Medtronic

Onyx Frontier™

Zotarolimus-Eluting Coronary Stent System
Rapid Exchange Delivery System

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 Onyx Frontier zotarolimus-eluting coronary stent system are sterile.

1 Symbol glossary

Explanation of symbols that may appear on package labeling

Refer to the device labeling to see which symbols apply to this product.

Standard title:

ISO 15223-1:2016 Cor 2017: Medical Devices — Symbols to be used with medical device labels, labeling and information to be supplied.

Symbol	Reference	Symbol title	Explanatory text
	ISO 15223-1, Clause 5.4.3	Consult instructions for use	Indicates the need for the user to consult the instructions for use.
	ISO 15223-1, Clause 5.2.8	Do not use if package is damaged	Indicates a medical device that should not be used if the package has been damaged or opened.
	ISO 15223-1, Clause 5.4.2	Do not reuse	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure.
	ISO 15223-1, Clause 5.1.5	Lot number	Indicates the manufacturer's batch code so that the batch or lot can be identified.
	ISO 15223-1, Clause 5.1.1	Manufacturer	Indicates the medical device manufacturer.
	ISO 15223-1, Clause 5.1.6	Catalog number	Indicates the manufacturer's catalogue number so that the medical device can be identified.
	ISO 15223-1, Clause 5.2.3	Sterilized using ethylene oxide	Indicates a medical device that has been sterilized using ethylene oxide.
	ISO 15223-1, Clause 5.1.4	Use-by date	Indicates the date after which the medical device is not to be used.
	ISO 15223-1, Clause 5.1.3	Date of manufacture	Indicates the date when the medical device was manufactured.

2 Onyx Frontier Zotarolimus-Eluting Coronary Stent System

The Medtronic Onyx Frontier zotarolimus-eluting coronary stent system (Onyx Frontier system) is a device/drug combination product that consists of the following device components: the Resolute Onyx coronary stent, a rapid exchange (RX) delivery system and a drug component (a formulation of zotarolimus in a polymer coating). The characteristics of the Onyx Frontier system are described in **Table 2-1**.

Table 2-1: Device component description and nominal dimensions

Component	Onyx Frontier zotarolimus-eluting coronary stent system			
	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	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	12, 15, 18, 22, 26, 30

Table 2-1: Device component description and nominal dimensions

Component	Onyx Frontier zotarolimus-eluting coronary stent system			
	Stent design 1 (small vessel)	**Stent design 2 (medium vessel)**	**Stent design 3 (large vessel)**	**Stent design 4 (extra-large vessel)**
Delivery System	Onyx Frontier	Onyx Frontier	Onyx Frontier	Resolute Onyx RX
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	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).			
Stent delivery balloon	Dual-layer Pebax™* balloon (stent designs 1, 2, and 3) or single-layer Pebax™* balloon (stent design 4), 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), 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	Proximal shaft OD: 2.1 F (0.69 mm) Distal shaft OD 2.0 – 4.0 mm: 2.8 F (0.92 mm) Distal shaft OD 4.5 and 5.0 mm: 3.2 F (1.07 mm)			

2.1 Device component description

The Onyx Frontier system consists of a balloon-expandable, intracoronary, drug-eluting stent (DES) premounted on a rapid exchange (RX) stent delivery system. The 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 2 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 RX delivery system (Figure 2-1) has an effective length of 140 cm.

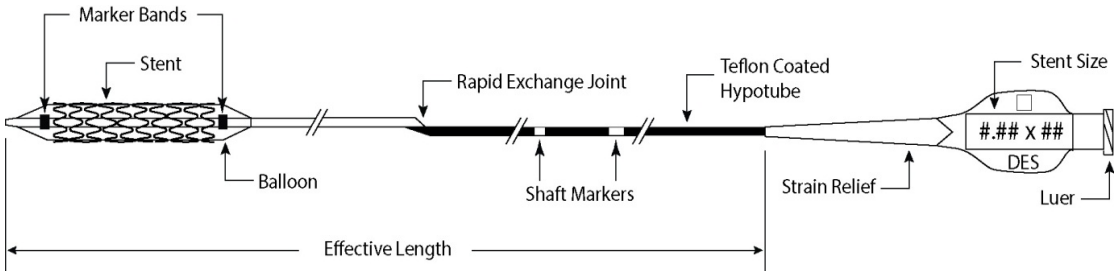

Figure 2-1: Rapid exchange (RX) delivery system (with stent)
Illustration is not to scale

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

Table 2-2: 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

2.2 Drug component description

The drug coating of the stent consists of the drug zotarolimus (the active ingredient) and the BioLinx polymer system (the inactive ingredient).

2.2.1 Zotarolimus

The active pharmaceutical ingredient utilized in the stent 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 2-2:

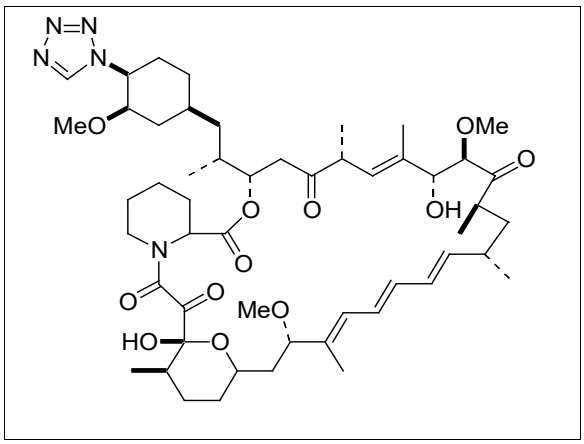

Figure 2-2: Zotarolimus chemical structure

Zotarolimus has extremely low water solubility and is a lipophilic compound that is freely soluble in propylene glycol, acetone, toluene, acetonitrile, ethanol, benzyl alcohol and DMSO. The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

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

2.2.2 Polymer system description

The stent consists 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 2-3:

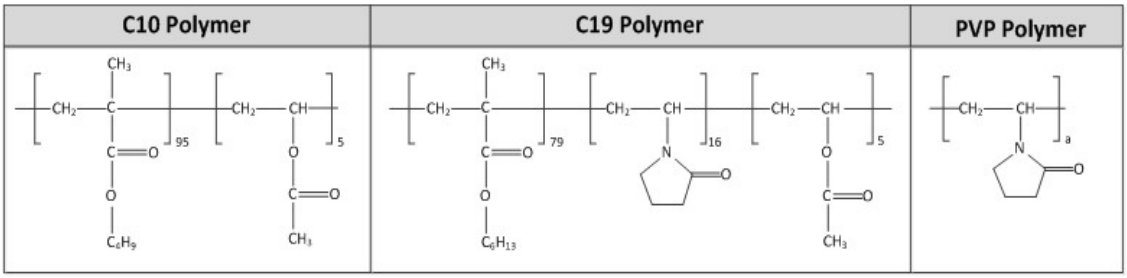

Figure 2-3: Chemical structure of the BioLinx polymer subunits

2.2.3 Product matrix and zotarolimus content

Table 2-3: Product matrix and nominal zotarolimus doses

Product number	Nominal expanded stent ID (mm)	Nominal unexpanded stent length (mm)	Nominal zotarolimus content (µg)
ONYXNG20008UX	2.0	8	51
ONYXNG22508UX	2.25	8	51
ONYXNG25008UX	2.5	8	51
ONYXNG27508UX	2.75	8	67
ONYXNG30008UX	3.0	8	67

Table 2-3: Product matrix and nominal zotarolimus doses

Product number	Nominal expanded stent ID (mm)	Nominal unexpanded stent length (mm)	Nominal zotarolimus content (µg)
ONYXNG35008UX	3.5	8	77
ONYXNG40008UX	4.0	8	77
ONYXNG20012UX	2.0	12	70
ONYXNG22512UX	2.25	12	70
ONYXNG25012UX	2.5	12	70
ONYXNG27512UX	2.75	12	94
ONYXNG30012UX	3.0	12	94
ONYXNG35012UX	3.5	12	108
ONYXNG40012UX	4.0	12	108
ONYXNG45012UX	4.5	12	132
ONYXNG50012UX	5.0	12	132
ONYXNG20015UX	2.0	15	85
ONYXNG22515UX	2.25	15	85
ONYXNG25015UX	2.5	15	85
ONYXNG27515UX	2.75	15	117
ONYXNG30015UX	3.0	15	117
ONYXNG35015UX	3.5	15	132
ONYXNG40015UX	4.0	15	132
ONYXNG45015UX	4.5	15	158
ONYXNG50015UX	5.0	15	158
ONYXNG20018UX	2.0	18	104
ONYXNG22518UX	2.25	18	104
ONYXNG25018UX	2.5	18	104
ONYXNG27518UX	2.75	18	140
ONYXNG30018UX	3.0	18	140
ONYXNG35018UX	3.5	18	156
ONYXNG40018UX	4.0	18	156
ONYXNG45018UX	4.5	18	188
ONYXNG50018UX	5.0	18	188
ONYXNG20022UX	2.0	22	127
ONYXNG22522UX	2.25	22	127
ONYXNG25022UX	2.5	22	127
ONYXNG27522UX	2.75	22	171
ONYXNG30022UX	3.0	22	171
ONYXNG35022UX	3.5	22	186
ONYXNG40022UX	4.0	22	186
ONYXNG45022UX	4.5	22	227
ONYXNG50022UX	5.0	22	227
ONYXNG20026UX	2.0	26	146
ONYXNG22526UX	2.25	26	146

Table 2-3: Product matrix and nominal zotarolimus doses

Product number	Nominal expanded stent ID (mm)	Nominal unexpanded stent length (mm)	Nominal zotarolimus content (µg)
ONYXNG25026UX	2.5	26	146
ONYXNG27526UX	2.75	26	198
ONYXNG30026UX	3.0	26	198
ONYXNG35026UX	3.5	26	221
ONYXNG40026UX	4.0	26	221
ONYXNG45026UX	4.5	26	265
ONYXNG50026UX	5.0	26	265
ONYXNG20030UX	2.0	30	168
ONYXNG22530UX	2.25	30	168
ONYXNG25030UX	2.5	30	168
ONYXNG27530UX	2.75	30	225
ONYXNG30030UX	3.0	30	225
ONYXNG35030UX	3.5	30	252
ONYXNG40030UX	4.0	30	252
ONYXNG45030UX	4.5	30	304
ONYXNG50030UX	5.0	30	304
ONYXNG22534UX	2.25	34	187
ONYXNG25034UX	2.5	34	187
ONYXNG27534UX	2.75	34	257
ONYXNG30034UX	3.0	34	257
ONYXNG35034UX	3.5	34	282
ONYXNG40034UX	4.0	34	282
ONYXNG22538UX	2.25	38	206
ONYXNG25038UX	2.5	38	206
ONYXNG27538UX	2.75	38	284
ONYXNG30038UX	3.0	38	284
ONYXNG35038UX	3.5	38	317
ONYXNG40038UX	4.0	38	317

3 Indications

The Onyx Frontier zotarolimus-eluting coronary stent system is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus or high bleeding risk, 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 Onyx Frontier zotarolimus-eluting coronary stent system is indicated for treating *de novo* chronic total occlusions and non-left main bifurcation lesions utilizing the provisional bifurcation stenting technique.

4 Contraindications

The Onyx Frontier 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 2.2.2 – Polymer system description**).

Coronary artery stenting is contraindicated for use in:

- Patients in whom antiplatelet 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.

5 Warnings

- Ensure that the inner package has not been opened or damaged as this would indicate that 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 bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.

6 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, myocardial infarction (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 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 10.8 – Pooled results of the Global RESOLUTE Clinical Trial Program** for more information).

6.1 Pre- and post-procedure antiplatelet regimen

In the Medtronic RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study and RESOLUTE ONYX 2.0 mm Clinical Study, the protocols specified administration of clopidogrel or ticlopidine (or any approved P2Y12 platelet inhibitor), including dosages before the procedure, and for a period of at least 6 months post-procedure. Aspirin was administered before the procedure concomitantly with a P2Y12 platelet inhibitor and then continued post-procedure to reduce the risk of thrombosis.

- In the Medtronic RESOLUTE ONYX Core (2.25 mm-4.0 mm) Clinical Study, 93.3%, 93.2%, 89.2%, and 52.2% of the subjects remained on dual antiplatelet therapy at 6 months, 8 months, 12 months, and 36 months, respectively.
- In the Medtronic RESOLUTE ONYX 2.0 mm Clinical Study, 91.1%, 87.1%, and 51% of the subjects remained on dual antiplatelet therapy at 6 months, 12 months, and 36 months, respectively.

6.1.1 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).

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.

The Academic Research Consortium (ARC) proposed a standardized definition for identifying patients at high bleeding risk (HBR)[3]. Additionally, evidence from a dedicated study of Resolute Onyx in HBR patients and those who are unable to tolerate long term DAPT after PCI has been published[4].

Based on the Onyx ONE Clear Analysis, the Resolute Onyx stent is safe and effective in patients at high risk of bleeding treated with one month of DAPT. The patients evaluated in the Onyx ONE Clear Analysis met the pre-defined criteria for high bleeding risk and were those whom in the opinion of their physician, the potential benefit of 1-Month DAPT outweighed the potential risk. In addition to at least one HBR risk factor, enrollment included 48.6% ACS patients (unstable angina 22.8%, Non-STEMI 21.7% and STEMI 4.2%). (see **Section 10.5.1 - Onyx ONE Clear Primary Analysis**).

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. Before PCI, if premature discontinuation of antiplatelet therapy is anticipated, physicians should carefully evaluate with the patient

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

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

3 Urban P, Mehran R, Colleran R, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. Circulation 2019;140:240-6

4 Windecker S, Latib A, Kedhi E, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. The New England Journal of Medicine 2020:10.1056/NEJMoa1910021.

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.

6.2 Use of multiple stents

The long-term effects of zotarolimus are currently unknown. The extent of the patient's exposure to the 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 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.

6.3 Use in conjunction with other procedures

The safety and effectiveness of using atherectomy devices with the stent have not been established.

6.4 Brachytherapy

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

6.5 Use in special populations

Information on use of the stent in certain special patient populations is derived from clinical studies of the Resolute stent system, which uses the same drug (zotarolimus) – **See Section 8 – Overview of clinical trials**

6.5.1 Pregnancy

Pregnancy Category C. There are no well-controlled studies in pregnant women or men intending to father children. The 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 stent and for 1 year after implantation. **See Section 7.6 – Pregnancy** under **Drug information**.

6.5.2 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 stent, taking into account the importance of the stent to the mother. **See Section 7.7 – Lactation** under **Drug information.**

6.5.3 Gender

Clinical studies of the Resolute stent did not suggest any significant differences in safety and effectiveness for male and female patients.

6.5.4 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.

6.5.5 Pediatric use

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

6.5.6 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.

6.5.7 Lesion/vessel characteristics

The safety and effectiveness of the 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, or ostial lesions.
- Patients with diffuse disease or poor flow distal to identified lesions.
- Patients with 3 vessel disease.

6.6 Drug interactions

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

6.7 Magnetic resonance imaging (MRI) safety information

MR Conditional

MRI Safety Information

Non-clinical testing has demonstrated that the Onyx Frontier stent is MR Conditional for single and overlapping lengths up to 120 mm. A person with the Onyx Frontier stent may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device name	Onyx Frontier
Static magnetic field strength [B_0]	Static magnetic field of 1.5 and 3 Tesla only
Maximum spatial field gradient	Maximum spatial gradient magnetic field of 3000 gauss/cm (30 T/m) or less
RF excitation	Circulatory polarized (CP)
RF transmit coil type	There are no Transmit Coil restrictions
Operating mode	Normal operating mode
Maximum whole-body SAR [W/kg]	Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0 W/kg (Normal Operating Mode)
Scan duration	15 continuous minutes of scan duration with 11 minutes wait time before more scanning
MR image artifact	In non-clinical testing, the image artifact caused by the device extended approximately 10 mm from the Onyx Frontier stent when imaged with a spin echo pulse sequence and a 3 Tesla MRI system. The artifact can obscure the device lumen. Some manipulation of scan parameters may be needed to compensate for the artifact.

6.8 Stent handling precautions

- For single use only. The Onyx Frontier system is provided sterile. Do not resterilize or reuse this product. Note the use-by date on the product label. Do not use the product if the 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 Onyx Frontier 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 (for example, rolling the mounted stent with your fingers) may cause coating damage, contamination, or dislodgement of the stent from the delivery system balloon.
- The Onyx Frontier system must not be exposed to any direct handling or contact with liquids before 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 stent delivery systems should not be used in conjunction with any other stents or for post-dilatation.

6.9 Stent placement precautions

- The vessel must be pre-dilated with an appropriately sized balloon. Refer to the pre-dilatation balloon sizing described in **Section 14.5 – Delivery procedure**. Failure to do so may increase the risk of placement difficulty and procedural complications.
- Do not prepare or pre-inflate the balloon before stent deployment other than as directed. Use the balloon purging technique described in **Section 14 – 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 2-1**).
- After preparation of the stent delivery system, do not induce negative pressure on the delivery catheter before 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 (for example, 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 6 - 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 the instructions in **Section 6 - 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 (for example, 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.

6.10 Stent/system removal precautions

If removal of a stent system is required before 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.

6.11 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 coating.
- Post-dilatation: All efforts should be made to ensure 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 6.7 – Magnetic resonance imaging (MRI) safety information** above.
- Antiplatelet therapy should be administered post-procedure (see **Precautions – Section 6.1 - Pre- and post-procedure antiplatelet regimen**). Patients who require early discontinuation of antiplatelet therapy (for example, 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.

7 Drug information

7.1 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.

7.2 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.

7.3 Pharmacokinetics of the stent

The pharmacokinetics information for the Onyx Frontier system is derived from a study conducted on the Resolute system. The Onyx Frontier system is similar to the Resolute 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 Onyx Frontier 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 7-1**.

Table 7-1: 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 7-1** 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.

7.4 Pharmacokinetics following multi-dose intravenous administration of zotarolimus

Zotarolimus pharmacokinetic activity has been determined following intravenous administration in healthy subjects. **Table 7-2** provides a summary of the pharmacokinetic analysis.

Table 7-2: Pharmacokinetic parameters (mean ± standard deviation) in patients following multi-dose intravenous administration of zotarolimus

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

Notes
¥ N = 16
$ Harmonic mean ± pseudo-standard deviation
[b] Clearance data is calculated using compartmental methods.
All other data presented in Table 7-2 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.

7.5 Mutagenesis, carcinogenicity, and reproductive toxicology

7.5.1 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.

7.5.2 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.

7.5.3 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.

7.6 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 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 stents coated with 300 µg zotarolimus total dose.

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

7.7 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.

8 Overview of clinical trials

8.1 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), the RESOLUTE ONYX 2.0 mm Clinical Study conducted in the US and Japan, and the RESOLUTE ONYX Post-Approval Study (PAS) – which consists of the Primary Cohort, the XLV Cohort, and the Bifurcation Cohort.

Table 8-1 summarizes the clinical trial designs for the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study, the RESOLUTE ONYX 2.0 mm Clinical Study, and the RESOLUTE ONYX PAS.

Table 8-1: The RESOLUTE ONYX Clinical Program

	RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study	RESOLUTE ONYX 2.0 mm Clinical Study	RESOLUTE ONYX Post-Approval Study Primary Cohort	RESOLUTE ONYX Post-Approval Study XLV Cohort	RESOLUTE ONYX Post-Approval Study Bifurcation Cohort
Study type	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Historical controlled trial	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a performance goal	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a performance goal	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Descriptively evaluate the TLF rate	▪ Prospective ▪ Multi-center ▪ Non-randomized ▪ Compared to a performance goal
Study site location	United States	United States and Japan	United States and Europe	United States and Europe	United States and Europe
Number of subjects enrolled	75	101	416	101	205

Table 8-1: The RESOLUTE ONYX Clinical Program

	RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study	RESOLUTE ONYX 2.0 mm Clinical Study	RESOLUTE ONYX Post-Approval Study Primary Cohort	RESOLUTE ONYX Post-Approval Study XLV Cohort	RESOLUTE ONYX Post-Approval Study Bifurcation Cohort
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	▪ Lesions located in separate target vessels with at least one of the target lesions amenable to treatment with a 2.0 to 4.0 mm stent ▪ Lesion(s) length ≤35 mm	▪ Lesions located in separate target vessels with at least one of the target lesions amenable to treatment with a 4.5 or 5.0 mm stent ▪ Lesion(s) length ≤35 mm	▪ Single *de novo* bifurcated lesion amenable to treatment with a 2.0 to 5.0 mm stent with provisional stenting technique ▪ Lesion(s) length ≤35 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	Stent diameter: 2.0 to 4.0 mm Stent length: 8 to 38 mm	Stent diameter: 4.5 to 5.0 mm Stent length: 12 to 30 mm	Stent diameter: 2.0 to 5.0 mm Stent length: 8 to 38 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	Resolute Onyx stent on a rapid exchange (RX) or over-the-wire (OTW) stent delivery system	Resolute Onyx stent on a rapid exchange (RX) or over-the-wire (OTW) stent delivery system	Resolute Onyx stent on a rapid exchange (RX) or over-the-wire (OTW) 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	Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.	Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.	Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on percutaneous coronary interventions and the Instructions for Use of the device.
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)	30 days, 6 months, 1 year, 2 years, 3 years: clinical or contact	30 days, 6 months, 1 year, 2 years, 3 years: clinical or contact	30 days, 6 months, 1 year, 2 years, 3 years: clinical or contact
Status	8 months: clinical and angiographic follow-up is complete	13 months: clinical and angiographic follow-up is complete	12 months: clinical follow-up is complete	Enrollment complete, in follow-up	Enrollment complete, 2-year follow-up complete

8.2 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 Onyx Frontier 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 5 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 8-2**. 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 8-2**). 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 8-2 summarizes the clinical trial designs for the Global RESOLUTE Clinical Trial Program and RESOLUTE INTEGRITY US Post-Market Study.

Table 8-2: 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 8-2: 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 8-2: 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 years (contact)
Status	60-month follow-up is complete. 551 subjects qualified for 18-month follow-up	60-month follow-up is complete	36-month follow-up is complete	60-month follow-up complete	60-month follow-up is complete	60-month follow-up is complete	24-month follow-up is complete	36-month follow-up is complete

Table 8-2: 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)

* The RESOLUTE US trial is composed of 4 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.

9 Clinical outcomes

9.1 Clinical outcomes for RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study and RESOLUTE ONYX 2.0 mm Clinical Study

Table 9-1: 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)
Follow-up (12-months)		
Target lesion failure (TLF)[2]	9.3% (7/75)	5.0% (5/101)
Target vessel failure (TVF)[3]	14.7% (11/75)	5.0% (5/101)
MACE[4]	13.3% (10/75)	5.0% (5/101)
Cardiac death or target vessel MI (TVMI)[5]	4.0% (3/75)	3.0% (3/101)
Death or TVMI	6.7% (5/75)	3.0% (3/101)
Death	2.7% (2/75)	0.0% (0/101)
Cardiac death	0.0% (0/75)	0.0% (0/101)
Non-cardiac death	2.7% (2/75)	0.0% (0/101)
TVMI (extended historical definition)[6]	4.0% (3/75)	3.0% (3/101)
Clinically-driven TLR[7]	5.3% (4/75)	2.0% (2/101)
Clinically-driven TVR[8]	10.7% (8/75)	2.0% (2/101)
Stent thrombosis (ARC) definite/probable[9]	1.3% (1/75)	0.0% (0/101)
Early thrombosis (≤30 days)	1.3% (1/75)	0.0% (0/100)
Late thrombosis (31-360 days)	0.0% (0/75)	0.0% (0/101)
Latest follow-up (36-months)		
Target lesion failure (TLF)[2]	14.7% (11/75)	13.9% (14/101)

Table 9-1: 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]
Target vessel failure (TVF)[3]	18.7% (14/75)	14.9% (15/101)
MACE[4]	21.3% (16/75)	14.9% (15/101)
Cardiac death or target vessel MI (TVMI)[5]	9.3% (7/75)	5.9% (6/101)
Death or TVMI	14.7% (11/75)	6.9% (7/101)
Death	8.0% (6/75)	3.0% (3/101)
Cardiac death	2.7% (2/75)	2.0% (2/101)
Non-cardiac death	5.3% (4/75)	1.0% (1/101)
TVMI (extended historical definition)[6]	8.0% (6/75)	4.0% (4/101)
Clinically-driven TLR[7]	8.0% (6/75)	7.9% (8/101)
Clinically-driven TVR[8]	13.3% (10/75)	10.9% (11/101)
Stent thrombosis (ARC) definite/probable[9]	1.3% (1/75)	0.0% (0/101)
Early thrombosis (≤30 days)	1.3% (1/75)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/75)	0.0% (0/101)
Very late thrombosis (>360 days)	0.0% (0/75)	0.0% (0/101)

Table 9-1: 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
12-month timeframe includes follow-up window (360 days ± 30 days).
36-month timeframe includes follow-up window (1080 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 vess 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] 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 10 - 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 9-2** below.

Table 9-2: 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)	7.1% (4/56)
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)	7.1% (4/56)
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)	8.9% (5/56)
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)	1.8% (1/56)
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)	1.8% (1/56)
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% (0/56)

Table 9-2: 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)
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)	5.4% (3/56)
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)	1.8% (1/56)
Non-Q wave MI	1.2% (16/1390)	3.5% (40/1132)	3.8% (43/1142)	2.5% (59/2337)	5.8% (8/139)	4.0% (4/100)	2.7% (6/222)	2.2% (5/226)	3.6% (2/56)
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)	7.1% (4/56)
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)	1.8% (1/56)
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)	1.8% (1/56)
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% (0/56)
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)	1.8% (1/56)
Latest follow-up	**60 months**	**60 months**		**36 months**	**60 months**	**60 months**	**60 months**	**24 months**	**36 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)	10.7% (6/56)
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)	12.5% (7/56)
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)	17.9% (10/56)
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)	3.6% (2/56)
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)	1.8% (1/56)
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)	1.8% (1/56)
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)	5.4% (3/56)
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)	1.8% (1/56)
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)	3.6% (2/56)
Cardiac death or TVMI	6.7% (89/1329)	11.5% (129/1123)	10.6% (120/1133)	7.0% (161/2284)	8.1% (11/136)	5.1% (5/98)	8.8% (19/217)	5.9% (13/219)	7.1% (4/56)
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)	7.1% (4/56)
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)	5.4% (3/56)

Table 9-2: 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)
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)	5.4% (3/56)
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)	1.8% (1/56)

Notes
N = The total number of subjects enrolled.
The numbers are % (count/number of eligible subjects).
Subjects are only counted once for each time period.
The definitions of the outcomes are presented as table notes to Table 9-1.
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 2 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 9-3**, **Table 9-4**, and **Table 9-5** below.

Table 9-3: 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)

Table 9-3: 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	1.3% (10/760)	2.1% (16/750)	6.4% (48/751)	7.4% (55/745)
Non-cardiac death	0.1% (1/760)	1.2% (9/750)	4.0% (30/751)	5.8% (43/745)
Cardiac death or TVMI	5.4% (41/760)	6.4% (48/750)	11.9% (89/751)	12.2% (91/745)
TVMI	4.2% (32/760)	4.7% (35/750)	5.9% (44/751)	6.0% (45/745)
Q wave MI	0.7% (5/760)	0.5% (4/750)	1.3% (10/751)	0.9% (7/745)
Non-Q wave MI	3.7% (28/760)	4.1% (31/750)	4.8% (36/751)	5.1% (38/745)
Stent thrombosis ARC defined				
Definite/probable	1.7% (13/759)	0.9% (7/749)	2.5% (19/751)	2.0% (15/745)
Definite	1.2% (9/759)	0.4% (3/749)	1.7% (13/751)	0.9% (7/745)
Probable	0.7% (5/759)	0.5% (4/749)	0.9% (7/751)	1.1% (8/745)

Notes
N = The total number of subjects enrolled.
Subjects are only counted once for each time period.
Numbers are % (count/number of eligible subjects).
The definitions of the outcomes are presented as table notes to Table 9-1.
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 9-4: 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)

Table 9-4: 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)
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 9-1.
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 9-5: 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).

9.2 Potential adverse events

9.2.1 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

9.2.2 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

9.2.3 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 or hypertension
- Incomplete stent apposition
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis

- Peripheral ischemia or peripheral nerve injury
- Renal failure
- Restenosis of the stented artery
- Shock or pulmonary edema
- Stable or unstable angina
- Stent deformation, collapse, or fracture
- Stent migration or embolization
- Stent misplacement
- Stroke or transient ischemic attack
- Thrombosis (acute, subacute, or late)

10 Clinical studies

10.1 Results of the RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study

Primary objective: The purpose of this study was 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 were to also undergo 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 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 ($p = 0.027$), 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 to 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 10-1**: RESOLUTE ONYX - primary endpoint analysis
- **Table 10-2**: RESOLUTE ONYX - clinical and Angio / IVUS outcomes
- **Table 10-3**: RESOLUTE ONYX - ARC defined definite/probable stent thrombosis through 8 months

Table 10-1: 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 months	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	0.027
– PP set	0.24 ± 0.05 (66)	0.35 ± 0.05 (89)	-0.15	-0.02	0.20	< 0.001	0.027
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
– PP set	0.22 ± 0.05	0.35 ± 0.05	-0.16	-0.03	0.20	< 0.001	0.023

[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 10-2: 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)
Noncardiac 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)	

Table 10-2: 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]
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)
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)
Safety measures (to 1080 days)	
Target lesion failure (TLF)	14.7% (11/75)
Target vessel failure (TVF)	18.7% (14/75)
MACE	21.3% (16/75)
Cardiac death or target vessel MI (TVMI)	9.3% (7/75)
Death or TVMI	14.7% (11/75)
Death	8.0% (6/75)
Cardiac death	2.7% (2/75)
Non-cardiac death	5.3% (4/75)
TVMI (extended historical definition)	8.0% (6/75)
Clinically-driven TLR	8.0% (6/75)
Clinically-driven TVR	13.3% (10/75)
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)
Very Late thrombosis (>360 days)	0.0% (0/75)
Angiography (8 months)	
Percent diameter stenosis (% DS)	
In-stent	
n	73
Mean±SD	15.56 ± 16.75

Table 10-2: 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]
Median (1Q, 3Q)	14.86 (5.26, 22.24)
Min, max	-21.18, 82.89
In-segment	
n	73
Mean±SD	25.84 ± 14.20
Median (1Q, 3Q)	22.35 (17.71, 29.75)
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	1.88 ± 0.49
Median (1Q, 3Q)	1.89 (1.58, 2.19)
Min, max	0.45, 3.10
Late luminal loss (mm)	
In-stent	
n	73
Mean±SD	0.24 ± 0.39
Median (1Q, 3Q)	0.18 (0.03, 0.37)
Min, max	-0.49, 2.06
In-segment	
n	73
Mean±SD	0.16 ± 0.37
Median (1Q, 3Q)	0.13 (-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	

Table 10-2: 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]
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 9-1.
[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 10-3: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – ARC defined definite/probable stent thrombosis through 36 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 (31-360 days)	0.0% (0/75)
Very late thrombosis (>360 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.

Table 10-3: RESOLUTE ONYX Core (2.25 mm – 4.0 mm) Clinical Study – ARC defined definite/probable stent thrombosis through 36 months

	RESOLUTE ONYX (N=75 subjects N=85 lesions) %(m/n)[1]

36-month timeframe includes follow-up window (1080 days ± 30 days).
See Table 9-1 for the definition of the ARC defined stent thrombosis.

10.2 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 require 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 were to undergo 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 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%, $p < 0.001$). The primary endpoint was also analyzed by gender, resulting in a TLF rate of 7.0% (5/71) 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 10-4**: RESOLUTE ONYX 2.0 mm - primary endpoint analysis
- **Table 10-5**: RESOLUTE ONYX 2.0 mm - clinical and angiographic outcomes
- **Table 10-6**: RESOLUTE ONYX 2.0 mm - ARC defined definite/probable stent thrombosis through 12 months
- **Table 10-7**: RESOLUTE ONYX 2.0 mm – primary endpoint analysis by gender

Table 10-4: 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%

[1] The one-sided upper 95% CI is calculated by binomial (exact) distribution
[2] The lesions with a Resolute Onyx 2.0 mm stent are included in the analysis. For 2 or more lesions with Resolute Onyx 2.0 mm stents per subject, the lesion is randomly selected.
[3] All target lesions are included in the analysis.

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Safety measures (to 180 days)	
Target lesion failure (TLF)[2]	4.0% (4/101)
Target vessel failure (TVF)[3]	4.0% (4/101)
MACE[4]	4.0% (4/101)
Cardiac death or target vessel MI (TVMI)	3.0% (3/101)
Death or TVMI	3.0% (3/101)
Death	0.0% (0/101)
Cardiac death	0.0% (0/101)
Non-cardiac death	0.0% (0/101)
TVMI (extended historical definition)	3.0% (3/101)
Clinically-driven TLR	1.0% (1/101)
Clinically-driven TVR	1.0% (1/101)
Stent thrombosis (ARC) definite/probable	0.0% (0/101)
Safety measures (to 360 days)	
Target lesion failure (TLF)[2]	5.0% (5/101)
Target vessel failure (TVF)[3]	5.0% (5/101)
MACE[4]	5.0% (5/101)
Cardiac death or target vessel MI (TVMI)	3.0% (3/101)
Death or TVMI	3.0% (3/101)
Death	0.0% (0/101)
Cardiac death	0.0% (0/101)
Non-cardiac death	0.0% (0/101)
TVMI (extended historical definition)	3.0% (3/101)
Clinically-driven TLR	2.0% (2/101)
Clinically-driven TVR	2.0% (2/101)

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Stent thrombosis (ARC) definite/probable	0.0% (0/101)
Early thrombosis (≤30 days)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/101)
Safety measures (up to 1080 days)	
Target lesion failure (TLF)[2]	13.9% (14/101)
Target vessel failure (TVF)[3]	14.9% (15/101)
MACE[4]	14.9% (15/101)
Cardiac death or target vessel MI (TVMI)	5.9% (6/101)
Death or TVMI	6.9% (7/101)
Death	3.0% (3/101)
Cardiac death	2.0% (2/101)
Non-cardiac death	1.0% (1/101)
TVMI (extended historical definition)	4.0% (4/101)
Clinically-driven TLR	7.9% (8/101)
Clinically-driven TVR	10.9% (11/101)
Stent thrombosis (ARC) definite/probable	0.0% (0/101)
Early thrombosis (≤30 days)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/101)
Very late thrombosis (>360 days)	0.0% (0/101)
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)
Min, max	0.00, 2.20
In-segment	
N	25

Table 10-5: RESOLUTE ONYX 2.0 mm Clinical Study – clinical and angiographic outcomes

Safety and effectiveness measures	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
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 10-6: RESOLUTE ONYX 2.0 mm Clinical Study – ARC defined definite/probable stent thrombosis through 12 months

	RESOLUTE ONYX 2.0 mm (N=101 subjects N=104 lesions) %(m/n)[1]
Stent thrombosis	0.0% (0/101)
Early thrombosis (≤30 days)	0.0% (0/101)
Late thrombosis (31-360 days)	0.0% (0/101)

Table 10-7: 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	7.0% (5/71)	0.0% (0/30)

10.3 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[5,6]. 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

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

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

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

Subjects from the 38 mm Length sub-study are not included in this Resolute Pooled Analysis of Subjects with Diabetes Mellitus. Additional information is provided in **Section 10.4** 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 10-8**: RESOLUTE diabetes mellitus cohort - primary endpoint analysis
- **Table 10-9**: 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 10-10**: RESOLUTE diabetes mellitus cohort - ARC defined definite/probable stent thrombosis events through 12 months

Table 10-8: 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 10-9: 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)

Table 10-9: 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)

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 9-1.

Table 10-10: 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 to 1 day)	0.1% (1/867)
Subacute (2 to 30 days)	0.1% (1/867)
Late (31 to 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.

10.4 Subjects with diabetes mellitus in the RESOLUTE 38 mm length group

Additional information is provided in **Table 10-11** for the RESOLUTE 38 mm length group in subjects with diabetes mellitus.

Table 10-11: RESOLUTE 38 mm length group: all 38 mm subjects, insulin-dependent DM subjects (IDDM), mon-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)

Table 10-11: RESOLUTE 38 mm length group: all 38 mm subjects, insulin-dependent DM subjects (IDDM), mon-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)
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)

10.5 Subjects receiving short-term DAPT

The Onyx ONE Clear Primary Analysis subject population was formed by pooling data from eligible subjects enrolled into the Onyx ONE US & Japan Trial (a prospective, multi-center, single-arm trial, which enrolled subjects in the United States and Japan) with data from eligible subjects treated with Resolute Onyx only in the Onyx ONE Global RCT (a prospective, multi-center, randomized trial [See Section 10.5.2]).

10.5.1 Onyx ONE Clear Primary Analysis

Primary Objective: To assess the safety and effectiveness of the Resolute Onyx stent with use of one-month DAPT in subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment.

Population: Subjects with an indication for percutaneous coronary intervention deemed at high risk for bleeding and/or candidates for one-month DAPT who are acceptable candidates to receive treatment with the Resolute Onyx stent.

Design: The Onyx ONE US & Japan Trial is a prospective, multi-center, post-market single-arm study which enrolled subjects undergoing attempted PCI. Subjects received DAPT through one month, before transitioning to SAPT thereafter.

Eligible subjects enrolled in the Onyx ONE US & Japan Trial (N=751) combined with eligible subjects from the Resolute Onyx arm of the Onyx ONE Global RCT (N=1018) (See Section 10.5.2) to form an Onyx As Treated population (Onyx AT).

The one-month clear population excluded subjects who interrupted or discontinued DAPT (greater than 3 cumulative days) within the first month of procedure (2.1%), those who experienced adverse events that would prohibit them from discontinuing DAPT beyond one month (3.4%), who did not intend to transition from DAPT to SAPT one month after procedure (6.2%), and who were lost to follow-up (3.1%). Peri-procedural MIs did not exclude subjects from being considered as one-month clear.

Assessment of the use of Resolute Onyx stents in HBR patients was based on analyses combining outcomes from patients compared to a pre-specified performance goal (PG). The PG was based on a clinically acceptable margin added to an expected composite event rate of cardiac death, and myocardial infarction (CD/MI) rate at 12 months, adapted from historical short DAPT studies with high-bleeding risk patient populations (LEADERS FREE[7], ZEUS[8,9], and SENIOR[10]). The expected CD/MI rate between one month and one year was estimated to be 6.8%.

The PG for the composite event rate of CD/MI at one-year post-procedure in a one-month clear population was 9.7% based on an estimated CD/MI rate of 6.8% and a one sided 0.025 significance level.

Demographics: The mean age was 74.0 ± 9.5, 67.7% (1019/1506) were male, 72.4% (1091/1506) reported dyslipidemia, 84.0% (1265/1506) had hypertension, 9.4% (141/1498) were current smokers, 39.4% (593/1506) were diabetic 13.7% (206/1506) reported as insulin dependent], 26.3% (396/1506) had a prior MI, and 48.6% (701/1441) were classified as having acute coronary syndrome.

The mean number of high bleeding risk criteria was 1.6±0.8. The most common HBR qualifying features were age $\geq$ 75 years, 59.0% (889/1506), long-term oral anticoagulation use, 41.0% (617/1506), anemia (hemoglobin level <11 g/dL) or recent transfusion, 14.4% (217/1506) and chronic kidney disease (creatinine clearance <40ml/min, 12.5% (188/1506).

Primary endpoint: The composite rate of cardiac death and myocardial infarction (CD/MI) at one year for a one-month clear population [timeframe: one month to one year].

Results: The Onyx As Treated (Onyx AT) one-month clear population was defined as the primary analysis population for the study. The CD/MI rate at one year for the Onyx ONE Clear cohort was 7.0% (104/1491) with the upper limit of 95% confidence interval of 8.4% which was lower than the prespecified performance goal of 9.7%.

The Onyx ONE Clear Primary Analysis results are presented in **Table 10-12** and **Table 10-13**.

Post hoc analyses by gender and ACS vs non-ACS presentation for the primary endpoint are presented in **Table 10-14** and **Table 10-15**. For gender, CD/MI rates at one year were 7.6% (77/1010) in male subjects and 5.6% (27/481) in female subjects. Patients who presented with ACS had a CD/MI rate at 1 year of 7.9% (55/694) compared with 6.0% (44/733) for patients who did not present with ACS.

Table 10-12: Primary endpoint analysis – Onyx ONE Clear

Primary Endpoint at 12 month1	Resolute Onyx (N = 1506 Subjects)	Two-side 95% Confidence Interval2	Performance Goal	p-value	Primary Objective Met? (Yes or No)
Primary Analysis					
– Onyx ONE Clear	7.0% (104/1491)	[5.7%, 8.4%]	9.7%	<0.001	Yes
Best Case Analysis3					
– Onyx ONE Clear	6.9% (104/1506)	[5.7%, 8.3%]	9.7%	<0.001	Yes

[7] Urban P, Meredith IT, Abizaid A, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Engl J Med 2015;373:2038-4.

[8] Valgimigli M, Patialiakas A, Thury A, et al. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. J Am Coll Cardiol. 2015;65:805–15.

[9] Ariotti S, Adamo M, Costa F, et al. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. JACC Cardiovasc Interv 2016;9:426-36.

[10] Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018 Jan 6;391(10115):41-50.

Table 10-12: Primary endpoint analysis – Onyx ONE Clear

Primary Endpoint at 12 month1	Resolute Onyx (N = 1506 Subjects)	Two-side 95% Confidence Interval2	Performance Goal	p-value	Primary Objective Met? (Yes or No)
Worst Case Analysis4					
– Onyx ONE Clear	7.9% (119/1506)	[6.6%, 9.4%]	9.7%	0.009	Yes

[1] The primary endpoint is a composite of cardiac death, myocardial infarction at one year post-procedure.
[2] The two-sided 95% CI was calculated by binomial (exact) distribution carried out to assess statistical significance at the 0.025 level.
[3] Best case analysis imputed all the missing 12-month primary endpoint status as no.
[4] Worst case analysis imputed all the missing 12-month primary endpoint status as yes.

Table 10-13: Principal safety and effectiveness results – Onyx ONE Clear

Safety and effectiveness measures	RESOLUTE ONYX (N=1506 subjects N=1960 lesions) %(m/n)[1]
Safety measures (to 180 days)	
Target lesion failure (TLF)2	4.1% (61/1500)
Target vessel failure (TVF)3	4.5% (67/1500)
MACE4	6.0% (90/1500)
Cardiac death, MI, and definite/probable stent thrombosis	3.7% (56/1500)
Cardiac death or MI	3.7% (56/1500)
Cardiac death or target vessel MI (TVMI)	3.3% (50/1500)
Death or TVMI	4.9% (73/1500)
Death	2.5% (38/1500)
Cardiac death	1.0% (15/1500)
Non cardiac death	1.5% (23/1500)
TVMI (3rd UDMI)	2.5% (38/1500)
Clinically driven TLR	1.6% (24/1500)
Clinically driven TVR	2.2% (33/1500)
Stroke	0.7% (11/1500)
Stent thrombosis (ARC) definite/probable	0.4% (6/1500)
Bleeding	
All BARC	7.3% (110/1500)
BARC 3-5	2.3% (34/1500)
BARC 2-5	6.5% (97/1500)
Safety measures (to 365 days)	
Target lesion failure (TLF)2	8.1% (121/1491)
Target vessel failure (TVF)3	8.8% (131/1491)
MACE4	11.7% (174/1491)
Cardiac death, MI, and definite/probable stent thrombosis	7.0% (104/1491)

Table 10-13: Principal safety and effectiveness results – Onyx ONE Clear

Safety and effectiveness measures	RESOLUTE ONYX (N=1506 subjects N=1960 lesions) %(m/n)[1]
Cardiac death or MI	7.0% (104/1491)
Cardiac death or target vessel MI (TVMI)	6.5% (97/1491)
Death or TVMI	9.7% (144/1491)
Death	6.0% (89/1491)
Cardiac death	2.6% (39/1491)
Non cardiac death	3.4% (50/1491)
TVMI (3rd UDMI)	4.4% (65/1491)
Clinically driven TLR	3.4% (50/1491)
Clinically driven TVR	4.3% (64/1491)
Stroke	1.5% (22/1491)
Stent thrombosis (ARC) definite/probable	0.7% (10/1491)
Bleeding	
All BARC	13.1% (195/1491)
BARC 3-5	4.0% (60/1491)
BARC 2-5	11.7% (175/1491)
Effectiveness measures	
Lesion success[5]	94.6% (1817/1920)
Device success[6]	93.3% (1790/1919)
Procedure success[7]	88.5% (1295/1463)

[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.
Third universal definition of MI is used for all the composite endpoints.

Table 10-14: Primary endpoint analysis by gender – Onyx ONE Clear

Primary endpoint	Male subjects Resolute Onyx (N=1019 subjects) % (m/n)	Female subjects Resolute Onyx (N=487 subjects) % (m/n)
CD/MI at 12 months	7.6% (77/1010)	5.6% (27/481)

Table 10-15: Primary endpoint analysis ACS vs. non-ACS patients- Onyx ONE Clear

Primary endpoint	Non-ACS (N=740 Subjects) (N=958 Lesions) %(m/n)[1]	ACS (N=701 Subjects) (N=914 Lesions) %(m/n)[1]
CD/MI at 12 months	6.0% (44/733)	7.9% (55/694)

10.5.2 The Onyx ONE Global RCT

Study design: The Onyx ONE Global RCT[11] was an international, randomized, single-blind trial that compared zotarolimus-eluting stents (Resolute Onyx) with polymer-free umirolimus–coated stents in patients at high bleeding risk. After PCI, patients were treated with one-month of DAPT, followed by SAPT. A total of 1996 HBR patients were randomly assigned in a 1:1 ratio to receive Resolute Onyx stents (1003 patients) or polymer-free drug-coated stents (993 patients).

Objective: The purpose of this clinical study was to evaluate the clinical safety of the Resolute Onyx stent as compared to the polymer-free drug coated stents with use of 1 month DAPT in subjects deemed at HBR and/or medically unsuitable for more than 1 month DAPT treatment. In the LEADERS-FREE trial, the same polymer-free drug-coated stent showed superiority in safety and effectiveness to a bare-metal stent in a similar HBR population treated with 1 month of DAPT.

Primary Endpoint: The composite rate of cardiac death, myocardial infarction, and stent thrombosis (definite/probable) at one year.

Results: At 1 year, the primary outcome was observed in 169 of 988 patients (17.1%) in the Resolute Onyx stent group and in 164 of 969 (16.9%) in the polymer-free drug-coated stent group (risk difference, 0.2 percentage points; upper boundary of the one-sided 97.5% confidence interval [CI], 3.5; noninferiority margin, 4.1; P = 0.01 for noninferiority). Among patients at HBR who received 1 month of DAPT after PCI, Resolute Onyx stents were noninferior to use of polymer-free drug-coated stents with regard to safety and effectiveness composite outcomes.

10.6 Subjects with chronic total occlusion

10.6.1 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.

[11] Windecker S, Latib A, Kedhi E, et al. Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk. New England Journal of Medicine 2020.

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

An estimated MACE rate was derived based on a weighted average of the reported rates for drug-eluting stents from the PRISON II[12] and EXPERT CTO[13] 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 10-16**, **Table 10-17**, and **Table 10-18**:

Table 10-16: 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 10-17: 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)

[12] 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.

[13] 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 10-17: Principal safety and effectiveness results

Safety and effectiveness measures	RESOLUTE CTO cohort (N=183 subjects) %(m/n)
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 definite/probable/possible)	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 to 6 months)	1.1% (2/183)
Definite	0.0% (0/183)
Probable	0.0% (0/183)
Possible	1.1% (2/183)
Safety measures (to 1 year/365 days)	
TLF	18.2% (33/181)
TVF	18.2% (33/181)
MACE	18.2% (33/181)
Cardiac death or MI	17.7% (32/181)
Death or MI	17.7% (32/181)
Death	2.8% (5/181)
Cardiac death	2.2% (4/181)
Non-cardiac death	0.6% (1/181)
MI	16.0% (29/181)
TLR	1.1% (2/181)
TVR	1.1% (2/181)
All stent thrombosis (ARC definite/probable/possible)	1.7% (3/181)
Stent thrombosis ARC definite/probable	0.6% (1/181)
Stent thrombosis ARC possible	1.1% (2/181)

Table 10-17: Principal safety and effectiveness results

Safety and effectiveness measures	RESOLUTE CTO cohort (N=183 subjects) %(m/n)
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 to 1 year)	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)

[1] CTO 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 10-18: 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)

10.6.2 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™* Liberté™* 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 **Table 10-19**:

Table 10-19: RESOLUTE pooled CTO analysis – safety and effectiveness results

Safety and effectiveness endpoints	RESOLUTE pooled CTO (N=358 patients) (N=527 lesions) %(m/n)[9]
Effectiveness measures	
Lesion success[6]	100.0% (526/526)
Device success[7]	94.1% (496/527)
Procedure success[8]	97.5% (348/357)
1 Year	
TLF[1]	4.5% (16/352)
TVF[2]	4.8% (17/352)
MACE[3]	5.7% (20/352)
Composite endpoint[4]	12.2% (43/352)
Cardiac death or TVMI	3.1% (11/352)
Death or TVMI	4.0% (14/352)
Death	1.7% (6/352)
Cardiac death	0.9% (3/352)
Non-cardiac death	0.9% (3/352)
TVMI (extended historical definition)	2.3% (8/352)
Clinically-driven TLR	2.0% (7/352)
Clinically-driven TVR	2.3% (8/352)
Stent thrombosis (ARC) definite/probable)	0.6% (2/352)
Early thrombosis (≤30 days)	0.3% (1/352)
Late thrombosis (>30 and ≤360 days)	0.3% (1/352)
Significant bleeding complications[5]	1.1% (4/352)
Stroke	0.9% (3/352)
3 Years	
TLF[1]	8.9% (31/347)
TVF[2]	10.1% (35/347)
MACE[3]	10.1% (35/347)
Composite endpoint[4]	18.4% (64/347)
Cardiac death or TVMI	6.6% (23/347)
Death or TVMI	7.8% (27/347)

Table 10-19: RESOLUTE pooled CTO analysis – safety and effectiveness results

Safety and effectiveness endpoints	RESOLUTE pooled CTO (N=358 patients) (N=527 lesions) %(m/n)[9]
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.

10.7 The RESOLUTE ONYX CTO Post-Approval Study (PAS)

The RESOLUTE ONYX CTO PAS is a retrospective study consisting of patient- and lesion-level analyses for 78 subjects with CTOs treated with Resolute Onyx. Patients enrolled in the Primary[14], XLV[14], and Bifurcation[15] Cohorts of the RESOLUTE ONYX Post-Approval Study (n=30; Onyx PAS CTO), the Onyx ONE Clear US & Japan Trial (n=13; Onyx ONE Clear CTO; Section 10.5.1), and the Onyx ONE Global RCT (n=35; Onyx ONE CTO; Section 10.5.2) comprise three complex CTO cohorts. Subjects were followed according to the procedures in each of the respective trials. The primary safety and effectiveness endpoint is freedom from MACE (death, myocardial infarction, and clinically-driven target lesion revascularization) at 30 days. Secondary endpoints include acute success (device, lesion, procedure), cardiac death, target vessel myocardial infarction (TVMI), target lesion revascularization (TLR), target lesion failure (TLF), target vessel failure (TVF), and stent thrombosis (ST). The RESOLUTE ONYX CTO PAS does not have a formal hypothesis, but descriptive statistics are provided. Clinical outcomes are reported through 2 years post-procedure on all patients.

Primary Objective: To demonstrate the generalizability of the performance of Resolute Onyx for the treatment of CTO in a real-world setting.

Population: CTO subjects with available two-year data from active post-market studies and trials utilizing Resolute Onyx. Seventy-eight (78) subjects representing a real-world patient population including those deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment make up the RESOLUTE ONYX CTO PAS cohort.

Design: The RESOLUTE ONYX CTO PAS was a global, retrospective analysis of subjects with CTOs treated with Resolute Onyx from the RESOLUTE ONYX Post-Approval Study (PAS; Onyx PAS CTO), the Onyx ONE Clear US & Japan Trial (Onyx One Clear CTO), and the Onyx ONE Global RCT (Onyx ONE CTO). The total number of enrolled study sites and subjects are presented in Table 10-20.

Table 10-20: Subjects from RESOLUTE ONYX CTO PAS

Study	Number of Sites	Total Number of Resolute Onyx Subjects[1]	Enrollment Time Frame	CTO PAS Cohort[2]
RESOLUTE ONYX PAS	28	703	30 MAR 2017 – 02 DEC 2019	30
Onyx ONE Global RCT	82	1029	02 NOV 2017 – 27 SEP 2018	35
Onyx ONE Clear US & Japan	47	752	01 OCT 2018 – 09 APR 2019	13

[1] Subjects who meet one of the following criteria:
- Implanted with at least one Resolute Onyx stent or
- Attempted (a Resolute Onyx stent was introduced into the guide catheter.)

[2] Subjects with at least one CTO lesion implanted or attempted with Resolute Onyx stent

Demographics: These three real-world studies each enrolled a highly complex patient population compounded by the complex lesion treatment of a CTO. Subject's median age was: 65 years (Onyx PAS CTO), 70 years (Onyx ONE CTO), and 75 years (Onyx ONE Clear CTO). The percentage male was as follows: 80% (Onyx PAS CTO), 74% (Onyx ONE CTO), and 85% (Onyx ONE Clear CTO).

[14] NCT03063749

[15] NCT03584464

Results:

Table 10-21: Subject Follow-up Visit Compliance (total in-window)

Resolute Onyx CTO Cohort	30-day	6-Month	12-Month	24-Month
Onyx PAS CTO	90.0% (27/30)	93.3% (28/30)	96.7% (29/30)	96.7% (29/30)
Onyx ONE CTO	91.4% (32/35)	91.2% (31/34)	100.0% (32/32)	100.0% (32/32)
Onyx ONE Clear CTO	84.6% (11/13)	100.0% (13/13)	100.0% (12/12)	100.0% (11/11)
Follow-up Compliance: Percentage of subjects with follow-up visit (30 days, 6 months, and 12 months) within the defined time window. Subjects that died or withdrew consent or lost-to-follow up before the lower limit of the window of each follow-up are excluded from the denominator, and they were not considered to be evaluable for this compliance table from the time that they died/withdrew/lost-to-follow up including any time points thereafter.				

Although not powered, freedom from MACE, defined as any death, myocardial infarction (per ARC definition), or clinically-driven target lesion revascularization (TLR) at 30-days was established as the primary endpoint for these cohorts. There were no deaths or TLRs reported for these subjects within the 30-day time point and therefore the incidence of MACE is reflective of the peri-procedural ARC MI rates. Freedom from MACE at 30 days for Onyx PAS CTO was 70%, Onyx ONE CTO was 88.6%, and Onyx ONE Clear CTO was 76.9%.

Composite safety rates are reflective of ARC MI events reported for Onyx PAS CTO where nine (9) subjects reported peri-procedural MI. There were no additional events reported for this cohort through 12 months. At the 24-month time point, one (1) TLR was reported resulting in a 3.3% TLR rate and contributing to an overall 33.3% (10/30) TLF, TVF, and MACE rate.

Safety rates for the Onyx ONE CTO cohort through the two-month time point are reflective of the four (4) peri-procedural MIs reported. One subject withdrew consent prior to the 2-month visit resulting in 34 subjects evaluable for the six- through 24-month analysis. At six months, one subject had confirmed definite stent thrombosis in the Mid LAD, but revascularization was deferred to a later date. Twelve-month events include two deaths, one of which was a cardiac death that also resulted in an MI adjudicated as unknown vessel-related MI, ARC sudden death bringing the MI rate to 14.7% (5/34). There was also a non-cardiac death reported resulting in a rate of 2.9% (1/34). One TLR was reported for this cohort resulting in a TVR/TLR rate of 2.9% (1/34), MACE rate of 20.6% (7/34), and a TLF/TVF rate of 17.6% (6/34). At the 24-month time point, one additional event, TLR/TVR was reported for this cohort.

Composite safety rates are also reflective of ARC MI rates for Onyx ONE Clear CTO where two (2) subjects reported peri-procedural MI and one (1) subject reported a spontaneous MI with no other events reported through the six-month time point. At twelve months, a TVR was reported for one subject resulting in a TVR rate of 7.7% (1/13); increasing the TVF rate to 30.8% (4/13). At the 24-month time point, two (2) non-cardiac deaths were reported for this cohort.

Resolute Onyx PAS CTO: Lesion success defined as attainment of <50% residual stenosis of the target lesion using any percutaneous method was 100% (47/47) and device success defined as attainment of <50% residual stenosis of the target lesion using only Resolute Onyx was reported at 97.9% (46/47). Procedure success defined as attainment of <50% residual stenosis of the target lesion and no in-hospital MACE was reported at 70.0% (21/30) where failures were solely driven by the nine (9) peri-procedural ARC MIs reported for this cohort.

Onyx ONE CTO: Lesion success and device success was 100% (55/55), and procedure success was 94.1% (32/34).

Onyx ONE Clear CTO: Lesion success and device success was reported at 100% (22/22) and procedure success was 84.6% (11/13).

Strengths of this analysis include that each of the three studies evaluated were executed similarly with respect to study logistics, monitoring, use of independent core labs, data analysis, and independent Clinical Event Committees (CEC). A limitation was that the CTO cohorts presented were not pre-specified or powered for comparison.

10.8 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 10-22** provides the total number of subjects included in the analyses.

Table 10-22: 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 Data set	**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 10-23**: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months
- **Table 10-24**: RESOLUTE pooled Analysis - ARC defined definite/probable stent thrombosis through 60 months
- **Table 10-25**: RESOLUTE pooled analysis - subset outcomes through 12 months
- **Table 10-26**: RESOLUTE pooled analysis – subset outcomes through 12 months
- **Table 10-27**: RESOLUTE pooled analysis – subset outcomes through 12 months

Table 10-23: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months

	All subjects (N = 5130)	On-label (N = 2780)
Outcomes at 12 months		

Table 10-23: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months

	All subjects (N = 5130)	On-label (N = 2780)
Composite safety and effectiveness		
TLF	6.6% (336/5098)	5.4% (150/2759)
TVF	7.5% (382/5098)	6.6% (181/2759)
MACE	7.5% (384/5098)	6.3% (174/2759)
Effectiveness		
Clinically-driven TVR	4.3% (220/5098)	3.7% (103/2759)
Clinically-driven TLR	3.3% (166/5098)	2.5% (69/2759)
Safety		
Total death	1.9% (98/5098)	1.6% (44/2759)
Cardiac-death	1.2% (60/5098)	0.9% (26/2759)
Non-cardiac death	0.7% (38/5098)	0.7% (18/2759)
TVMI	2.9% (149/5098)	2.4% (66/2759)
Cardiac death or TVMI	3.9% (200/5098)	3.3% (90/2759)
Stent thrombosis ARC defined		
Definite/probable	0.8% (40/5098)	0.3% (9/2759)
Definite	0.6% (29/5098)	0.2% (6/2759)
Probable	0.3% (13/5098)	0.1% (3/2759)
Outcomes at 36 months		
Composite safety and effectiveness		
TLF	10.8% (539/5012)	9.2% (249/2709)
TVF	13.0% (652/5012)	12.0% (324/2709)
MACE	13.5% (679/5012)	12.0% (325/2709)
Effectiveness		
Clinically-driven TVR	7.9% (397/5012)	7.5% (204/2709)
Clinically-driven TLR	5.3% (267/5012)	4.4% (119/2709)
Safety		
Total death	5.5% (275/5012)	5.0% (135/2709)
Cardiac death	3.1% (156/5012)	2.6% (70/2709)
Non-cardiac death	2.4% (119/5012)	2.4% (65/2709)
TVMI	3.8% (188/5012)	3.1% (84/2709)
Cardiac death or TVMI	6.5% (324/5012)	5.4% (145/2709)
Stent thrombosis ARC defined		
Definite/probable	1.1% (54/5012)	0.5% (13/2709)
Definite	0.7% (37/5012)	0.3% (7/2709)

Table 10-23: RESOLUTE pooled analysis - principal safety and effectiveness through 60 months

	All subjects (N = 5130)	On-label (N = 2780)
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)
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 ± 30 days).
60-month timeframe includes follow-up window (1800 days ± 30 days).
* Note: R-Int. follow-up ends at 3 years and is not included in this analysis.
The definitions of the outcomes are presented as table notes to Table 9-1.

Table 10-24: 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 to 30 days)	0.5% (13/2688)	0.2% (3/1937)
Late (31 to 360 days)	0.3% (8/2688)	0.2% (4/1937)
Very late (361 to 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).

Table 10-24: RESOLUTE pooled analysis - ARC defined definite/probable stent thrombosis through 60 months

	All subjects* (N = 2781)	On-label* (N = 2017)

60-month timeframe includes follow-up window (1800 days ± 30 days).
* Note: R-Int. follow-up ends at 3 years and is not included in this analysis.

Table 10-25: 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 10-26: 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 10-27: 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 9-1.
[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.

10.9 Results of the RESOLUTE ONYX Post-Approval Study Bifurcation Cohort

Primary objective: To assess the continued safety and efficacy of Resolute Onyx for the treatment of lesions in coronary arteries amenable to treatment with a Resolute Onyx 2.0 mm – 5.0 mm stent.

Design: The RESOLUTE ONYX PAS Bifurcation Cohort was a single arm, multi-center study evaluating approximately 200 subjects with ischemic heart disease attributable to stenotic bifurcation lesions in native coronary arteries amenable to treatment with Resolute Onyx stent sizes of 2.0 – 5.0 mm utilizing the provisional stenting technique. The Bifurcation Cohort was to consist of at least 200 subjects with approximately 15 eligible subjects that could be included for analysis from the Primary and XLV Cohorts, and an additional 185 subjects were to be prospectively recruited for the Bifurcation Cohort. Subjects were to be treated with the full stent size matrix, 2.0 mm – 5.0 mm stents. Subjects were enrolled in both the US and EU geographies, with no more than 99 subjects from European sites to be included in the analysis.

Primary endpoint: The primary endpoint for subjects participating in the Bifurcation Cohort is Target Vessel Failure (TVF), defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically-driven target vessel revascularization (TVR) by percutaneous or surgical methods, at 12 months.

Demographics: The mean age of Bifurcation Cohort subjects was 66.6 ± 10.7 years, with 78.5% (161/205) males, 30.2% (62/205) diabetics, 14.1% (29/205) current smokers, 19.5% (40/205) had prior MI, 35.1% (72/205) had prior PCI, 9.3% (19/205) had prior CABG, 77.1% (158/205) had hypertension, and 74.1% (152/205) reported hyperlipidemia.

Indications for the index procedure were due to one or more of the following: silent ischemia 14.2% (27/190), stable angina 36.3% (69/190), unstable angina 36.8% (70/190), MI 10.5% (20/190) of which 7.4% (14/190) occurred within 72 hours. Acute coronary syndrome (ACS) was reported in 47.4% (90/190) and positive functional study in 54.1% (111/205) of subjects at the time of the index procedure.

Results: Primary Endpoint Analysis is presented in **Table 10-28**. The rate of TVF in the Bifurcation Cohort ITT population at 12 months was 6.9% (14/204), fulfilling the pre-specified performance criterion (one-sided upper 95% CI of 10.5%, compared with the performance goal of 24.5%). Furthermore, the rate of TVF in the Tipping Point Analysis (worst-case analysis) was 7.3% (15/205) (one-sided upper 95% CI of 11.0%, compared with the performance goal of 24.5%).

These analyses are based on the intent-to-treat population. The results are presented in **Table 10-28**, **Table 10-29**, and **Table 10-30**.

Table 10-28 Primary Endpoint Analysis Performance Criterion

Primary Endpoint - TVF at 12 months	RESOLUTE ONYX PAS (N = 205 Subjects)	One-sided upper 95% Confidence Interval[1]	Performance Goal
Primary Analysis			
– ITT set	6.9% (14/204)	10.5%	24.5%
– PP set	6.2% (12/193)	9.9%	24.5%
Multiple Imputation2			
– ITT set	6.8%	9.7%	24.5%
– PP set	6.2%	9.0%	24.5%
Tipping Point Analysis3			
– ITT set	7.3% (15/205)	11.0%	24.5%
– PP set	6.7% (13/194)	10.4%	24.5%

Table 10-28 Primary Endpoint Analysis Performance Criterion

Primary Endpoint - TVF at 12 months	RESOLUTE ONYX PAS (N = 205 Subjects)	One-sided upper 95% Confidence Interval[1]	Performance Goal
Survival Analysis4			
– ITT set	7.1%	10.8%	24.5%
– PP set	6.4%	10.2%	24.5%
Sensitivity Analysis			
- Excluded extra subjects beyond 15% maximum enrollment per site[5]	7.1% (14/197)	10.9%	24.5%
- Excluded non-cardiac deaths from denominator[6]	7.0% (14/201)	10.7%	24.5%

[1] The one-sided upper 95% CI is calculated by binomial (exact) distribution or the Greenwood standard error.

[2] 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 TVF status at visits prior to dropout. The longest lesion length and the smallest baseline RVD are used for the subjects having 2 or more target lesions in the imputation model.

[3] Imputed as many 12-month TVF "yes" statuses as possible so that the one-side upper 95% confidence interval of 12-month TVF rate can be less than or equal to the performance goal.

[4] Survival analysis uses Kaplan-Meier rate and Greenwood formula for the standard error.

[5] Excluded the subjects who were enrolled after the site had enrolled 15% of the total ITT subjects.
The following subjects 004322494, 004322517, 004322529, 004322556, 004322557, 004322558, 004322568 were excluded from the site 004322 (North Shore University Hospital).

[6] Excluded the subjects (3351179, 3970067, 6088083) with non-cardiac deaths from the denominator.
Third UDMI is used for all the composite endpoints. All target lesions are included in the analysis.

Table 10-29 Principal Safety and Effectiveness Results

Safety and Effectiveness Measures	Bifurcation Cohort (N=205 Subjects N=267 Lesions) %(m/n)[1]
Safety Measures (at discharge)	
Target Lesion Failure (TLF)[2]	2.0% (4/205)
Target Vessel Failure (TVF)[3]	2.0% (4/205)
MACE[4]	2.0% (4/205)
Cardiac Death or Target Vessel MI (TVMI)	2.0% (4/205)
Death or TVMI	2.0% (4/205)
Death	0.0% (0/205)
Cardiac Death	0.0% (0/205)
Non Cardiac Death	0.0% (0/205)
TVMI (3rd UDMI)[5]	2.2% (4/205)
Clinically Driven TLR	0.0% (0/205)
Clinically Driven TVR	0.0% (0/205)
Safety Measures (to 30 days)	

Table 10-29 Principal Safety and Effectiveness Results

Safety and Effectiveness Measures	Bifurcation Cohort (N=205 Subjects N=267 Lesions) %(m/n)[1]
Target Lesion Failure (TLF)[2]	2.0% (4/205)
Target Vessel Failure (TVF)[3]	2.0% (4/205)
MACE[4]	2.0% (4/205)
Cardiac Death or Target Vessel MI (TVMI)	2.0% (4/205)
Death or TVMI	2.0% (4/205)
Death	0.0% (0/205)
Cardiac Death	0.0% (0/205)
Non Cardiac Death	0.0% (0/205)
TVMI (3rd UDMI)	2.0% (4/205)
Clinically Driven TLR	0.0% (0/205)
Clinically Driven TVR	0.0% (0/205)
Safety Measures (to 180 days)	
Target Lesion Failure (TLF)[2]	3.4% (7/204)
Target Vessel Failure (TVF)[3]	3.9% (8/204)
MACE[4]	4.9% (10/204)
Cardiac Death or Target Vessel MI (TVMI)	2.5% (5/204)
Death or TVMI	2.9% (6/204)
Death	1.0% (2/204)
Cardiac Death	0.5% (1/204)
Non Cardiac Death	0.5% (1/204)
TVMI (3rd UDMI)	2.0% (4/204)
Clinically Driven TLR	1.0% (2/204)
Clinically Driven TVR	1.5% (3/204)
Safety Measures (to 360 days)	
Target Lesion Failure (TLF)[2]	6.4% (13/204)
Target Vessel Failure (TVF)[3]	6.9% (14/204)
MACE[4]	8.3% (17/204)
Cardiac Death or Target Vessel MI (TVMI)	4.4% (9/204)
Death or TVMI	5.9% (12/204)
Death	2.9% (6/204)
Cardiac Death	1.5% (3/204)
Non Cardiac Death	1.5% (3/204)
TVMI (3rd UDMI)	2.9% (6/204)
Clinically Driven TLR	2.9% (6/204)

Table 10-29 Principal Safety and Effectiveness Results

Safety and Effectiveness Measures	Bifurcation Cohort (N=205 Subjects N=267 Lesions) %(m/n)[1]
Clinically Driven TVR	3.4% (7/204)
Safety Measures (to 720 days)	
Target Lesion Failure (TLF)[2]	8.0% (16/200)
Target Vessel Failure (TVF)[3]	9.0% (18/200)
MACE[4]	10.5% (21/200)
Cardiac Death or Target Vessel MI (TVMI)	5.5% (11/200)
Death or TVMI	7.0% (14/200)
Death	3.0% (6/200)
Cardiac Death	1.5% (3/200)
Non Cardiac Death	1.5% (3/200)
TVMI (3rd UDMI)	4.0% (8/200)
Clinically Driven TLR	4.5% (9/200)
Clinically Driven TVR	5.5% (11/200)
Stent Thrombosis (ARC) Definite/Probable	0.0% (0/200)
Early Thrombosis (<=30 days)	0.0% (0/200)
Late Thrombosis (31-360 days)	0.0% (0/200)
Very Late Thrombosis (361-720 days)	0.0% (0/200)
Effectiveness Measures	
Lesion Success[6]	98.9% (261/264)
Device Success[7]	97.3% (257/264)
Procedure Success[8]	96.6% (196/203)

[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] Denominator based on subjects with available lab results

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

[7] 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.

[8] 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.

Third UDMI is used for all the composite endpoints.

Table 10-30. ARC defined definite/probable Stent Thrombosis to 720 Days

Stent Thrombosis to 720 days	Bifurcation Cohort (N=205 Subjects) %(m/n)[1]
Stent Thrombosis	0.0% (0/200)
Early Thrombosis (≤30 days)	0.0% (0/200)
Late Thrombosis (31-360 days)	0.0% (0/200)
Very Late Thrombosis (>360 days)	0.0% (0/200)

[1] Numerator (m) is the number of patients with the specific classification, denominator (n) is the number of patients in the study group with known values, and percentage (%) was calculated as 100 × (m/n)

Target Vessel Myocardial Infarction by Definition: As the protocol definition of MI changed mid-trial, and because different definitions of MI (particularly peri-procedural MI) have a meaningful impact on MI rates, **Table 10-31** presents a comparison of the 3rd UDMI, Extended Historical, and SCAI peri-procedural MI definitions and **Table 10-32** presents CEC-adjudicated TVMI rates in the Bifurcation Cohort using those definitions.

Table 10-31. Comparison of Definitions Used by CEC to Adjudicate Per-Procedural MI

	3rd UDMI	Extended Historical	SCAI
Relationship to Study	Revised Protocol Definition	Original Definition	Alternative Per-Procedural MI Definition
Preferred Biomarker	Troponin	CK/CK-MB	CK-MB
Positivity Threshold	>5X URL for troponin and CK-MB	>3X URL for troponin and CK-MB	>10X URL for CK-MB >70X URL for troponin
Other Required Criteria	Evidence of ischemia (symptoms, angiographic findings, ECG, etc.)	None	None

Table 10-32. TVMI Rates by Definition

	3rd UDMI	Extended Historical	SCAI
TVMI[1]	2.9% (6/204)	12.7% (26/204)	- - -
Peri-procedural	2.2% (4/180)	12.8% (23/180)	5.0% (9/180)
Non-Q Wave	1.7% (3/180)	12.2% (22/180)	4.4% (8/180)
Spontaneous	1.0% (2/204)	1.5% (3/204)	- - -

[1] Denominator based on subjects with available lab results

Peri-procedural MI rates using any definition should be interpreted with caution as they are heavily influenced by the proportion of types of biomarkers and assays used by study sites. Specifically, troponin is a more sensitive marker than CK-MB, particularly after PCI. Troponin elevations meeting the Extended Historical criteria of >3X URL are much more common than CK-MB elevations meeting the same criteria. Although a definition may prefer the use of CK-MB (in other words, if both CK-MB and troponin are available, a PPMI adjudication should use CK-MB), CK-MB is frequently no longer available at study sites. The Bifurcation Cohort study switched to the 3rd UDMI definition, which prefers troponin and accounts for its increased sensitivity by also requiring ancillary clinical criteria, in order to account for this evolution in the standard of care.

11 Patient selection and treatment

See also **Section 6.5 - Use in special populations**. The risks and benefits described above should be carefully considered for each patient before use of the Onyx Frontier system. Factors to be utilized for patient selection should include an assessment of the risk of prolonged anticoagulation. In accordance with the 2016 American College of Cardiology / American Heart Association guidelines, administration of P2Y12 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, Resolute Onyx stent is safe and effective with one-month DAPT based on results of the Onyx ONE Clear Primary Analysis as described in **6.1.1 Oral antiplatelet therapy**. Aspirin should be administered concomitantly with an approved antiplatelet medication and then continued indefinitely.

12 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 and benefits tradeoff for the 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 Onyx Frontier 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.

13 How supplied

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

Contents: The package contains one (1) Resolute Onyx zotarolimus-eluting coronary stent mounted on either an Onyx Frontier rapid exchange (RX) or Resolute Onyx RX stent delivery system.

Storage: Store the product 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 the product and packaging in accordance with hospital, administrative and local government policy.

14 Directions for use

14.1 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, for example, rolling the mounted stent, may cause dislodgement of the stent from the delivery balloon.

14.2 Inspection before 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 the proximal and distal marker bands) on the balloon.

14.3 Materials required

Quantity	Material
N/A	Guide catheter [≥ 5 Fr (1.42 mm, 0.056 in) inner diameter]
2 to 3	20 cc syringe
1,000 u /500 cc	Heparinized normal saline
1	Guidewire [≤ 0.014 in (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

14.4 Preparation precaution

- **Do not** use product if the protective sheath is not present or the stent is damaged or 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.

14.4.1 Guidewire lumen flush

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

14.4.2 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 the protective sheath covering from the stent/balloon. Removing the protective sheath will also remove the stylette.
4.	Inspect the stent to ensure that 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 the 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 to 30 seconds.
8.	Slowly release pressure to allow negative pressure to draw the mixture into the balloon lumen.
9.	Detach the syringe and leave a meniscus of mixture on the hub of the balloon lumen.
10.	Prepare the inflation device in standard manner and purge to remove all air from the syringe and tubing.

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

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

14.5 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 3 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 Onyx Frontier system into the coronary artery. Carefully advance the Onyx Frontier 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 – 6 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. The 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 – 6 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 the stent with bare hands.

14.6 Deployment procedure

Step	Action
1.	Before stent expansion, utilize high-resolution fluoroscopy to verify that the stent has not been damaged or shifted during positioning.
2.	Maintain inflation pressure for 15 to 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 stents should not be expanded to a diameter beyond the maximum diameter listed on the label. Do not dilate the 2.0, 2.25, and 2.5 mm stents to greater than 3.5 mm. Do not dilate the 2.75 and 3.0 mm stents greater than 4.0. Do not dilate the 3.5 and 4.0 mm stents to greater than 5.0 mm. Do not dilate the 4.5 mm and 5.0 mm stents to greater than 6.0 mm.**
4.	Fluoroscopic visualization during stent expansion should be used 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.

14.7 Removal procedure

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 the 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.

14.8 *In-vitro* information:

Table 14-1: Inflation pressure recommendations

Pressure			Stent nominal inner diameter (mm)								
ATM	kPa	Nominal and rated burst pressure	2.0	2.25	2.5	2.75	3.0	3.5	4.0	4.5	5.0
7 atm	709 kPa		1.80	1.95	2.20	2.50	2.75	3.20	3.70	4.10	4.55
8 atm	811 kPa		1.85	2.05	2.25	2.55	2.80	3.30	3.75	4.20	4.65
9 atm	912 kPa		1.90	2.10	2.35	2.60	2.90	3.35	3.85	4.30	4.80
10 atm	1013 kPa		1.95	2.15	2.40	2.70	2.95	3.40	3.90	4.40	4.90
11 atm	1115 kPa		2.00	2.20	2.45	2.75	3.00	3.50	3.95	4.45	4.95
12 atm	**1216 kPa**	**Nominal**	**2.05**	**2.25**	**2.50**	**2.75**	**3.05**	**3.50**	**4.00**	**4.50**	**5.05**
13 atm	1317 kPa		2.10	2.30	2.55	2.80	3.05	3.55	4.10	4.55	5.10
14 atm	1419 kPa		2.10	2.30	2.60	2.85	3.10	3.60	4.10	4.60	5.15
15 atm	1520 kPa		2.15	2.35	2.65	2.90	3.15	3.65	4.15	4.65	5.20
16 atm	1621 kPa		2.20	2.40	2.70	2.95	3.20	3.70	4.20	**4.70**	**5.25**
17 atm	1723 kPa		2.20	2.45	2.70	3.00	3.25	3.75	4.25	4.80	5.30
18 atm	**1824 kPa**	**RBP**	**2.25**	**2.45**	**2.75**	**3.05**	**3.30**	**3.80**	**4.30**	4.85	5.35
19 atm	1925 kPa		2.30	2.50	2.80	3.10	3.35	3.85	4.35	-	-
20 atm	2027 kPa		2.35	2.55	2.85	3.15	3.40	3.90	4.45	-	-
21 atm	2128 kPa		2.40	2.60	2.90	3.20	3.50	4.00	4.50	-	-

14.9 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 14-2: Nominal stent diameters and dilatation limits

Nominal stent diameter	Dilatation limits
2.00 mm	3.50 mm
2.25 mm	3.50 mm
2.50 mm	3.50 mm
2.75 mm	4.00 mm
3.00 mm	4.00 mm
3.50 mm	5.00 mm
4.00 mm	5.00 mm
4.50 mm	6.00 mm
5.00 mm	6.00 mm

All efforts should be taken to ensure 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 stents should not be expanded to a diameter beyond the maximum diameter listed on the label. Do not dilate the 2.0 mm, 2.25 mm, and 2.5 mm stents to greater than 3.5 mm, 2.75 mm and 3.0 mm stents to greater than 4.0 mm, 3.5 mm and 4.0 mm stents to greater than 5.0 mm, and 4.5 mm and 5.0 mm stents to greater than 6.0 mm.**

14.10 Instructions for simultaneous use of 2 devices in guide catheter (kissing balloon technique)

6 Fr (2 mm) compatibility: Any combination of one 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 stent using the instructions provided (refer to **Section 14.5**).
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 before removing the other catheter and its associated guidewire.

14.11 Instructions for stenting of bifurcation lesions

The provisional technique of bifurcation stenting recommends a single stent placement in the Main Vessel (MV), finalized with proximal optimization technique (POT). POT includes performing post-dilatation to achieve full apposition of the stent proximal to the bifurcation and reduce the risk of side branch (SB) compromise.

If inadequate results are found in the SB such as: threatened SB closure, TIMI flow <3, dissection type B or worse, or residual stenosis >80%, the provisional bifurcation stenting technique recommends placing a second stent in the SB as a bailout. As per cardiology societal recommendations, two-stent techniques following single stent provisional bifurcation stenting including T, TAP, and Culotte stenting may be utilized as needed. However, the RESOLUTE ONYX PAS Bifurcation Cohort did not evaluate the safety and effectiveness of two-stent bifurcation techniques, including planned (upfront) two-stent bifurcation techniques (such as DK-crush). Additionally, two-stent bifurcation techniques may introduce additional forces and/or failure modes to the stents, and the performance of the Resolute Onyx stent has not been evaluated under these conditions in nonclinical testing.

15 Reuse precaution statement

For single use only.

Do not resterilize or reuse.

Disclaimer of warranty

The warnings contained in the product labeling provide more detailed information and are considered an integral part of this disclaimer of warranty. Although the product has been manufactured under carefully controlled conditions, Medtronic has no control over the conditions under which this product is used. Medtronic, therefore, disclaims all warranties, both express and implied, with respect to the product, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Medtronic shall not be liable to any person or entity for any medical expenses or any direct, incidental, or consequential damages caused by any use, defect, failure, or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort, or otherwise. No person has any authority to bind Medtronic to any representation or warranty with respect to the product.

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