Medtronic

Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System
Rapid Exchange and Over-the-Wire Delivery Systems

INSTRUCTIONS FOR USE

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

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

1 RESOLUTE ONYX™ ZOTAROLIMUS-ELUTING CORONARY STENT SYSTEM

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

Table 1-1: Device Component Description and Nominal Dimensions

Component		Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Rapid Exchange and Over-the-Wire Delivery Systems			
		Stent Design 1 (Small Vessel)	Stent Design 2 (Medium Vessel)	Stent Design 3 (Large Vessel)	Stent Design 4 (Extra Large Vessel)
Available Stent Diameters (mm)		2.0, 2.25, 2.5	2.75, 3.0	3.5, 4.0	(RX Only) – 4.5, 5.0
Available Stent Lengths (mm)		8, 12, 15, 18, 22, 26, 30, 34*, 38* *34, 38 mm lengths not available in 2.0 mm	8, 12, 15, 18, 22, 26, 30, 34, 38	8, 12, 15, 18, 22, 26, 30, 34, 38	(RX Only) – 12, 15, 18, 22, 26, 30
Stent Material and Geometry		A continuous sinusoid pattern stent manufactured from a composite metal material, consisting of a cobalt-based alloy shell conforming to ASTM F562 and a platinum-iridium alloy core conforming to ASTM B684.			
Drug Component		A coating of polymers loaded with zotarolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.6 μg/mm^2 which results in a maximum nominal drug content of 317 μg on the stent with the largest surface area (4.0 x 38 mm).			
Delivery Systems Effective (Working) Length		140 cm			
Delivery System Luer Adapter Ports	RX	Single access port to the inflation lumen. A guidewire exit port is located approximately 25 cm from the tip. Designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
	OTW	Y-Connector with side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
Stent Delivery Balloon		Single-layer Pebax balloon, wrapped over an inner member tubing with 2 radiopaque marker bands to locate the stent edges.			
Balloon Inflation Pressure		Nominal Inflation Pressure: 12 ATM (1216 kPa) Rated Burst Pressure: 2.0-4.0 mm = 18 ATM (1824 kPa), RX Only: 4.5-5.0 mm = 16 ATM (1621kPa)			
Minimum Guide Catheter Inner Diameter		≥5 F (1.42 mm, 0.056 in)			
Catheter Shaft Outer Diameter	RX	Proximal Shaft OD: 2.1 F (0.69 mm) Distal Shaft OD 2.0 – 4.0 mm: 2.7 F (0.91 mm) Distal Shaft OD 4.5 and 5.0 mm: 3.2 F (1.07 mm)			

Table 1-1: Device Component Description and Nominal Dimensions

Component		Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System Rapid Exchange and Over-the-Wire Delivery Systems			
		Stent Design 1 (Small Vessel)	Stent Design 2 (Medium Vessel)	Stent Design 3 (Large Vessel)	Stent Design 4 (Extra Large Vessel)
	OTW	Proximal Shaft OD: 3.4 F (1.12 mm) Distal Shaft OD: 2.7 F (0.91 mm)			

Device Component Description

The Medtronic Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (Resolute Onyx™ system) consists of a balloon-expandable, intracoronary, drug-eluting stent (DES) premounted on a Rapid Exchange (RX) or an Over-the-Wire (OTW) stent delivery system. The Resolute Onyx™ stent is manufactured from a composite material of cobalt alloy and platinum-iridium alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The stents are available in multiple lengths and diameters. The delivery system has two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014-inch (0.36-mm) guidewires and 1.42-mm (5-Fr/0.056-in) minimum inner diameter guide catheters. The Resolute Onyx™ RX delivery system (Figure 1-1) and the Resolute Onyx™ OTW delivery system (Figure 1-2) have an effective length of 140 cm.

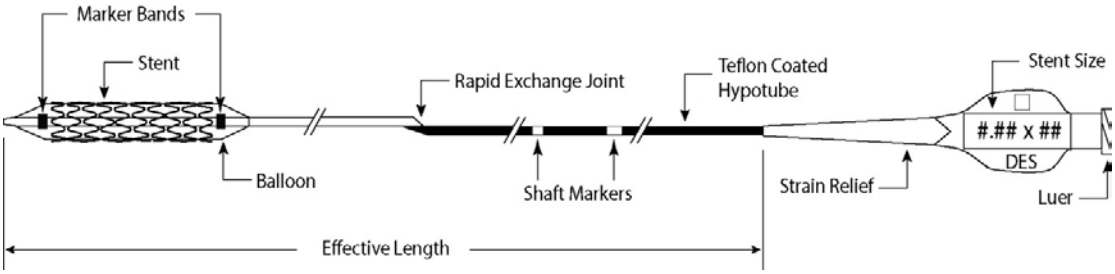

Figure 1-1: Resolute Onyx™ Rapid Exchange (RX) Delivery System (with Stent)
Illustration is not to scale

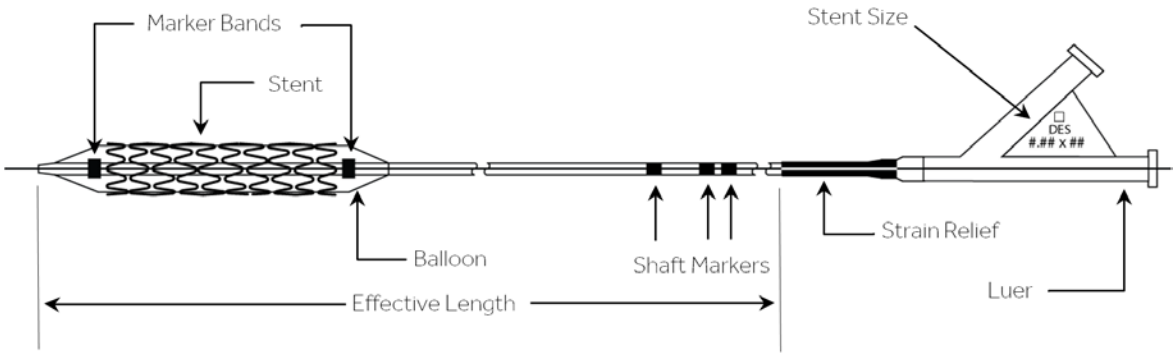

Figure 1-2: Resolute Onyx™ Over-the-Wire (OTW) Delivery System (with Stent)
Illustration is not to scale

The stent is crimped on various sizes of delivery catheter balloons, which range from 2.0 mm to 5.0 mm. The Resolute Onyx™ available stent sizes are listed in Table 1-2.

Table 1-2: Resolute Onyx™ Stent Sizes

Diameter (mm)	Stent Length (mm)								
	8	12	15	18	22	26	30	34	38
2.0	✓	✓	✓	✓	✓	✓	✓	-	-
2.25	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.75	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.5	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.0	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.5	-	✓*	✓*	✓*	✓*	✓*	✓*	-	-
5.0	-	✓*	✓*	✓*	✓*	✓*	✓*	-	-

"-" Denotes stent length is not available
"*" Not available for OTW

1.1 Drug Component Description

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

1.1.1 Zotarolimus

The active pharmaceutical ingredient utilized in the Resolute Onyx™ 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 1-3:

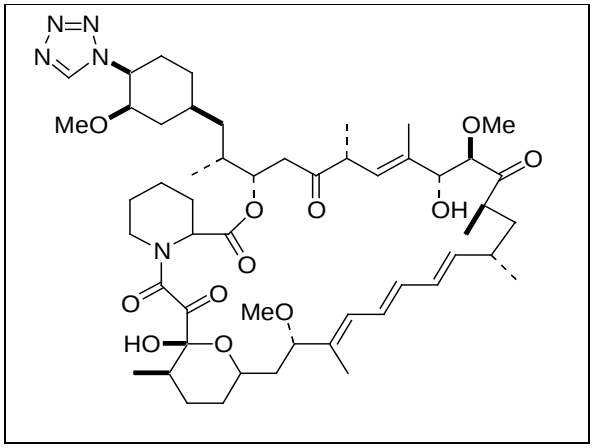

Figure 1-3: Zotarolimus Chemical Structure

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.

1.1.2 Polymer System Description

The Resolute Onyx™ 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 1-4:

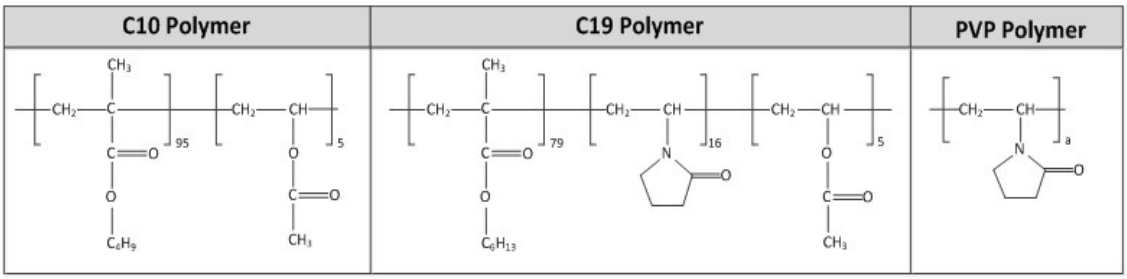

Figure 1-4: Chemical Structure of the BioLinx™ Polymer Subunits

1.1.3 Product Matrix and Zotarolimus Content

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

Product Number RX	Product Number OTW	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RONYX20008UX	RONYX20008W	2.0	8	51
RONYX22508UX	RONYX22508W	2.25	8	51
RONYX25008UX	RONYX25008W	2.5	8	51
RONYX27508UX	RONYX27508W	2.75	8	67
RONYX30008UX	RONYX30008W	3.0	8	67
RONYX35008UX	RONYX35008W	3.5	8	77
RONYX40008UX	RONYX40008W	4.0	8	77
RONYX20012UX	RONYX20012W	2.0	12	70
RONYX22512UX	RONYX22512W	2.25	12	70
RONYX25012UX	RONYX25012W	2.5	12	70
RONYX27512UX	RONYX27512W	2.75	12	94
RONYX30012UX	RONYX30012W	3.0	12	94
RONYX35012UX	RONYX35012W	3.5	12	108
RONYX40012UX	RONYX40012W	4.0	12	108
RONYX45012UX	-	4.5	12	132
RONYX50012UX	-	5.0	12	132
RONYX20015UX	RONYX20015W	2.0	15	85
RONYX22515UX	RONYX22515W	2.25	15	85
RONYX25015UX	RONYX25015W	2.5	15	85
RONYX27515UX	RONYX27515W	2.75	15	117
RONYX30015UX	RONYX30015W	3.0	15	117
RONYX35015UX	RONYX35015W	3.5	15	132
RONYX40015UX	RONYX40015W	4.0	15	132
RONYX45015UX	-	4.5	15	158
RONYX50015UX	-	5.0	15	158
RONYX20018UX	RONYX20018W	2.0	18	104
RONYX22518UX	RONYX22518W	2.25	18	104
RONYX25018UX	RONYX25018W	2.5	18	104
RONYX27518UX	RONYX27518W	2.75	18	140
RONYX30018UX	RONYX30018W	3.0	18	140
RONYX35018UX	RONYX35018W	3.5	18	156
RONYX40018UX	RONYX40018W	4.0	18	156
RONYX45018UX	-	4.5	18	188
RONYX50018UX	-	5.0	18	188
RONYX20022UX	RONYX20022W	2.0	22	127
RONYX22522UX	RONYX22522W	2.25	22	127
RONYX25022UX	RONYX25022W	2.5	22	127

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

Product Number RX	Product Number OTW	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
RONYX27522UX	RONYX27522W	2.75	22	171
RONYX30022UX	RONYX30022W	3.0	22	171
RONYX35022UX	RONYX35022W	3.5	22	186
RONYX40022UX	RONYX40022W	4.0	22	186
RONYX45022UX	-	4.5	22	227
RONYX50022UX	-	5.0	22	227
RONYX20026UX	RONYX20026W	2.0	26	146
RONYX22526UX	RONYX22526W	2.25	26	146
RONYX25026UX	RONYX25026W	2.5	26	146
RONYX27526UX	RONYX27526W	2.75	26	198
RONYX30026UX	RONYX30026W	3.0	26	198
RONYX35026UX	RONYX35026W	3.5	26	221
RONYX40026UX	RONYX40026W	4.0	26	221
RONYX45026UX	-	4.5	26	265
RONYX50026UX	-	5.0	26	265
RONYX20030UX	RONYX20030W	2.0	30	168
RONYX22530UX	RONYX22530W	2.25	30	168
RONYX25030UX	RONYX25030W	2.5	30	168
RONYX27530UX	RONYX27530W	2.75	30	225
RONYX30030UX	RONYX30030W	3.0	30	225
RONYX35030UX	RONYX35030W	3.5	30	252
RONYX40030UX	RONYX40030W	4.0	30	252
RONYX45030UX	-	4.5	30	304
RONYX50030UX	-	5.0	30	304
RONYX22534UX	RONYX22534W	2.25	34	187
RONYX25034UX	RONYX25034W	2.5	34	187
RONYX27534UX	RONYX27534W	2.75	34	257
RONYX30034UX	RONYX30034W	3.0	34	257
RONYX35034UX	RONYX35034W	3.5	34	282
RONYX40034UX	RONYX40034W	4.0	34	282
RONYX22538UX	RONYX22538W	2.25	38	206
RONYX25038UX	RONYX25038W	2.5	38	206
RONYX27538UX	RONYX27538W	2.75	38	284
RONYX30038UX	RONYX30038W	3.0	38	284
RONYX35038UX	RONYX35038W	3.5	38	317
RONYX40038UX	RONYX40038W	4.0	38	317

2 INDICATIONS

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to de novo lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.0 mm to 5.0 mm. In addition, the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is indicated for treating *de novo* chronic total occlusions.

3 CONTRAINDICATIONS

The Resolute Onyx™ System is contraindicated for use in:

- Patients with known hypersensitivity or allergies to aspirin, heparin, bivalirudin, clopidogrel, prasugrel, ticagrelor, ticlopidine, drugs such as zotarolimus, tacrolimus, sirolimus, everolimus, or similar drugs or any other analogue or derivative.
- Patients with a known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum) or platinum-iridium alloy.
- Patients with a known hypersensitivity to the BioLinx® polymer or its individual components (see details in **Section 1.1.2 – Polymer System Description**).

Coronary artery stenting is contraindicated for use in:

- Patients in whom anti-platelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or stent delivery system.

4 WARNINGS

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

5 PRECAUTIONS

- Only physicians who have received adequate training should perform implantation of the stent.
- Subsequent stent restenosis or occlusion may require repeat catheter-based treatments (including balloon dilatation) of the arterial segment containing the stent. The long term outcome following repeat catheter-based treatments of previously implanted stents is not well characterized.
- The risks and benefits of stent implantation should be assessed for patients with a history of severe reaction to contrast agents.
- Do not expose or wipe the product with organic solvents such as alcohol.
- The use of a DES outside of the labeled indications, including use in patients with 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, stent deployment, and balloon withdrawal. Before withdrawing the stent delivery system, confirm complete balloon deflation using fluoroscopy to avoid arterial damage caused by guiding catheter movement into the vessel.

- 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 9.5 – Pooled Results of the Global RESOLUTE Clinical Trial Program** for more information).

5.1 Pre- and Post-Procedure Antiplatelet Regimen

In the Medtronic RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study, RESOLUTE ONYX 2.0 mm Clinical Study, and in the Global RESOLUTE studies; 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 (or any approved antiplatelet/thienopyridine in the RESOLUTE ONYX Core Clinical Study) 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 (or any approved antiplatelet/thienopyridine) and then continued indefinitely to reduce the risk of thrombosis. In the Medtronic RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study, 93.3%, 93.2% and 89% of the subjects remained on dual antiplatelet therapy at 6 months, 8 months and 12 months, respectively. In the Medtronic RESOLUTE ONYX 2.0 mm Clinical Study, 93.0% and 90.0% of the subjects remained on dual antiplatelet therapy at 6 months and 12 months, respectively. In the RESOLUTE US Primary Enrollment Group, 95.9%, 93.8% and 46.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE AC Clinical Trial, 93.1%, 84.2% and 11.0% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE International Study, 95.9%, 91.1% and 34.6% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 36 months, respectively. In the RESOLUTE FIM Clinical Trial, 79.1%, 58.1% and 39.4% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE Japan Clinical Trial, 99.0%, 94.9% and 62.5% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively. In the RESOLUTE 38 mm Length Group, 92.8%, 91.4% and 61.5% of the patients remained on dual antiplatelet therapy at 6 months, 12 months and 60 months, respectively.

5.1.1 Oral Antiplatelet Therapy

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

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

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

Consistent with the DAPT Study,[2] and the 2016 ACC/AHA guidelines, longer duration of DAPT may be considered in patients at higher ischemic risk with lower bleeding risk.

In patients at higher risk of bleeding, DAPT discontinuation may be reasonable after 3 months in stable patients or 6 months in ACS patients.

Decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference.

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

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

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

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

5.2 Use of Multiple Stents

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

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

Potential interactions of the Resolute Onyx™ 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 atherectomy devices with Resolute Onyx™ stent have not been established.

5.4 Brachytherapy

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

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

5.5 Use in Special Populations

Information on use of the Resolute Onyx™ 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**

5.5.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women or men intending to father children. The Resolute Onyx™ 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 Onyx™ stent and for 1 year after implantation. **See Section 6.6 – Pregnancy** under **Drug Information**.

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 Onyx™ 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.

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 Onyx™ stent in patients below the age of 18 years have not been established.

5.5.6 Geriatric Use

The RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study, the RESOLUTE ONYX 2.0 mm Clinical Study, and the RESOLUTE clinical studies did not have an upper age limit. Among the 1,242 patients treated with the Resolute stent in the RESOLUTE US Main Study, which included 2.25 mm to 3.5 mm stents, 617 patients were age 65 or older and 88 patients were age 80 or older. A post hoc analysis of patients treated with the Resolute stent showed no significant differences 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 Onyx™ 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 < 2.0 mm or > 5.0 mm.
- Patients with evidence of an acute ST-elevation 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 3 vessel disease.

5.6 Drug Interactions

The effect of potential drug interactions on the safety or effectiveness of the Resolute Onyx™ 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 Onyx™ 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 Onyx™ stent.

5.7 Magnetic Resonance Imaging (MRI) Safety Information

Non-clinical testing has demonstrated that the Resolute Onyx™ stent is MR Conditional for single and overlapping lengths up to 120 mm. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 and 3 Tesla only
- Maximum spatial gradient magnetic field of 3000 gauss/cm (30 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0 W/kg (Normal Operating Mode)

Under the scan conditions defined above, the Resolute Onyx™ stent is expected to produce a maximum temperature rise of 4.3°C after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extended approximately 10 mm from the Resolute Onyx™ stent when imaged with a spin echo pulse sequence and a 3 Tesla MRI system. The artifact does obscure the device lumen.

5.8 Stent Handling Precautions

- For single use only. The Resolute Onyx™ 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 Onyx™ 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 Onyx™ 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 Onyx™ stent delivery systems 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) Safety Information** 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 Onyx™ Stent

The pharmacokinetics information for the Resolute Onyx™ stent system is derived from a study conducted on the Resolute stent system. The Resolute Onyx™ 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 Onyx™ stent system.

The pharmacokinetics (PK) of zotarolimus delivered from the Resolute Stent have 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
$AUC_{0\text{-}24}$	(ng•h/mL)	34.19 ± 4.39¥	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
$t_{1/2}$$	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL[b]	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

Notes

¥ N = 16;

$ Harmonic mean ± pseudo-standard deviation

[b] Clearance data is calculated using compartmental methods.

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

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

6.5 Mutagenesis, Carcinogenicity and Reproductive Toxicology

6.5.1 Mutagenesis

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

6.5.2 Carcinogenicity

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

6.5.3 Reproductive Toxicology

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

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

6.6 Pregnancy

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

Administration of zotarolimus to pregnant female rats in a developmental toxicity study at an intravenous dosage of 60 µg/kg/day resulted in 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 Onyx™ 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 Onyx™ stents coated with 300 µg zotarolimus total dose.

Effective contraception should be initiated before implanting a Resolute Onyx™ stent and continued for one year post-stent implantation. The Resolute Onyx™ 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 RESOLUTE ONYX Clinical Program

The RESOLUTE ONYX Clinical Program currently includes the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study, conducted in the United States (US) and the RESOLUTE ONYX 2.0 mm Clinical Study conducted in the US and Japan.

Table 7-1 summarizes the clinical trial designs for the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study and the RESOLUTE ONYX 2.0 mm Clinical Study.

Table 7-1: The RESOLUTE ONYX Clinical Program

	RESOLUTE ONYX™ Core (2.25 mm – 4.0 mm) Clinical Study	RESOLUTE ONYX 2.0 mm Clinical Study
Study Type	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a Performance Goal
Study Site Location	United States	United States and Japan
Number of Subjects Enrolled	75	101
Lesion Criteria	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤35 mm ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ Single or two de novo lesions located in separate target vessels with at least one of the target lesions amenable to treatment with a 2.0 mm study stent ▪ Lesion(s) length ≤ 27 mm ▪ Target vessel with RVD between 2.0 to 2.25 mm
Stent Sizes (Resolute Onyx™)	Stent diameter: 2.25 to 4.0 mm Stent length: 8 to 38 mm	Stent diameter: 2.0 mm Stent length: 8 to 30 mm
Product Used	Resolute Onyx™ Stent on a Rapid Exchange (RX) stent delivery system	Resolute Onyx™ Stent on a Rapid Exchange (RX) stent delivery system
Post-procedure Antiplatelet Therapy	Aspirin indefinitely and market approved thienopyridine (clopidogrel, prasugrel, ticagrelor, ticlopidine, etc) for a minimum of 6 months in all subjects, and up to 12 months in subjects who are not at high risk of bleeding	Aspirin indefinitely and market approved thienopyridine (clopidogrel, prasugrel, ticagrelor, ticlopidine, etc) for a minimum of 6 months in all subjects, and up to 12 months in subjects who are not at high risk of bleeding
Follow-up	30 days, 6 months, 1 to 3 years: clinical or contact 8 months: clinical and angiographic, IVUS (subset)	30 days, 6 months, 1 to 3 years: clinical or contact 13 months: clinical and angiographic, IVUS (subset)
Status	8 months: clinical and angiographic follow-up is complete	13 months: clinical and angiographic follow-up is complete

Supportive RESOLUTE and RESOLUTE INTEGRITY data:

The Resolute Onyx™ stent is an iterative design update to the Resolute Integrity™ stent, utilizing the same continuous sinusoid manufacturing technology with slight modifications incorporated to provide a lower crossing profile and thus improved deliverability over predicate products. Given the similarities between the Resolute stent system and the Resolute Onyx™ stent system, and supportive bench and animal study information, the findings from the RESOLUTE clinical studies are applicable to the Resolute Onyx™ 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 7-2. 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 7-2). In addition, the RESOLUTE INTEGRITY US Post Market Study, a prospective, multi-center evaluation of the procedural and clinical outcomes of subjects who were treated with the Medtronic Resolute Integrity™ Zotarolimus-Eluting Coronary Stent System was designed to assess the

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

Table 7-2 summarizes the clinical trial designs for the Global RESOLUTE Clinical Trial Program and RESOLUTE INTEGRITY US Post-Market Study.

Table 7-2: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

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

Table 7-2: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG)	RESOLUTE INTEGRITY US (XL Sub-study)
Lesion Criteria	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤27 mm for the Primary Enrollment Group, ≤35 mm for the 38 mm Length Group ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.0 mm	▪ No limitation to number of lesion(s)/ vessel(s) treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.0 mm	▪ Single *de novo* lesion ▪ Lesion length from 14 to 27 mm ▪ Target vessel with RVD between 2.5 and 3.5 mm	▪ Single or two *de novo* lesions located in separate coronary arteries ▪ Lesion(s) length ≤27 mm ▪ Target vessel with RVD between 2.5 to 3.5 mm	▪ Single or two *de novo* lesions located in separate target vessels ▪ Lesion(s) length ≤35 mm ▪ Target vessel with RVD between 3.0 to 4.0 mm ▪ Patients may have received treatment of up to two lesions second lesion RVD (2.25 to 4.2 mm), if the lesions were located in separate target vessels.	▪ Single target lesion or two target lesions located in separate target vessels PEG: ▪ Target lesion ≤27 mm ▪ Target vessel with RVD between 2.25 to 4.2 mm	▪ . Single target lesion or two target lesions located in separate target vessels XL: ▪ Target lesion ≤ 35 mm treated or lesion length ▪ Target vessel with RVD between 2.25 to 4.2 mm.
Stent Sizes (Resolute)	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm for the Primary Enrollment Group, 38 mm for the 38 mm Length Group	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 38 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 2.5 – 3.5 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 38 mm	Stent diameter: 2.25 – 4.0 mm Stent length: 8 – 30 mm	Stent diameter: 3.0 – 4.0 mm Stent Length: 34-38 mm
Product Used	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange AV100 Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Stent on the Rapid Exchange Sprint Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System	Resolute Integrity Stent on the Rapid Exchange MicroTrac Delivery System
Post-procedure Antiplatelet Therapy	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine ≥ 6 months	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine,for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated	Aspirin indefinitely and clopidogrel/ticlopidine for ≥ 6 months in all subjects, up to 12 months if tolerated

Table 7-2: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG)	RESOLUTE INTEGRITY US (XL Sub-study)
Follow-up	2.25 mm - 3.5 mm Main Study: 30 days and 9 months: clinical; 6, 12 and 18 months, 2-5 years: telephone 4.0 mm Sub-study: 8 months: clinical and angiographic; 6, 12 and 18 months, 2-5 years: telephone 2.25 mm - 3.5 mm Angio/IVUS Sub-study: 8 months: clinical and angiographic/ IVUS;6, 12 and 18 months, 2-5 years: telephone 38 mm Length Sub-study: 30 days (R-US) and 9 months clinical visits (preferred) or patient contact 30 days (R-Asia), 6, 12, 18 months then annually at 2, 3, 4, 5 years	30 days and 12 months: clinical 13 months (455 subject subset): angiographic 6 months and 2-5 years: telephone	30 days, 6 months, 1-3 years: clinical or telephone	30 days: clinical 4 (30 subject subset) and 9 months (100 subject subset): clinical and angiographic/IVUS 6 months and 1-5 years: telephone	30 days and 12 months: clinical 8 months: angiographic/IVUS 6, 9 and 18 months and 2-5 years: telephone	30 days, 6, 9 (Clinical Visit), 12, 18 months then annually at 2 - 5 years	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact)	30 days (Contact); 6 months (Contact); 12 months (Clinic Visit with 12-lead ECG) and 2 years: (Contact) 3-5 years (contact)

Table 7-2: RESOLUTE and RESOLUTE INTEGRITY Clinical Trials Overview

	Global RESOLUTE Clinical Trial Program					RESOLUTE Asia 38 mm Cohort	RESOLUTE INTEGRITY US Post-Market Study	
	RESOLUTE US*	RESOLUTE AC[1]	RESOLUTE Int[2]	RESOLUTE FIM[3]	RESOLUTE Japan		RESOLUTE INTEGRITY US (PEG)	RESOLUTE INTEGRITY US (XL Sub-study)
Status	60-month follow-up is complete. 551 subjects qualified for 18-month follow-up	60-month follow-up is complete	36-month follow-up is complete	60-month follow-up complete	60-month follow-up is complete	60-month follow-up is complete	24-month follow-up is complete	12-month follow-up is complete

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

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

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

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

8 CLINICAL OUTCOMES

8.1 Clinical Outcomes for RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study and RESOLUTE ONYX 2.0 mm Clinical Study

Table 8-1: Resolute Onyx™ Clinical Outcomes

Safety and Effectiveness Measures	RESOLUTE ONYX Core (2.25 mm - 4.0 mm) Clinical Study (N=75 Subjects N=85 Lesions) %(m/n)[1]	RESOLUTE ONYX 2.0 mm Clinical Study (N=101 Subjects N=104 Lesions) %(m/n)[1]
In-Hospital		
Target Lesion Failure (TLF)[2]	4.0% (3/75)	2.0% (2/101)
Target Vessel Failure (TVF)[3]	4.0% (3/75)	2.0% (2/101)
MACE[4]	4.0% (3/75)	2.0% (2/101)
Cardiac Death or Target Vessel MI (TVMI)[5]	2.7% (2/75)	2.0% (2/101)
Death or TVMI	2.7% (2/75)	2.0% (2/101)
Death	0.0% (0/75)	0.0% (0/101)
Cardiac Death	0.0% (0/75)	0.0% (0/101)
Non Cardiac Death	0.0% (0/75)	0.0% (0/101)
TVMI (Extended historical definition)[6]	2.7% (2/75)	2.0% (2/101)
Clinically Driven TLR[7]	1.3% (1/75)	0.0% (0/101)
Clinically Driven TVR[8]	1.3% (1/75)	0.0% (0/101)
Stent Thrombosis (ARC) Definite/Probable[9]	1.3% (1/75)	0.0% (0/101)
30 Days		
MACE	4.0% (3/75)	2.0% (2/101)
Latest Follow-up (12-Months)		
Target Lesion Failure (TLF)[2]	9.5% (7/74)	5.0% (5/100)
Target Vessel Failure (TVF)[3]	14.9% (11/74)	5.0% (5/100)
MACE[4]	13.5% (10/74)	5.0% (5/100)
Cardiac Death or Target Vessel MI (TVMI)[5]	4.1% (3/74)	3.0% (3/100)
Death or TVMI	6.8% (5/74)	3.0% (3/100)
Death	2.7% (2/74)	0.0% (0/100)
Cardiac Death	0.0% (0/74)	0.0% (0/100)
Non Cardiac Death	2.7% (2/74)	0.0% (0/100)
TVMI (Extended historical definition)[6]	4.1% (3/74)	3.0% (3/100)
Clinically Driven TLR[7]	5.4% (4/74)	2.0% (2/100)
Clinically Driven TVR[8]	10.8% (8/74)	2.0% (2/100)
Stent Thrombosis (ARC) Definite/Probable[9]	1.4% (1/74)	0.0% (0/100)
Early Thrombosis (<=30 days)	1.4% (1/74)	0.0% (0/100)
Late Thrombosis (31-360 days)	0.0% (0/74)	0.0% (0/100)

Table 8-1: Resolute Onyx™ Clinical Outcomes

Safety and Effectiveness Measures	RESOLUTE ONYX Core (2.25 mm - 4.0 mm) Clinical Study (N=75 Subjects N=85 Lesions) %(m/n)[1]	RESOLUTE ONYX 2.0 mm Clinical Study (N=101 Subjects N=104 Lesions) %(m/n)[1]

Notes

[1]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
8-month timeframe includes follow-up window (360 days ± 30 days).
[2]Target Lesion Failure (TLF) is defined as any Cardiac Death, Clinically Driven Target Lesion Revascularization by PCI or CABG or Target Vessel MI.
[3]Target Vessel Failure (TVF) is defined as any Cardiac Death, Clinically Driven Target Vessel Revascularization by PCI or CABG or Target Vessel MI.
[4]Major adverse cardiac events (MACE) is defined as composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or clinically driven target lesion revascularization (repeat PTCA or CABG).
[5]Cardiac death/TVMI is defined as Cardiac Death or Myocardial Infarction not clearly attributable to a non-target vessel.
[6]TVMI is composed of both Q wave and non-Q wave MI which are not clearly attributable to a non-target vessel.
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.]
[7]Target Lesion Revascularization (TLR) is defined as a clinically-driven repeat intervention of the target lesion by PCI or CABG
[8]Target Vessel Revascularization (TVR) is defined as any clinically-driven repeat intervention of the target vessel by PCI or CABG.
[9] ARC defined Stent Thrombosis.

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

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

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

The Global RESOLUTE Clinical Trial Program has evaluated the performance of the Resolute stent in subjects, including those with diabetes mellitus, with symptomatic ischemic heart disease in *de novo* lesions of native coronary arteries. The RESOLUTE INTEGRITY US Post-Market Approval Study assessed the safety and efficacy of the Resolute Integrity™ Stent for the treatment of de novo lesions in native coronary arteries. Clinical Outcomes are shown in Table 8-2 below.

Table 8-2: Clinical Outcomes from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US[1]	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
	Resolute (N = 1402)	Resolute (N = 1140)	Xience V® (N = 1152)	Resolute (N = 2349)	Resolute (N = 139)	Resolute (N = 100)	Resolute (N = 223)	Resolute Integrity (PEG) (N=230)	RESOLUTE INTEGRITY US (XL Sub-study) (N=56)
In-Hospital									
TLF	1.3% (18/1402)	3.7% (42/1140)	4.5% (52/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
TVF	1.3% (18/1402)	3.8% (43/1140)	4.7% (54/1152)	2.6% (61/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
MACE	1.3% (18/1402)	3.8% (43/1140)	4.9% (56/1152)	2.7% (63/2349)	4.3% (6/139)	2.0% (2/100)	3.6% (8/223)	1.7% (4/230)	1.8% (1/56)
Total Death	0.0% (0/1402)	0.1% (1/1140)	0.8% (9/1152)	0.3% (7/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Cardiac Death	0.0% (0/1402)	0.1% (1/1140)	0.6% (7/1152)	0.3% (6/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Cardiac Death	0.0% (0/1402)	0.0% (0/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
TVMI[5]	1.1% (16/1402)	3.1% (35/1140)	3.6% (42/1152)	2.2% (51/2349)	4.3% (6/139)	2.0% (2/100)	3.1% (7/223)	1.7% (4/230)	1.8% (1/56)
Q wave MI	0.1% (1/1402)	0.3% (3/1140)	0.4% (5/1152)	0.3% (8/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	0.0% (0/56)
Non-Q Wave MI	1.1% (15/1402)	2.8% (32/1140)	3.2% (37/1152)	1.8% (43/2349)	4.3% (6/139)	2.0% (2/100)	2.7% (6/223)	1.7% (4/230)	1.8% (1/56)
Cardiac Death or TVMI	1.1% (16/1402)	3.2% (36/1140)	4.0% (46/1152)	2.4% (56/2349)	4.3% (6/139)	2.0% (2/100)	3.6% ((8/223)	1.7% (4/230)	1.8% (1/56)
Clinically Driven TVR	0.1% (2/1402)	0.9% (10/1140)	0.9% (10/1152)	0.4% 10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
TLR	0.1% (2/1402)	0.7% (8/1140)	0.7% (8/1152)	0.4% (10/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.4% (1/230)	0.0% (0/56)
Non-TL TVR	0.0% (0/1402)	0.4% (4/1140)	0.2% (2/1152)	0.0% (1/2349)	0.0% (0/139)	0.0% (0/100)	0.0% (0/223)	0.0% (0/230)	0.0% (0/56)
ARC Def/Prob ST	0.0% (0/1402)	0.6% (7/1140)	0.3% (4/1152)	0.4% (9/2349)	0.0% (0/139)	0.0% (0/100)	0.4% (1/223)	0.0% (0/230)	1.8% (1/56)
30 Days									
MACE	1.4% (20/1399)	4.4% (50/1133)	5.2% (60/1146)	3.3% (78/2345)	4.3% (6/139)	3.0% (3/100)	4.5% (10/223)	3.0% (7/230)	3.6% (2/56)
12 Months									
TLF	4.7% (65/1390)	8.1% (92/1132)	8.5% (97/1142)	7.1% (165/2337)	7.2% (10/139)	4.0% (4/100)	5.4% (12/222)	4.9% (11/226)	7.4% (4/54)
TVF	6.2% (86/1390)	8.9% (101/1132)	9.7% (111/1142)	7.7% (180/2337)	7.2% (10/139)	5.0% (5/100)	6.8% (15/222)	7.1% (16/226)	7.4% (4/54)
MACE	5.5% (77/1390)	8.6% (97/1132)	9.8% (112/1142)	8.3% (193/2337)	8.6% (12/139)	5.0% (5/100)	6.3% (14/222)	5.8% (13/226)	9.3% (5/54)
Total Death	1.4% (19/1390)	1.6% (18/1132)	2.7% (31/1142)	2.4% (57/2337)	2.2% (3/139)	1.0% (1/100)	0.9% (2/222)	1.8% (4/226)	1.9% (1/54)
Cardiac Death	0.7% (10/1390)	1.3% (15/1132)	1.7% (19/1142)	1.5% (34/2337)	0.7% (1/139)	0.0% (0/100)	0.9% (2/222)	1.3% (3/226)	1.9% (1/54)

Table 8-2: Clinical Outcomes from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US[1]	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
Non-Cardiac Death	0.6% (9/1390)	0.3% (3/1132)	1.1% (12/1142)	1.0% (23/2337)	1.4% (2/139)	1.0% (1/100)	0.0% (0/222)	0.4% (1/226)	0.0% (0/54)
TVMI	1.3% (18/1390)	4.2% (48/1132)	4.2% (48/1142)	3.0% (71/2337)	5.8% (8/139)	4.0% (4/100)	3.6% (8/222)	2.2% (5/226)	5.6% (3/54)
Q wave MI	0.1% (2/1390)	0.8% (9/1132)	0.4% (5/1142)	0.5% (12/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.0% (0/226)	1.9% (1/54)
Non-Q Wave MI	1.2% (16/1390)	3.5% (40/1132)	3.8% (43/1142)	2.5% (59/2337)	5.8% (8/139)	4.0% (4/100)	2.7% (6/222)	2.2% (5/226)	5.6% (3/54)
Cardiac Death or TVMI	2.0% (28/1390)	5.3% (60/1132)	5.5% (63/1142)	4.2% (99/2337)	6.5% (9/139)	4.0% (4/100)	4.5% (10/222)	3.5% (8/226)	7.4% (4/54)
Clinically Driven TVR	4.6% (64/1390)	4.9% (55/1132)	4.8% (55/1142)	4.2% (99/2337)	0.7% (1/139)	1.0% (1/100)	2.7% (6/222)	4.4% (10/226)	1.9% (1/54)
TLR	2.9% (40/1390)	3.9% (44/1132)	3.4% (39/1142)	3.5% (81/2337)	0.7% (1/139)	0.0% (0/100)	1.4% (3/222)	2.2% (5/226)	1.9% (1/54)
Non-TL TVR	2.2% (30/1390)	1.9% (21/1132)	2.2% (25/1142)	1.2% (27/2337)	0.0% (0/139)	1.0% (1/100)	1.4% (3/222)	2.2% (5/226)	0.0% (0/54)
ARC Def/Prob ST	0.1% (2/1390)	1.6% (18/1132)	0.7% (8/1142)	0.9% (20/2337)	0.0% (0/139)	0.0% (0/100)	0.9% (2/222)	0.9% (2/226)	1.9% (1/54)
Latest Follow-up	60 Months	60 Months		36 Months	60 Months	60 Months	60 Months	24 Months	
TLF	12.3% (164/1329)	17.0% (191/1123)	16.2% (183/1133)	11.4% (261/2284)	11.0% (15/136)	6.1% (6/98)	13.8% (30/217)	9.1% (20/219)	
TVF	17.5% (233/1329)	20.0% (225/1123)	19.1% (216/1133)	12.9% (294/2284)	13.2% (18/136)	10.2% (10/98)	17.1% (37/217)	12.3% (27/219)	
MACE	18.0% (239/1329)	21.9% (246/1123)	21.6% (245/1133)	14.4% (329/2284)	16.2% (22/136)	14.3% (14/98)	17.5% (38/217)	11.0% (24/219)	
Total Death	9.6% (127/1329)	11.0% (123/1123)	10.8% (122/1133)	6.1% (139/2284)	6.6% (9/136)	7.1% (7/98)	6.5% (14/217)	2.7% (6/219)	
Cardiac Death	4.1% (55/1329)	6.5% (73/1123)	5.7% (65/1133)	3.6% (82/2284)	1.5% (2/136)	1.0% (1/98)	4.1% (9/217))	1.8% (4/219)	
Non-Cardiac Death	5.4% (72/1329)	4.5% (50/1123)	5.0% (57/1133)	2.5% (57/2284)	5.1% (7/136)	6.1% (6/98)	2.3% (5/217)	0.9% (2/219)	
TVMI	3.2% (43/1329)	5.7% (64/1123)	5.7% (65/1133)	3.9% (89/2284)	6.6% (9/136)	4.1% (4/98)	6.0% (13/217)	4.1% (9/219)	
Q wave MI	0.4% (5/1329)	1.3% (15/1123)	0.8% (9/1133)	0.9% (20/2284)	0.0% (0/136)	0.0% (0/98)	0.9% (2/217)	0.9% (2/219)	
Non-Q Wave MI	2.9% (38/1329)	4.6% (52/1123)	4.9% (56/1133)	3.0% (69/2284)	6.6% (9/136)	4.1% (4/98)	5.1% (11/217)	3.2% (7/219)	
Cardiac Death or TVMI	6.7% (89/1329)	11.5% (129/1123)	10.6% (120/1133)	7.0% (161/2284)	8.1% (11/136)	5.1% (5/98)	8.8% (19/217)	5.9% (13/219)	
Clinically Driven TVR	12.5% (166/1329)	11.4% (128/1123)	10.9% (123/1133)	7.4% (168/2284)	5.1% (7/136)	5.1% (5/98)	9.7% (21/217)	8.2% (18/219)	

Table 8-2: Clinical Outcomes from Post-Procedure Through Latest Available Follow-up

	RESOLUTE US[1]	RESOLUTE AC		RESOLUTE Int	RESOLUTE FIM	RESOLUTE Japan	38 mm Length Sub-study R-US N = 114 R-Asia N = 109	RESOLUTE INTEGRITY US	
TLR	6.5% (86/1329)	7.8% (88/1123)	7.1% (81/1133)	5.7% (130/2284)	2.9% (4/136)	1.0% (1/98)	6.0% (13/217)	5.0% (11/219)	
Non-TL TVR	8.1% (107/1329)	6.1% (68/1123)	6.1% (69/1133)	2.6% (59/2284)	2.2% (3/136)	4.1% (4/98)	3.7% (8/217)	4.1% (9/219)	
ARC Def/Prob ST	0.5% (7/1329)	2.4% (27/1123)	1.7% (19/1133)	1.1% (26/2284)	0.0% (0/136)	0.0% (0/98)	1.4% (3/217)	1.8% (4/219)	

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.
The definitions of the outcomes are presented as table notes to Table 8-1
In-hospital is defined as hospitalization less than or equal to the discharge date
12-month timeframe includes follow-up window (360 days ± 30 days).
24-month timeframe includes follow-up window (720 days ±30 days).
36-month timeframe includes follow-up window (1080 days ± 30 days).
60-month timeframe includes follow-up window (1800 days ± 30 days).
[1] Primary Enrollment Group consisted of 1402 subjects, including 1242 subjects in the 2.25 mm - 3.5 mm Main Study, 100 subjects in the 2.25 mm - 3.5 mm Angio/IVUS Sub-study and 60 subjects in the 4.0 mm Sub-study. The Primary Enrollment Group does not include the 38 mm Length Sub-study.

In the RESOLUTE All-Comers (R-AC) trial, a randomized trial comparing the Resolute™ ZES with the Xience V™* EES for treatment of patients with coronary lesions who had minimal exclusion criteria, there were similar safety and efficacy outcomes between the two stents. Through 5 years of follow-up, the clinical effectiveness of the Resolute ZES was sustained in the complex and non-complex cohorts as shown in Table 8-3, Table 8-4, and Table 8-5 below.

Table 8-3: R-AC Clinical Outcomes (Complex Cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Complex Cohort			
	12 Months		60 Months	
	Resolute (N = 764)	Xience V® (N = 756)	Resolute (N = 764)	Xience V® (N = 756)
TLF	8.8% (67/760)	10.0% (75/750)	18.2% (137/751)	18.4% (137/745)
TVF	9.7% (74/760)	11.3% (85/750)	22.1% (166/751)	21.3% (159/745)
MACE	9.1% (69/760)	11.7% (88/750)	22.5% (169/751)	24.6% (183/745)
EFFECTIVENESS				
Clinically Driven TVR	5.5% (42/760)	5.6% (42/750)	13.4% (101/751)	11.7% (87/745)
TLR	4.3% (33/760)	4.1% (31/750)	8.9% (67/751)	8.1% (60/745)
TLR, PCI	3.9% (30/760)	3.2% (24/750)	8.1% (61/751)	6.7% (50/745)
TLR, CABG	0.4% (3/760)	1.1% (8/750)	1.2% (9/751)	1.7% (13/745)
SAFETY				
Total Death	1.4% (11/760)	3.3% (25/750)	10.4% (78/751)	13.2% (98/745)
Cardiac Death	1.3% (10/760)	2.1% (16/750)	6.4% (48/751)	7.4% (55/745)
Non-Cardiac Death	0.1% (1/760)	1.2% (9/750)	4.0% (30/751)	5.8% (43/745)

Table 8-3: R-AC Clinical Outcomes (Complex Cohort)

COMPOSITE SAFETY AND EFFECTIVENESS	Complex Cohort			
	12 Months		60 Months	
	Resolute (N = 764)	Xience V® (N = 756)	Resolute (N = 764)	Xience V® (N = 756)
Cardiac Death or TVMI	5.4% (41/760)	6.4% (48/750)	11.9% (89/751)	12.2% (91/745)
TVMI	4.2% (32/760)	4.7% (35/750)	5.9% (44/751)	6.0% (45/745)
Q wave MI	0.7% (5/760)	0.5% (4/750)	1.3% (10/751)	0.9% (7/745)
Non-Q wave MI	3.7% (28/760)	4.1% (31/750)	4.8% (36/751)	5.1% (38/745)
Stent Thrombosis ARC defined				
Definite/Probable	1.7%(13/759)	0.9%(7/749)	2.5% (19/751)	2.0% (15/745)
Definite	1.2%(9/759)	0.4%(3/749)	1.7% (13/751)	0.9% (7/745)
Probable	0.7%(5/759)	0.5%(4/749)	0.9% (7/751)	1.1% (8/745)

Notes

N = The total number of subjects enrolled.

Subjects are only counted once for each time period.

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

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

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

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

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 8-4: R-AC Clinical Outcomes (Non-Complex Cohort)

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
The definitions of the outcomes are presented as table notes to Table 8-1.
12-month timeframe includes follow-up window (360± 30 days)
60-month timeframe includes follow-up window (1800 days ± 30 days).
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 8-5: R-AC ARC Defined Definite/Probable Stent Thrombosis Through 60 Months (All Subjects, and Complex and Non-Complex Subjects)

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

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (Count/Number of Eligible Subjects).
12-month timeframe includes follow-up window (360 ± 30 days)
60-month timeframe includes follow-up window (1800 days ± 30 days).
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).

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 ONYX Core (2.25 mm – 4.0 mm) Clinical Study

Primary Objective: The purpose of this study is to assess the safety and efficacy of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System for the treatment of de novo lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.2 mm.

Design: The Medtronic RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study is a single arm, open label, multi-center trial that enrolled 75 subjects with ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with stenting. Subjects may have received treatment of one or two lesions with stent diameters 2.25 mm - 4.0 mm, one lesion per target vessel, for a maximum of two target vessels. Only one lesion may have been treated in a single target vessel. All treatments with the study stents were to be performed during a single index procedure. All enrolled subjects had an 8 month angiogram to assess late lumen loss. The first 20 subjects also underwent an IVUS assessment at baseline and 8 months.

Primary Endpoint: In-stent Late Lumen Loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA).

Follow-up was performed at 30 days, 6, and 8 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 those who were not at a high risk of bleeding.

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

Results: The primary end point of in-stent Late Lumen Loss (LL) at 8-months post-procedure as measured by quantitative coronary angiography (QCA) demonstrated not only non-inferiority ($p < 0.001$), but also superiority ($p = 0.029$), when compared to the historical control in-stent late loss value from the RESOLUTE US Angio/IVUS Sub-study.

The RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study outcomes at 8-months are consistent with the 9 month clinical outcomes of the RESOLUTE US 2.25-3.5 mm Angio/IVUS Sub-study that evaluated a similar patient population (with mandated angiographic follow up at 8 months).

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

- Table 9-1: RESOLUTE ONYX™ - Primary Endpoint Analysis
- Table 9-2: RESOLUTE ONYX™ - Clinical and Angio / IVUS Outcomes
- Table 9-3: RESOLUTE ONYX™ - ARC Defined Definite/Probable Stent Thrombosis Through 8 Months

Table 9-1: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – Primary Endpoint Analysis (Non-inferiority Test with Propensity Score Adjustment)

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

Table 9-1: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – Primary Endpoint Analysis (Non-inferiority Test with Propensity Score Adjustment)

Primary Endpoint – In-stent Late Lumen Loss at 8 month	RESOLUTE ONYX Core (N=75 Subjects N=85 Lesions)	Historical Control Resolute (N=100 Subjects N=104 Lesions)	Difference: RESOLUTE ONYX Core - Historical Control[1]	Upper One-sided 95% CI[2]	Non-Inferiority Margin	Non-Inferiority P value	Superiority P value[3]
– PP set	0.23 ± 0.05	0.35 ± 0.05	-0.15	-0.02	0.20	< 0.001	0.028

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

Table 9-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – Clinical and Angio / IVUS Outcomes

	RESOLUTE ONYX (N=75 Subjects N=85 Lesions) %(m/n)[1]
Safety Measures (to 180 days)	
Target Lesion Failure (TLF)	5.3% (4/75)
Target Vessel Failure (TVF)	8.0% (6/75)
MACE	8.0% (6/75)
Cardiac Death or Target Vessel MI (TVMI)	2.7% (2/75)
Death or TVMI	4.0% (3/75)
Death	1.3% (1/75)
Cardiac Death	0.0% (0/75)
Non Cardiac Death	1.3% (1/75)
TVMI (Extended historical definition)	2.7% (2/75)
Clinically Driven TLR	2.7% (2/75)
Clinically Driven TVR	5.3% (4/75)
Stent Thrombosis (ARC) Definite/Probable	1.3% (1/75)
Safety Measures (to 240 days)	
Target Lesion Failure (TLF)	6.7% (5/75)
Target Vessel Failure (TVF)	12.0% (9/75)
MACE	9.3% (7/75)
Cardiac Death or Target Vessel MI (TVMI)	2.7% (2/75)
Death or TVMI	4.0% (3/75)
Death	1.3% (1/75)
Cardiac Death	0.0% (0/75)
Non Cardiac Death	1.3% (1/75)

Table 9-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – Clinical and Angio / IVUS Outcomes

	RESOLUTE ONYX (N=75 Subjects N=85 Lesions) %(m/n)[1]
TVMI (Extended historical definition)	2.7% (2/75)
Clinically Driven TLR	4.0% (3/75)
Clinically Driven TVR	9.3% (7/75)
Stent Thrombosis (ARC) Definite/Probable	1.3% (1/75)
Early Thrombosis (<=30 days)	1.3% (1/75)
Late Thrombosis (31-240 days)	0.0% (0/75)
Angiography (8 months)	
Percent Diameter Stenosis (% DS)	
In-stent	
n	73
Mean±SD	15.70 ± 16.65
Median (1Q, 3Q)	14.86 (5.33, 22.24)
Min, Max	-21.18, 82.89
In-segment	
n	73
Mean±SD	25.50 ± 14.26
Median (1Q, 3Q)	22.06 (17.42, 29.64)
Min, Max	4.99, 82.89
Minimal Lumen Diameter (mm)	
In-stent	
n	73
Mean±SD	2.13 ± 0.55
Median (1Q, 3Q)	2.14(1.80, 2.45)
Min, Max	0.45, 3.69
In-segment	
n	73
Mean±SD	1.89 ± 0.49
Median (1Q, 3Q)	1.91 (1.59, 2.20)
Min, Max	0.45, 3.10
Late Luminal Loss (mm)	
In-stent	
n	73
Mean±SD	0.24 ± 0.39
Median (1Q, 3Q)	0.20(0.03, 0.37)
Min, Max	-0.49, 2.06

Table 9-2: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – Clinical and Angio / IVUS Outcomes

	RESOLUTE ONYX (N=75 Subjects N=85 Lesions) %(m/n)[1]
In-segment	
n	73
Mean±SD	0.15 ± 0.38
Median (1Q, 3Q)	0.11 (-0.03, 0.29)
Min, Max	-0.65, 1.88
In-Stent Binary Angiographic Restenosis (BAR) Rate	5.5% (4/73)
In-Segment Binary Angiographic Restenosis (BAR) Rate	8.2% (6/73)
IVUS (8 months)	
Incomplete stent apposition	
Persistent	10.0% (2/20)
Late	0.0% (0/20)
Neointimal hyperplastic volume (mm^3)	
n	17
Mean±SD (N)	9.88 ± 9.38
Median (Q1,Q3)	6.80 (2.20, 18.10)
Min, Max	0.00, 27.20
Percent volume obstruction	
n	17
Mean±SD (N)	6.88 ± 8.00
Median (Q1,Q3)	4.52 (1.48, 8.79)
Min, Max	0.00, 31.38
Effectiveness Measures	
Lesion Success[2]	100.0% (85/85)
Device Success[3]	100.0% (85/85)
Procedure Success[4]	96.0% (72/75)

[1] Numerator (m) is the number of Subjects with the specific classification, denominator (n) is the number of Subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)
The definitions of the outcomes are presented as table notes to Table 8-1

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

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

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

8-month timeframe includes follow-up window (240 days ± 14 days).
Extended historical definition of MI is used for all the composite endpoints.

Table 9-3: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – ARC Defined Definite/Probable Stent Thrombosis Through 8 Months

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

Notes

[1]N = The total number of subjects enrolled.

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

Subjects are only counted once for each time period.

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

See Table 8-1 for the definition of the ARC defined Stent Thrombosis.

9.2 Results of the RESOLUTE ONYX 2.0 mm Clinical Study

Primary Objective: The purpose of this study is to assess the safety and efficacy of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System for the treatment of de novo lesions in native coronary arteries that allows the use of a 2.0 mm diameter stent.

Design: The Medtronic RESOLUTE ONYX 2.0 mm Clinical Study is a single arm, open label, multi-center trial that enrolled 101 subjects in the US and Japan with ischemic heart disease attributable to stenotic lesions of the native coronary arteries that are amenable to percutaneous treatment with stenting. Subjects may have received treatment of one or two lesions with stent diameter 2.0 mm, one lesion per target vessel, for a maximum of two target vessels. Only one lesion may have been treated in a single target vessel. All treatments with the study stents were to be performed during a single index procedure. The first 20 subjects underwent an angiogram assessment at 13 months.

Primary Endpoint: Target Lesion Failure (TLF) at 12-months post-procedure, defined as Cardiac Death, Target Vessel Myocardial Infarction (TVMI) (Q wave or non-Q wave) or Target Lesion Revascularization by percutaneous or surgical methods.

Follow-up was performed at 30 days, 6, 12, and 13 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 those who were not at a high risk of bleeding.

Demographics: The mean age was 67.3 years with 70.3% (71/101) of subjects being males. Of the subjects enrolled, 46.5% (47/101) had diabetes mellitus, 11.9% (12/101) were current smokers, 35.7% (35/98) had prior MI, 59.4% (60/101) had prior PCI, 82.2% (83/101) had hypertension, and 94.1% (95/101) reported hyperlipidemia. Baseline lesion characteristics include 36.6% (37/101) of subjects with LAD lesions, a mean lesion length of 12.59 ± 6.27mm, and 65.4% (68/104) ACC/AHA type B2/C lesions. The mean RVD was 1.91 ± 0.26 mm and the percentage diameter stenosis was 65.83 ± 10.89%.

Results: The rate of TLF in the ITT primary analysis set at 12 months was 5.0% (5/100), fulfilling the pre-specified performance criterion (upper 1-sided 95% CI of 10.2%, compared with the performance goal of 19%, $p < 0.001$). Furthermore, the rate of TLF in the ITT worst case analysis set was 5.9% (6/101) (upper 1-sided 95% CI of 11.4%, compared with the performance goal of 19%). The primary endpoint was also analyzed by gender, resulting in a TLF rate of 7.1% (5/70) in male subjects and 0.0% (0/30) in female subjects.

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

- Table 9-4: RESOLUTE ONYX™ 2.0 mm - Primary Endpoint Analysis
- Table 9-5: RESOLUTE ONYX™ 2.0 mm - Clinical and Angiographic Outcomes
- Table 9-6: RESOLUTE ONYX™ 2.0 mm - ARC Defined Definite/Probable Stent Thrombosis Through 12 Months
- Table 9-7: RESOLUTE ONYX™ 2.0 mm – Primary Endpoint Analysis by Gender

Table 9-4: RESOLUTE ONYX 2.0 mm Clinical Study – Primary Endpoint Analysis

Primary Endpoint - TLF at 12-month	Resolute Onyx 2.0mm (N = 101 Subjects)	One-side upper 95% Confidence Interval[1]	Performance Goal
Primary Analysis – with analysis lesion only [2]			
– ITT set	5.0% (5/100)	10.2%	19%
– PP set	2.2% (2/90)	6.8%	19%
Secondary Analysis – with all lesions included [3]			
– ITT set	5.0% (5/100)	10.2%	19%
– PP set	2.2% (2/90)	6.8%	19%
Multiple Imputation[4]			
– ITT set	5.0%	8.6%	19%
– PP set	2.3%	4.9%	19%
Tipping Point Analysis[5]			
– ITT set	5.9% (6/101)	11.4%	19%
– PP set	3.3% (3/91)	8.3%	19%
Worst Case Analysis[6]			
– ITT set	5.9% (6/101)	11.4%	19%
– PP set	3.3% (3/91)	8.3%	19%

[1] The one-sided upper 95% CI is calculated by binomial (exact) distribution
[2] The lesions with a Resolute Onyx 2.0mm stent are included in the analysis. For 2 or more lesions with Resolute Onyx 2.0mm stents per subject, the lesion is randomly selected.
[3] All target lesions are included in the analysis.
[4] The covariates to be used in the imputation model are lesion-length, baseline RVD, age, sex, diabetes, history of MI, Canadian Cardiovascular Society Angina Class, and TLF-missing status at visits prior to dropout. The longest lesion length and the smallest baseline RVD are used for the subjects have 2 or more target lesions in the imputation model.
[5] Impute the most 12-month TLF-missing status as yes so that the one-side upper 95% confidence interval of 12-month TLF rate can be less than or equal to the performance goal.
[6] Impute all the 12-month TLF-missing status as yes.

Table 9-5: RESOLUTE ONYX 2.0 mm Clinical Study – Clinical and Angiographic Outcomes

Safety and Effectiveness Measures	RESOLUTE ONYX 2.0mm (N=101 Subjects N=104 Lesions) %(m/n)[1]
Safety Measures (to 180 days)	
Target Lesion Failure (TLF)[2]	4.0% (4/100)
Target Vessel Failure (TVF)[3]	4.0% (4/100)
MACE[4]	4.0% (4/100)
Cardiac Death or Target Vessel MI (TVMI)	3.0% (3/100)
Death or TVMI	3.0% (3/100)

Table 9-5: RESOLUTE ONYX 2.0 mm Clinical Study – Clinical and Angiographic Outcomes

Safety and Effectiveness Measures	RESOLUTE ONYX 2.0mm (N=101 Subjects N=104 Lesions) %(m/n)[1]
Death	0.0% (0/100)
Cardiac Death	0.0% (0/100)
Non Cardiac Death	0.0% (0/100)
TVMI (Extended historical definition)	3.0% (3/100)
Clinically Driven TLR	1.0% (1/100)
Clinically Driven TVR	1.0% (1/100)
Stent Thrombosis (ARC) Definite/Probable	0.0% (0/100)
Safety Measures (to 360 days)	
Target Lesion Failure (TLF)[2]	5.0% (5/100)
Target Vessel Failure (TVF)[3]	5.0% (5/100)
MACE[4]	5.0% (5/100)
Cardiac Death or Target Vessel MI (TVMI)	3.0% (3/100)
Death or TVMI	3.0% (3/100)
Death	0.0% (0/100)
Cardiac Death	0.0% (0/100)
Non Cardiac Death	0.0% (0/100)
TVMI (Extended historical definition)	3.0% (3/100)
Clinically Driven TLR	2.0% (2/100)
Clinically Driven TVR	2.0% (2/100)
Stent Thrombosis (ARC) Definite/Probable	0.0% (0/100)
Early Thrombosis (<=30 days)	0.0% (0/100)
Late Thrombosis (31-360 days)	0.0% (0/100)
Angiography (13 months)	
Percent Diameter Stenosis (% DS)	
In-stent	
n	25
Mean±SD	22.49 ± 26.89
Median (Q1, Q3)	15.66 (9.57, 31.72)
Min, Max	-26.71, 100.00
In-segment	
n	25
Mean±SD	37.92 ± 21.54
Median (Q1, Q3)	31.72 (23.54, 42.50)
Min, Max	14.06, 100.00
Minimal Lumen Diameter (mm)	
In-stent	
n	25
Mean±SD	1.55 ± 0.52
Median (Q1, Q3)	1.63 (1.53, 1.81)

Table 9-5: RESOLUTE ONYX 2.0 mm Clinical Study – Clinical and Angiographic Outcomes

Safety and Effectiveness Measures	RESOLUTE ONYX 2.0mm (N=101 Subjects N=104 Lesions) %(m/n)[1]
Min, Max	0.00, 2.20
In-segment	
n	25
Mean±SD	1.25 ± 0.46
Median (Q1, Q3)	1.44 (1.09, 1.52)
Min, Max	0.00, 1.77
Late Luminal Loss (mm)	
In-stent	
n	25
Mean±SD	0.26 ± 0.48
Median (Q1, Q3)	0.06 (0.00, 0.33)
Min, Max	-0.42, 1.58
In-segment	
n	25
Mean±SD	0.25 ± 0.41
Median (Q1, Q3)	0.21 (-0.08, 0.42)
Min, Max	-0.39, 1.30
In-Stent Binary Angiographic Restenosis (BAR) Rate	12.0% (3/25)
In-Segment Binary Angiographic Restenosis (BAR) Rate	20.0% (5/25)
Effectiveness Measures	
Lesion Success[5]	99.0% (103/104)
Device Success[6]	96.2% (100/104)
Procedure Success[7]	97.0% (98/101)

[1]Numerator (m) is the number of Subjects with the specific classification, denominator (n) is the number of Subjects in the study group with known values, and percentage (%) was calculated as 100 × (m/n)
[2]Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.
[3]Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target vessel revascularization (TVR) by percutaneous or surgical methods.
[4]Defined as death, myocardial infarction (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically driven/clinically indicated) by percutaneous or surgical methods.
[5]The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method.
[6]The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using the assigned device only.
[7]The attainment of < 30% residual stenosis by QCA (or < 20% by visual assessment) AND TIMI flow 3 after the procedure, using any percutaneous method without the occurrence of MACE during the hospital stay.
Extended historical definition of MI is used for all the composite endpoints.

Table 9-6: RESOLUTE ONYX 2.0 mm Clinical Study – ARC Defined Definite/Probable Stent Thrombosis Through 12 Months

Stent Thrombosis	0.0% (0/100)
Early Thrombosis (<=30 days)	0.0% (0/100)
Late Thrombosis (31-360 days)	0.0% (0/100)

Table 9-7 RESOLUTE ONYX 2.0 mm - Primary Endpoint Analysis by Gender

Primary Endpoint	Male (N = 71 Subjects)	Female (N = 30 Subjects)
Target Lesion Failure to 12 months	7.1% (5/70)	0.0% (0/30)

9.3 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[3,4]. 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 (AC)
- RESOLUTE International (Int)
- RESOLUTE United States (US), 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).

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

4 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.

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 0** 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 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 9-8: RESOLUTE Diabetes Mellitus Cohort - Primary Endpoint Analysis
- Table 9-9: 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 9-10: RESOLUTE Diabetes Mellitus Cohort - ARC Defined Definite/Probable Stent Thrombosis Events through 12 Months

Table 9-8: 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 9-9: 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.

Table 9-10: 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.

9.4 Subjects with Diabetes Mellitus in the RESOLUTE 38 mm Length Group

Additional information is provided in Table 9-11 for the RESOLUTE 38 mm Length Group in subjects with Diabetes Mellitus.

Table 9-11: 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)

9.5 Subjects with Chronic Total Occlusion

The PERSPECTIVE Study – RESOLUTE CTO Cohort

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

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

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

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

An estimated MACE rate was derived based on a weighted average of the reported rates for drug-eluting stents from the PRISION II[5] and EXPERT CTO[6] studies. Due to difference in the definition of myocardial infarction used in the PRISON II study, an adjustment for the MACE rate was made to approximate the MACE rate if the ARC definition of myocardial infarction had been applied. The weighted average produced an estimated MACE rate of 16.6% using the ARC definition of MI. The performance goal (PG) for the pre-specified RESOLUTE CTO Cohort analysis was 25.2% based on the estimated MACE rate of 16.6% and a one-sided 95% CI.

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

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

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

The PERSPECTIVE Study results are presented in Table 9-12, Table 9-13, and Table 9-14:

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

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

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

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

Table 9-13: Principal Safety and Effectiveness Results

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

Table 9-13: Principal Safety and Effectiveness Results

Safety and Effectiveness Measures	RESOLUTE CTO cohort (N=183 Subjects) %(m/n)
MACE	18.2% (33/181)
Cardiac Death or MI	17.7% (32/181)
Death or MI	17.7% (32/181)
Death	2.8% (5/181)
Cardiac Death	2.2% (4/181)
Non-Cardiac Death	0.6% (1/181)
MI	16.0% (29/181)
TLR	1.1% (2/181)
TVR	1.1% (2/181)
All Stent Thrombosis (ARC Def/Prob/Poss)	1.7% (3/181)
Stent Thrombosis ARC Definite/Probable	0.6% (1/181)
Stent Thrombosis ARC Possible	1.1% (2/181)
Early Stent Thrombosis (0 to 30 days)	0.6% (1/181)
Definite	0.6% (1/181)
Probable	0.0% (0/181)
Possible	0.0% (0/181)
Late Stent Thrombosis (31 days – 1year)	1.1% (2/181)
Definite	0.0% (0/181)
Probable	0.0% (0/181)
Possible	1.1% (2/181)
Effectiveness Measures	
Clinical success[1]	92.3% (169/183)
Technical success[2]	96.2% (175/182)

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

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

Table 9-14: RESOLUTE CTO Cohort – Primary Endpoint Analysis by Gender

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

Global RESOLUTE Clinical Program – RESOLUTE Pooled CTO

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

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

- RESOLUTE International

  The RESOLUTE International Study (R-Int) was a prospective, multi-center, non-randomized, single-arm, observational study of the Resolute stent in a real world subject population. A total 2349 subjects were enrolled into the study. Subjects were

followed for 3 years post-procedure. A total of 186 subjects from the R-Int study were included in the RESOLUTE Pooled CTO analysis.

- RESOLUTE China Randomized Controlled Trial

  The RESOLUTE China Randomized Controlled Trial (R-China RCT) was a prospective, multi-center, randomized, open-label study designed to assess the non-inferiority of the Resolute stent compared to the Taxus Liberte stent for in-stent late lumen loss. A total of 198 subjects were treated with the Resolute stent. Subjects were followed for 5 years post-procedure. A total of 15 subjects from the R-China RCT study were included in the RESOLUTE Pooled CTO analysis.

- RESOLUTE China Registry

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

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

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

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

Table 9-15: RESOLUTE Pooled CTO Analysis – Safety and Effectiveness Results

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n)[9]
Effectiveness Measures	
Lesion Success[6]	100.0% (526/526)
Device Success[7]	94.1% (496/527)
Procedure Success[8]	97.5% (348/357)
1 Year	
TLF[1]	4.5% (16/352)
TVF[2]	4.8% (17/352)
MACE[3]	5.7% (20/352)
Composite Endpoint[4]	12.2% (43/352)
Cardiac Death or TVMI	3.1% (11/352)
Death or TVMI	4.0% (14/352)
Death	1.7% (6/352)
Cardiac Death	0.9% (3/352)
Non Cardiac Death	0.9% (3/352)
TVMI (Extended historical definition)	2.3% (8/352)
Clinically Driven TLR	2.0% (7/352)
Clinically Driven TVR	2.3% (8/352)
Stent Thrombosis (ARC) Definite/Probable)	0.6% (2/352)

Table 9-15: RESOLUTE Pooled CTO Analysis – Safety and Effectiveness Results

Safety and Effectiveness Endpoints	RESOLUTE Pooled CTO (N=358 Patients) (N=527 Lesions) %(m/n)[9]
Early Thrombosis(<=30 days)	0.3% (1/352)
Late Thrombosis(>30 and <=360 days)	0.3% (1/352)
Significant Bleeding Complications[5]	1.1% (4/352)
Stroke	0.9% (3/352)
3 Years	
TLF[1]	8.9% (31/347)
TVF[2]	10.1% (35/347)
MACE[3]	10.1% (35/347)
Composite Endpoint[4]	18.4% (64/347)
Cardiac Death or TVMI	6.6% (23/347)
Death or TVMI	7.8% (27/347)
Death	5.5% (19/347)
Cardiac Death	4.3% (15/347)
Non Cardiac Death	1.2% (4/347)
TVMI (Extended historical definition)	3.2% (11/347)
Clinically Driven TLR	3.2% (11/347)
Clinically Driven TVR	4.3% (15/347)
Stent Thrombosis (ARC) Definite/Probable)	1.2% (4/347)
Early Thrombosis(<=30 days)	0.3% (1/347)
Late Thrombosis(>30 and <=360 days)	0.3% (1/347)
Very Late Thrombosis(>360 days)	0.9% (3/347)
Significant Bleeding Complications[5]	1.2% (4/347)
Stroke	1.7% (6/347)

1.Cardiac death, target vessel myocardial infarction (Q wave and non Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods.
2.Cardiac death, target vessel myocardial infarction or clinically-driven target vessel revascularization.
3.Death, myocardial infarction, (Q wave and non Q-wave), emergent coronary bypass surgery, or repeat target lesion revascularization (clinically driven/clinically indicated) by percutaneous or surgical methods.
4.The combined clinical outcome of (all cause) mortality, Myocardial Infarction (Q-wave and non Q-wave), or (any) revascularization.
5.Bleeding complication is defined as a procedure related hemorrhagic event that requires a transfusion or surgical repair. These may include a hematoma requiring treatment of retroperitoneal bleed.
Significant Bleeding complication is defined as the bleeding complication that has at least one of the following scenarios:
- Bleedings that led to an interruption of anti-platelet medication;
- Bleedings that require transfusion;
- Intracerebral bleedings; or
- Bleedings that resulted in substantial hemodynamic compromise requiring treatment

6.The attainment of <50% residual stenosis of the target lesion using any percutaneous method.
7.The attainment of <50% residual stenosis of the target lesion using only the assigned device.
8.The attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.
9.Numerator (m) is the number of patients (or lesions) with the specific classification, denominator (n) is the number of patients (or lesions) in the study group with known values, and percentage () was calculated as 100 × (m/n)
Extended historical definition of MI is used for all the composite endpoints.

9.6 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 9-16 below provides the total number of subjects included in the analyses.

Table 9-16: Subjects Included in the Analyses by Clinical Study

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

The on-label subgroup includes all enrolled subjects except those that had a total occlusion, target lesions involving a bifurcation lesion, target lesions involving a Saphenous Vein Graft lesion (SVG), an In-Stent Restenosis (ISR) target lesion, a subject having an Acute Myocardial Infarction (AMI) (≤72 hrs), subjects with a demonstrated Left-Ventricular Ejection Fraction (LVEF) less than 30%, target lesions located in an unprotected Left Main Artery, subjects with ≥ 3 treated vessels, subjects with a serum creatinine of > 2.5 mg/dl, a lesion length > 27 mm, 2 or more lesions treated per vessel, and target lesions with the presence of a thrombus.

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

- Table 9-17: RESOLUTE Pooled Analysis - Principal Safety and Effectiveness Through 60 Months
- Table 9-18: RESOLUTE Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months
- Table 9-19: RESOLUTE Pooled Analysis - Subset Outcomes Through 12 Months
- Table 9-20: RESOLUTE Pooled Analysis – Subset Outcomes Through 12 Months
- Table 9-21: RESOLUTE Pooled Analysis – Subset Outcomes Through 12 Months

Table 9-17: RESOLUTE Pooled Analysis - Principal Safety and Effectiveness Through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
Outcomes at 12 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	6.6% (336/5098)	5.4% (150/2759)
TVF	7.5% (382/5098)	6.6% (181/2759)
MACE	7.5% (384/5098)	6.3% (174/2759)
EFFECTIVENESS		
Clinically Driven TVR	4.3% (220/5098)	3.7% (103/2759)
Clinically Driven TLR	3.3% (166/5098)	2.5% (69/2759)
SAFETY		

Table 9-17: RESOLUTE Pooled Analysis - Principal Safety and Effectiveness Through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
Total Death	1.9% (98/5098)	1.6% (44/2759)
Cardiac Death	1.2% (60/5098)	0.9% (26/2759)
Non-Cardiac Death	0.7% (38/5098)	0.7% (18/2759)
TVMI	2.9% (149/5098)	2.4% (66/2759)
Cardiac Death or TVMI	3.9% (200/5098)	3.3% (90/2759)
Stent Thrombosis ARC defined		
Definite/Probable	0.8% (40/5098)	0.3% (9/2759)
Definite	0.6% (29/5098)	0.2% (6/2759)
Probable	0.3% (13/5098)	0.1% (3/2759)
Outcomes at 36 Months		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	10.8% (539/5012)	9.2% (249/2709)
TVF	13.0% (652/5012)	12.0% (324/2709)
MACE	13.5% (679/5012)	12.0% (325/2709)
EFFECTIVENESS		
Clinically Driven TVR	7.9% (397/5012)	7.5% (204/2709)
Clinically Driven TLR	5.3% (267/5012)	4.4% (119/2709)
SAFETY		
Total Death	5.5% (275/5012)	5.0% (135/2709)
Cardiac Death	3.1% (156/5012)	2.6% (70/2709)
Non-Cardiac Death	2.4% (119/5012)	2.4% (65/2709)
TVMI	3.8% (188/5012)	3.1% (84/2709)
Cardiac Death or TVMI	6.5% (324/5012)	5.4% (145/2709)
Stent Thrombosis ARC defined		
Definite/Probable	1.1% (54/5012)	0.5% (13/2709)
Definite	0.7% (37/5012)	0.3% (7/2709)
Probable	0.4% (19/5012)	0.2% (6/2709)
Outcomes at 60 Months*		
COMPOSITE SAFETY AND EFFECTIVENESS		
TLF	14.0% (376/2688)	12.3% (239/1937)
TVF	18.1% (486/2688)	16.5% (320/1937)
MACE	19.4% (521/2688)	18.2% (352/1937)
EFFECTIVENESS		
Clinically Driven TVR	11.4% (306/2688)	10.6% (205/1937)

Table 9-17: RESOLUTE Pooled Analysis - Principal Safety and Effectiveness Through 60 Months

	All Subjects (N = 5130)	On-label (N = 2780)
TLR	6.7% (179/2688)	5.8% (112/1937)
SAFETY		
Total Death	9.9% (266/2688)	9.7% (188/1937)
Cardiac Death	4.9% (131/2688)	4.3% (83/1937)
Non-Cardiac Death	5.0% (135/2688)	5.4% (105/1937)
TVMI	4.5% (120/2688)	3.9% (76/1937)
Cardiac Death or TVMI	8.7% (234/2688)	7.5% (145/1937)
Stent Thrombosis ARC defined		
Definite/Probable	1.3% (34/2688)	0.8% (15/1937)
Definite	0.8% (22/2688)	0.5% (9/1937)
Probable	0.5% (13/2688)	0.3% (6/1937)

Notes
N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
36-month timeframe includes follow-up window (1080 days ± 30days).
60-month timeframe includes follow-up window (1800 days ± 30days)
* Note: R-Int. follow-up ends at three years and is not included in this analysis.
The definitions of the outcomes are presented as table notes to Table 8-1.

Table 9-18: RESOLUTE Pooled Analysis - ARC Defined Definite/Probable Stent Thrombosis Through 60 Months

	All Subjects* (N = 2781)	On-label* (N = 2017)
Stent Thrombosis	1.3% (34/2688)	0.8% (15/1937)
Early (0 - 30 days)	0.5% (13/2688)	0.2% (3/1937)
Late (31 – 360 days)	0.3% (8/2688)	0.2% (4/1937)
Very Late (361 – 1440 days)*	0.5% (14/2688)	0.4% (8/1937)

N = The total number of subjects enrolled.
Numbers are % (Count/Number of Eligible Subjects).
Subjects are only counted once for each time period.
12-month time frame includes follow-up window (360 days ± 30 days).
60-month timeframe includes follow-up window (1800 days ± 30 days).
* Note: R-Int. follow-up ends at three years and is not included in this analysis.

Table 9-19: 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 9-20: 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 9-21: 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
[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 Populations**. The risks and benefits described above should be carefully considered for each patient before use of the Resolute Onyx™ 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 at least 6 months in stable ischemic heart disease patients and for at least 12 months in patients with acute coronary syndrome (ACS). In patients at higher risk of bleeding, DAPT discontinuation may be reasonable after 3 months in stable patients or 6 months in ACS patients (see **Section 5.1 - Pre- and Post-Procedure Antiplatelet Regimen**). Aspirin should be administered concomitantly with an approved antiplatelet medication and then continued indefinitely. The safety and effectiveness of the Resolute Onyx™ stent have not been evaluated in patients at high bleeding risk or 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 Onyx™ 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 Representative for return information.

CONTENTS: Package contains one (1) Resolute Onyx™ Zotarolimus-Eluting Coronary Stent mounted on either a Rapid Exchange (RX) or an Over-the-Wire (OTW) stent delivery system.

STORAGE: Store in the original container. Store at 25ºC (77ºF); excursions permitted to 15 - 30ºC (59 - 86ºF). 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.

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

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

13.5 Delivery Procedure

Step	Action
1.	Prepare the vascular access site according to standard practice.
2.	**Pre-dilate the lesion with a PTCA catheter.** Pre-dilatation must be performed using a balloon with the following three characteristics: • A diameter at least 0.5 mm smaller than the treatment stent. • A length equal to or shorter than the lesion length to be dilated. • A length shorter than the stent to be implanted.
3.	Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as widely as possible. ***Note:*** If resistance is encountered, **do not force passage**. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine.
4.	Ensure guide catheter stability before advancing the Resolute Onyx™ System into the coronary artery. Carefully advance the Resolute Onyx™ System into the hub of the guide catheter.
5.	Advance the stent delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Use the radiopaque balloon markers to position the stent across the lesion; perform angiography to confirm the position of the stent. If the position of the stent is not optimal, it should be carefully repositioned or removed (see **Precautions – 5 Stent/System Removal Precautions**). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
6.	Sufficiently tighten the rotating hemostatic valve. Stent is now ready to be deployed.

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

13.6 Deployment Procedure

Step	Action
1.	Prior to stent expansion, utilize high-resolution fluoroscopy to verify the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3.	**Do not exceed Rated Burst Pressure (RBP). The RBP is 18 atm for the 2.0 mm to 4.0 mm stent diameters and 16 atm for the 4.5 mm and 5.0 mm stent diameters. The Resolute Onyx™ stents should not be expanded to a diameter beyond the maximum labeled diameter listed on the label. Do not dilate the 2.0, 2.25, and 2.5 mm stents to greater than 3.25 mm. Do not dilate the 2.75 and 3.0 mm stents greater than 3.75. Do not dilate the 3.5 and 4.0 mm stents to greater than 4.75 mm. Do not dilate the 4.5 mm and 5.0 mm stents to greater than 5.75 mm.**
4.	Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum stent diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameters). Optimal stent expansion and proper apposition requires that the stent be in full contact with the arterial wall.

13.7 Removal Procedures

Step	Action
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		2.0	2.25	2.5	2.75	3.0	3.5	4.0	4.5 (RX Only)	5.0 (RX Only)
7 atm	709 kPa		1.85	2.05	2.25	2.45	2.75	3.05	3.60	4.10	4.55
8 atm	811 kPa		1.90	2.10	2.30	2.55	2.80	3.15	3.70	4.20	4.65
9 atm	912 kPa		1.90	2.15	2.35	2.60	2.90	3.25	3.80	4.30	4.80
10 atm	1013 kPa		1.95	2.20	2.45	2.65	2.95	3.35	3.85	4.40	4.90
11 atm	1115 kPa		2.00	2.25	2.50	2.70	3.00	3.40	3.95	4.45	4.95
12 atm	1216 kPa	Nominal	2.05	2.30	2.55	2.75	3.05	3.45	4.00	4.50	5.05
13 atm	1317 kPa		2.05	2.35	2.55	2.80	3.10	3.50	4.05	4.55	5.10
14 atm	1419 kPa		2.10	2.35	2.60	2.80	3.10	3.55	4.05	4.60	5.15
15 atm	1520 kPa		2.10	2.35	2.60	2.85	3.15	3.55	4.10	4.65	5.20
16 atm	1621 kPa		2.15	2.40	2.65	2.90	3.20	3.60	4.15	4.70	5.25
17 atm	1723 kPa		2.15	2.40	2.70	2.90	3.20	3.65	4.20	4.80	5.30
18 atm	1824 kPa	RBP	2.20	2.45	2.70	2.95	3.25	3.70	4.25	4.85	5.35
19 atm	1925 kPa		2.20	2.45	2.75	3.00	3.30	3.75	4.30	-	-
20 atm	2027 kPa		2.25	2.50	2.75	3.00	3.35	3.80	4.35	-	-
21 atm	2128 kPa		2.25	2.50	2.80	3.05	3.40	3.80	4.40	-	-

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:

Table 13-2: Nominal Stent Diameters and Dilatation Limits

Nominal Stent Diameter	Dilatation Limits
2.00 mm	3.25 mm
2.25 mm	3.25 mm
2.50 mm	3.25 mm
2.75 mm	3.75 mm
3.00 mm	3.75 mm
3.50 mm	4.75 mm
4.00 mm	4.75 mm
4.50 mm (RX Only)	5.75 mm
5.00 mm (RX Only)	5.75 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 Onyx™ stents should not be expanded to a diameter beyond the maximum labeled diameter listed on the label. Do not dilate the 2.0 mm, 2.25 mm, and 2.5 mm stents to greater than 3.25 mm, 2.75 mm and 3.0 mm stents to greater than 3.75 mm, 3.5 mm and 4.0 mm stents to greater than 4.75 mm, and 4.5 mm and 5.0 mm stents to greater than 5.75 mm.**

13.10 Instructions for Simultaneous Use of Two Devices in Guide Catheter (Kissing Balloon Technique)

RX Only:

6 Fr (2 mm) Compatibility—Any combination of one Resolute Onyx™ RX Stent (models 2.0 mm to 4.0 mm) and one balloon catheter (Sprinter Legend™ RX models 1.25 mm to 3.5 mm up to 30 mm length, Euphora™ RX models 1.5 to 3.5 mm up to 30 mm length, or NC Euphora™ RX models 2.0 mm to 3.5 mm up to 27 mm length) can be used simultaneously within a 6 Fr (2 mm)/GC/MID 1.8 mm (0.070 in) guide catheter.

The technique can be performed as per the instructions listed below:

1. Insert the Resolute Onyx™ RX Stent using the instructions provided (refer to Section 13.5).
2. Insert a second guidewire and a balloon catheter, track to the target site and inflate the balloon.
3. Removing the catheters: Remove one catheter and its associated guidewire completely prior to removing the other catheter and its associated guidewire.

14 REUSE PRECAUTION STATEMENT

For single use only.

Do not Resterilize or Reuse.

DISCLAIMER OF WARRANTY

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M055193T001 Rev 1D