month timeframe includes follow-up window (720 days ± 30 days).
See **Table 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 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 results are presented in the following tables:

- **Table 9-29:** RESOLUTE International - Principal Safety and Effectiveness
- **Table 9-30:** RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

Table 9-29: RESOLUTE International - Principal Safety and Effectiveness

Outcomes at 12 Months	(N = 2349)
COMPOSITE SAFETY AND EFFECTIVENESS	
TLF	7.0% (162/2299)
TVF	7.7% (177/2299)
MACE	8.2% (188/2299)
EFFECTIVENESS	
Clinically Driven TVR	4.2% (97/2299)
TLR	3.4% (79/2299)
TLR, PCI	3.1% (72/2299)
TLR, CABG	0.3% (8/2299)
Non-TL TVR	1.1% (26/2999)
Non-TL TVR, PCI	1.1% (26/2299)
Non-TL TVR, CABG	0.0% (0/2299)
SAFETY	
Total Death	2.4% (56/2299)
Cardiac Death	1.4% (33/2299)
Non-Cardiac Death	1.0% (23/2299)
Cardiac Death or MI	4.3% (98/2299)
TVMI	3.1% (71/2299)
Q wave MI	0.5% (12/2299)
Non-Q wave MI	2.6% (59/2299)
Stent Thrombosis ARC defined	
Definite/Probable	0.9% (20/2299)
Definite	0.7% (15/2299)
Probable	0.3% (6/2299)

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month timeframe includes follow-up window (360 days ± 30 days).
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 9-30: RESOLUTE International - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
See **Table 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, $p_{non\text{-}inferiority}<0.001$.

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 9-31:** RESOLUTE FIM - Primary Endpoint Analysis
- **Table 9-32:** RESOLUTE FIM - Principal Safety and Effectiveness

- **Table 9-33:** RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis through 48 Months
- **Table 9-34:** RESOLUTE FIM - Angiographic and IVUS Results

Table 9-31: 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 9-32: RESOLUTE FIM - Principal Safety and Effectiveness

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
9-month timeframe includes follow-up window (270 days ± 14 days).
12-month timeframe includes follow-up window (360 days ± 30 days).
48-month timeframe includes follow-up window (1440 days ± 30 days).
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 9-33: RESOLUTE FIM - ARC Defined Definite/Probable Stent Thrombosis Through 48 Months

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
48-month time frame includes follow-up window (1440 days ± 30 days).
See **Table 9-4** for the definition of the ARC defined Stent Thrombosis

Table 9-34 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: 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 ± 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.

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

Table 9-35: RESOLUTE Japan - Primary Endpoint Analysis

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

Table 9-37: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis through 12 Months

Table 9-38: RESOLUTE Japan - Angiographic and IVUS Results

Table 9-35: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 9-36: RESOLUTE Japan - Principal Safety and Effectiveness

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month timeframe includes follow-up window (360 days ± 30 days).
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 9-37: RESOLUTE Japan - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month timeframe includes follow-up window (360 days ± 30 days).
See **Table 9-4** for the definition of the ARC defined Stent Thrombosis.

Table 9-38: RESOLUTE Japan - Angiographic and IVUS Results

Outcomes at 8 Months	(N = 100, M = 108)
ANGIOGRAPHIC RESULTS	
MLD (mm), In-stent	
Post-Procedure	2.79 ± 0.40 (108)
8-Month	2.66 ± 0.46 (107)
MLD (mm), In-segment	
Post-Procedure	2.45 ± 0.43 (108)
8-Month	2.35 ± 0.47 (107)
% DS, In-stent	
Post-Procedure	3.28 ± 7.19 (108)
8-Month	6.52 ± 9.20 (107)
% DS, In-segment	
Post-Procedure	15.23 ± 7.39 (108)
8-Month	17.71 ± 8.72 (107)
Late Loss (mm)	
In-stent	0.12 ± 0.22 (107)
In-segment	0.10 ± 0.25 (107)
Binary Restenosis	
In-stent	0.0% (0/107)
In-segment	0.0% (0/107)
IVUS RESULTS	
Neointimal Volume (mm^3)	3.10 ± 4.46 (98)
% Volume Obstruction	2.10 ± 2.66 (98)
Incomplete Apposition	7.8% (8/102)
Persistent	4.9% (5/102)
Late Acquired	2.9% (3/102)

Notes
N = The total number of subjects enrolled.
M = The number of lesions at baseline.
Numbers are % (Count/Number of Evaluable Lesions) or Mean ± SD (Number of Evaluable Lesions).
Subjects are only counted once for each time period.

9.6 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[2,3]. 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 9.6.1** for the Resolute US 38 mm Length Group for subjects with Diabetes Mellitus.

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

---

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

3 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.

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 9-39**: RESOLUTE Diabetes Mellitus Cohort - Primary Endpoint Analysis
- **Table 9-40:** 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 9-41:** RESOLUTE Diabetes Mellitus Cohort - ARC Defined Definite/Probable Stent Thrombosis Events through 12 Months

Table 9-39: 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 9-40: 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 9-41: 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.

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

Additional information is provided in **Table 9-42** for the RESOLUTE US 38 mm Length Group in subjects with Diabetes Mellitus.

Table 9-42: 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)

9.7 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 9-43** below provides the total number of subjects included in the analyses.

Table 9-43: 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	764
RESOLUTE US	1402	1402
RESOLUTE Japan	100	100
Pooled Resolute Dataset	**5130**	**2781**
Subjects from the 38 mm Length sub-study were not included in the RESOLUTE pooled analysis		

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 9-44**: Resolute Pooled Analysis - Principal Safety and Effectiveness
- **Table 9-45:** Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis* through 12 Months

Table 9-44: Resolute Pooled Analysis - Principal Safety and Effectiveness Through 12 Months

	All Subjects (N = 5130)	On-label (N = 2781)
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	6.6% (333/5044)	5.4% (149/2734)
TVF	7.5% (379/5044)	6.6% (180/2734)
MACE	7.5% (378/5044)	6.3% (171/2734)
EFFECTIVENESS		
Clinically Driven TVR	4.3% (217/5044)	3.7% (101/2734)
TLR	3.2% (163/5044)	2.5% (67/2734)
SAFETY		
Total Death	1.9% (96/5044)	1.6% (43/2734)

	All Subjects (N = 5130)	On-label (N = 2781)
Cardiac Death	1.1% (58/5044)	0.9% (25/2734)
Non-Cardiac Death	0.8% (38/5044)	0.7% (18/2734)
TVMI	3.0% (150/5044)	2.5% (67/2734)
Cardiac Death or TVMI	3.9% (199/5044)	3.3% (90/2734)
Stent Thrombosis ARC defined		
Definite/Probable	0.8% (40/5044)	0.3% (9/2734)
Definite	0.6% (29/5044)	0.2% (6/2734)
Probable	0.3% (13/5044)	0.1% (3/2734)

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
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 9-45: Resolute Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

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

N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
See **Table 9-4** for the definition of the ARC defined Stent Thrombosis.

9.7.1 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).[4] 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[5], 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

[4] 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.

[5] 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.

(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 9-46describes the baseline and demographic characteristics by gender for subjects in the pooled on-label analysis. 783/2781 (28.2%) subjects were female and 1998/2781 (71.8%) were male. Female patients at baseline were older, had higher rates of diabetes and hypertension, and had smaller reference vessel diameters (RVD).

Table 9-4644: Baseline Characteristics of Male vs. Female for Pooled On-Label Resolute Patients

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

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

The pooled Resolute stent on-label use data were evaluated retrospectively for gender-based clinical outcomes. **Table 9-47**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. Although event rates were numerically higher in women (except for non-cardiac death), the results suggest that the safety and effectiveness profile of the Resolute stent is generalizable to both males and females.

Table 9-47: Resolute Pooled On-Label Gender (Male vs. Female) – Principal Safety and Effectiveness Through 12 Months

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

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
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.
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.

9.7.2 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 9-48**, **Table 9-49**, **Table 9-50**). 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 9-48: 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 9-49: 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 9-50: 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 System. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. Administration of $P2Y_{12}$ platelet inhibitor is recommended pre-procedure and for a period of 12 months post-procedure for patients who are not at high risk of bleeding (see **Section 5.1 - Pre- and Post-Procedure Antiplatelet Regimen**). Aspirin should be administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely. Stenting is generally avoided in patients at risk of bleeding and for those with contraindicated anticoagulation therapy.

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 this 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 ºC (77 ºF); excursions permitted to 15-30 ºC (59-86 ºF). 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 [≥ 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 [≤ 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.
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.

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.

The exclusions and limitations set out above are not intended to and should not be construed so as to contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected.

MANUFACTURER:
MEDTRONIC, INC.
710 Medtronic Parkway
Minneapolis, MN 55432
U.S.A.
Tel: (+1-763) 514-4000
Fax: (+1-763) 514-4879
www.medtronic.com

U.S. CUSTOMER SERVICE / PRODUCT INQUIRIES
Tel: (+1-888) 283-7868
Fax: (+1-800) 838-3103

M724130B001 Rev 1C