SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Eluting Coronary Stent System

Device Trade Name: Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System

Device Procode: NIQ

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160043/S034

Date of FDA Notice of Approval: September 22, 2020

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System (Resolute Onyx) PMA (P160043) was previously approved on April 28, 2017 and is indicated for improving coronary luminal diameters in patients, including those with diabetes mellitus, with symptomatic ischemic heart disease due to de novo lesions of length ≤ 35 mm in native coronary arteries with reference vessel diameters of 2.0 mm to 5.0 mm. In addition, the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is indicated for treating de novo chronic total occlusions. The SSEDs to support these indications are available on the following CDRH websites and are incorporated into the current SSED by reference here.

- P160043:
  https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160043

- P160043/S001:
  https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160043S001
- P160043/S012:
  https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160043S012

The current supplement was submitted to expand the indication for the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System to include patients at high bleeding risk.

II. INDICATIONS FOR USE

The Resolute Onyx™ 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 Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System is indicated for treating *de novo* chronic total occlusions.

III. CONTRAINDICATIONS

The Resolute Onyx™ Zotarolimus-Eluting Coronary Stent 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

Coronary artery stenting is contraindicated for use in:

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Resolute Onyx labeling.

V. DEVICE DESCRIPTION

The Resolute Onyx is a device/drug combination product comprised of the following device components:

- A Resolute Onyx coronary stent and delivery system. The delivery system is available in a rapid exchange (RX) and an over-the-wire (OTW) configuration.
- A drug/polymer coating component, which consists of a formulation of zotarolimus contained in a BioLinx® polymer.

The characteristics of Resolute Onyx are described in **Table 1**.

Table 1: Device Component Description and Nominal Dimensions

		Stent Design 1 (Small Vessel)	Stent Design 2 (Medium Vessel)	Stent Design 3 (Large Vessel)	Stent Design 4 (Extra Large)
Available Stent Diameters (mm)		2.0, 2.25, 2.5	2.75, 3.0	3.5, 4.0	(RX Only) – 4.5, 5.0
Available Stent Lengths (mm)		8, 12, 15, 18, 22, 26, 30, 34*, 38* * 34, 38 mm lengths not available in 2.0	8, 12, 15, 18, 22, 26, 30, 34, 38	8, 12, 15, 18, 22, 26, 30, 34, 38	(RX Only) – 12, 15, 18, 22, 26, 30
Stent Material and Geometry		A continuous sinusoid pattern stent manufactured from a composite metal material, consisting of a cobalt-based alloy shell conforming to ASTM F562 and a platinum-iridium alloy core conforming to ASTM B684.			
Drug Component		A coating of polymers loaded with zotarolimus in a formulation applied to the entire surface of the stent at a dose of approximately 1.6 μg/mm^2 which results in a maximum nominal drug content of 317 μg on the stent with the largest surface area (4.0 x 38 mm).			
Delivery System Working Length		140 cm			
Delivery System Luer Adapter Ports	RX	Single access port to the inflation lumen. A guidewire exit port is located approximately 25 cm from the tip. Designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
	OTW	Y-Connector with side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen designed for guidewire less than or equal to 0.014 inch (0.36 mm).			
Stent Delivery Balloon		Single-layer Pebax balloon, wrapped over an inner member tubing with 2 radiopaque marker bands to locate the stent edges.			
Balloon Inflation Pressure		Nominal Inflation Pressure: 12 ATM (1216 kPa) Rated Burst Pressure: 2.0-4.0mm = 18 ATM (1824 kPa), RX only: 4.5-5.0mm = 16 ATM (1621kPa)			
Minimum Guide Catheter Inner Diameter		≥5 F (1.42 mm, 0.056 in)			
Catheter Shaft Outer Diameter	RX	Proximal Shaft OD, 2.0-5.0mm: 2.1 F (0.69 mm) Distal Shaft OD, 2.0-4.0mm: 2.7 F (0.91 mm) Distal Shaft OD, 4.5 and 5.0mm: 3.2 F (1.07 mm)			
	OTW	Proximal Shaft OD: 3.4 F (1.12 mm) Distal Shaft OD: 2.7 F (0.91 mm)			

The shelf life for the Resolute Onyx is 24 months.

A. Device Component Description

The Resolute Onyx stent system consists of a balloon-expandable, intracoronary, drug-eluting stent (DES) premounted on a stent delivery system (RX or OTW). The Resolute Onyx stent is manufactured from a composite material of cobalt alloy and platinum-iridium alloy and is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. The Resolute Onyx stent is coated with a Parylene C primer, a Biolinx™ polymer, and the active pharmaceutical ingredient (API), zotarolimus, with a nominal drug dose density of approximately 1.6 $\mu g/mm^2$.

Resolute Onyx is available in multiple lengths and diameters. The delivery systems have two radiopaque markers to aid in the placement of the stent during fluoroscopy and is compatible with 0.014-inch (0.36-mm) guidewires and 1.42-mm (5-Fr/0.056-in) minimum inner diameter guide catheters. The stent is crimped on various sizes of delivery catheter balloons, which range from 2.0 mm to 5.0 mm. See **Table 1**, above, for full list of diameter ranges available on each delivery system (RX and OTW).

B. Drug Component Description

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

1. Active Ingredient: Zotarolimus

   The active pharmaceutical ingredient in the Resolute Onyx 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-tetrazoyl-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy- 6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

   The chemical structure of zotarolimus is shown in **Figure 1**.

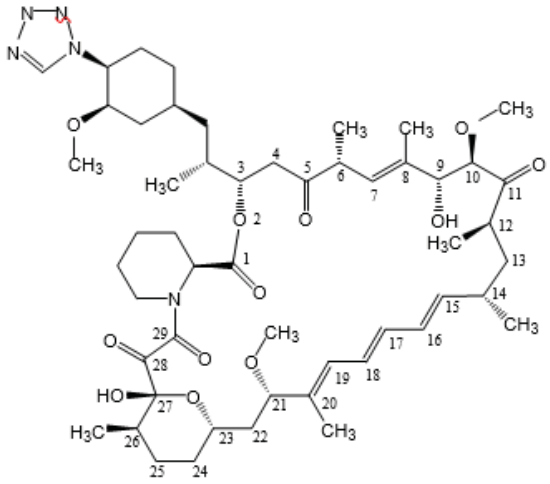

Figure 1: Chemical Structure of Zotarolimus

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

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

2. Inactive Ingredient

BioLinx® Polymer

The Resolute Onyx stent is covered with 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 of C10 polymer, C19 polymer, and polyvinyl pyrrolidone (PVP).

The structural formula of the BioLinx® polymer subunits are shown in **Figure 2**.

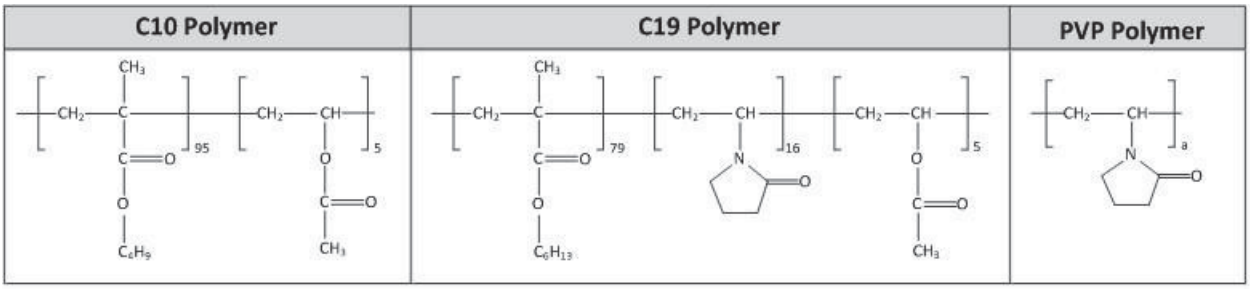

Figure 2: Chemical Structure of BioLinx® Polymer Sub-units

Table 2: Resolute Onyx Product Matrix and Nominal Zotarolimus Content

Product Number Resolute Onyx RX	Product Number Resolute Onyx OTW	Nominal Expanded Stent ID RX (mm)	Nominal Unexpanded Stent Length RX & OTW	Nominal Zotarolimus Content RX (µg)	Nominal Zotarolimus Content OTW (µg)
RONYX20008UX	RONYX20008W	2.0	8	51	51
RONYX22508UX	RONYX22508W	2.25		51	51
RONYX25008UX	RONYX25008W	2.5		51	51
RONYX27508UX	RONYX27508W	2.75		67	67
RONYX30008UX	RONYX30008W	3.0		67	67
RONYX35008UX	RONYX35008W	3.5		77	77
RONYX40008UX	RONYX40008W	4.0		77	77
RONYX20012UX	RONYX20012W	2.0	12	70	70
RONYX22512UX	RONYX22512W	2.25		70	70
RONYX25012UX	RONYX25012W	2.5		70	70
RONYX27512UX	RONYX27512W	2.75		94	94
RONYX30012UX	RONYX30012W	3.0		94	94
RONYX35012UX	RONYX35012W	3.5		108	108
RONYX40012UX	RONYX40012W	4.0		108	108
RONYX45012UX	Not Available	4.5		132	Not Available
RONYX50012UX	Not Available	5.0		132	Not Available
RONYX20015UX	RONYX20015W	2.0	15	85	85
RONYX22515UX	RONYX22515W	2.25		85	85
RONYX25015UX	RONYX25015W	2.5		85	85
RONYX27515UX	RONYX27515W	2.75		117	117
RONYX30015UX	RONYX30015W	3.0		117	117
RONYX35015UX	RONYX35015W	3.5		132	132
RONYX40015UX	RONYX40015W	4.0		132	132
RONYX45015UX	Not Available	4.5		158	Not Available
RONYX50015UX	Not Available	5.0		158	Not Available
RONYX20018UX	RONYX20018W	2.0	18	104	104
RONYX22518UX	RONYX22518W	2.25		104	104
RONYX25018UX	RONYX25018W	2.5		104	104
RONYX27518UX	RONYX27518W	2.75		140	140
RONYX30018UX	RONYX30018W	3.0		140	140
RONYX35018UX	RONYX35018W	3.5		156	156
RONYX40018UX	RONYX40018W	4.0		156	156
RONYX45018UX	Not Available	4.5		188	Not Available
RONYX50018UX	Not Available	5.0		188	Not Available
RONYX20022UX	RONYX20022W	2.0	22	127	127
RONYX22522UX	RONYX22522W	2.25		127	127
RONYX25022UX	RONYX25022W	2.5		127	127
RONYX27522UX	RONYX27522W	2.75		171	171
RONYX30022UX	RONYX30022W	3.0		171	171
RONYX35022UX	RONYX35022W	3.5		186	186
RONYX40022UX	RONYX40022W	4.0		186	186
RONYX45022UX	Not Available	4.5		227	Not Available
RONYX50022UX	Not Available	5.0		227	Not Available

Table 2: Resolute Onyx Product Matrix and Nominal Zotarolimus Content

Product Number Resolute Onyx RX	Product Number Resolute Onyx OTW	Nominal Expanded Stent ID RX (mm)	Nominal Unexpanded Stent Length RX & OTW	Nominal Zotarolimus Content RX (µg)	Nominal Zotarolimus Content OTW (µg)
RONYX20026UX	RONYX20026W	2.0	26	146	146
RONYX22526UX	RONYX22526W	2.25		146	146
RONYX25026UX	RONYX25026W	2.5		146	146
RONYX27526UX	RONYX27526W	2.75		198	198
RONYX30026UX	RONYX30026W	3.0		198	198
RONYX35026UX	RONYX35026W	3.5		221	221
RONYX40026UX	RONYX40026W	4.0		221	221
RONYX45026UX	Not Available	4.5		265	Not Available
RONYX50026UX	Not Available	5.0		265	Not Available
RONYX20030UX	RONYX20030W	2.0	30	168	168
RONYX22530UX	RONYX22530W	2.25		168	168
RONYX25030UX	RONYX25030W	2.5		168	168
RONYX27530UX	RONYX27530W	2.75		225	225
RONYX30030UX	RONYX30030W	3.0		225	225
RONYX35030UX	RONYX35030W	3.5		252	252
RONYX40030UX	RONYX40030W	4.0		252	252
RONYX45030UX	Not Available	4.5		304	Not Available
RONYX50030UX	Not Available	5.0		304	Not Available
RONYX22534UX	RONYX22534W	2.25	34	187	187
RONYX25034UX	RONYX25034W	2.5		187	187
RONYX27534UX	RONYX27534W	2.75		257	257
RONYX30034UX	RONYX30034W	3.0		257	257
RONYX35034UX	RONYX35034W	3.5		282	282
RONYX40034UX	RONYX40034W	4.0		282	282
RONYX22538UX	RONYX22538W	2.25	38	206	206
RONYX25038UX	RONYX25038W	2.5		206	206
RONYX27538UX	RONYX27538W	2.75		284	284
RONYX30038UX	RONYX30038W	3.0		284	284
RONYX35038UX	RONYX35038W	3.5		317	317
RONYX40038UX	RONYX40038W	4.0		317	317

3. Mechanism of Action of Zotarolimus

In vitro, zotarolimus inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells and also demonstrated binding affinity with FKBP-12 (binding protein). The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR activity results in the inhibition of protein phosphorylation events associated with translation of mRNA and cell cycle control. **Table 2,** above, lists the nominal drug content present on each product included in the Resolute Onyx stent system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease. These may include exercise, diet, smoking cessation counseling, drug therapy, percutaneous coronary interventions (PCI) (such as angioplasty and placement of bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass surgery (CABG). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

US Marketing History

The Original PMA (P160043) for the Resolute Onyx™ Zotaralimus-Eluting Coronary Stent System received approval on April 28, 2017.

The Resolute Onyx is commercially available in the following countries:

Table 3: Resolute Onyx Commercial Availability

Albania	Germany	Namibia	Philippines
Algeria	Ghana	Nepal	Poland
Argentina	Greece	Netherlands	Portugal
Armenia	Guatemala	Barbados	Puerto Rico
Australia	Honduras	Brazil	Qatar
Austria	Hong Kong	Canada	Reunion
Azerbaijan	Hungary	Cayman Islands	Romania
Bahrain	Iceland	Chile	Russian Federation
Bangladesh	India	Curacao	Saudi Arabia
Belgium	Iran	French Guiana	Serbia
Bolivia	Iraq	Guadeloupe	Singapore
Bosnia and Herzegovina	Ireland	Guam	Slovakia
Botswana	Israel	Indonesia	Slovenia
Brunei Darussalam	Italy	Jamaica	South Africa
Bulgaria	Japan	Kosovo	Spain
Canary Islands	Jordan	Mauritius	Sri Lanka
Colombia	Kazakhstan	Mozambique	Sweden
Costa Rica	Kenya	New Caledonia	Switzerland
Croatia	Korea, Republic Of	Peru	Taiwan
Cyprus	Kuwait	Sudan	Tajikistan
Czech Republic	Kyrgyzstan	Syrian Arab Republic	Tanzania
Denmark	Latvia	Uganda	Thailand
Dominican Republic	Lebanon	Uzbekistan	Trinidad And Tobago
Ecuador	Liechtenstein	Virgin Islands, British	Tunisia
Egypt	Lithuania	Zambia	Turkey
El Salvador	Luxembourg	New Zealand	United Arab Emirates
Estonia	Malaysia	Nicaragua	United Kingdom
Ethiopia	Malta	North Macedonia	United States
Fiji	Martinique	Norway	Venezuela
Finland	Mexico	Oman	Vietnam

France	Moldova	Pakistan	Yemen
Gabon	Montenegro	Panama	
Georgia	Morocco	Paraguay	

The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events (e.g., complications) in alphabetical order that may be associated with coronary stent use in native coronary arteries include, but are not limited to:

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

- Stent misplacement
- Stroke/transient ischemic attack
- Thrombosis (acute, subacute, or late)

Adverse events that have been associated with the intravenous injection of zotarolimus in humans include but are not limited to:

- Anemia
- Diarrhea
- Dry skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

Potential adverse events related to the BioLinx® polymer include but are not limited to:

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

IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported non-clinical laboratory studies can be found in the SSED for each of the original PMAs (P110013 and P160043). Because these previously collected data sufficiently represent the performance of the device for the new indications for use, no new non-clinical testing was conducted.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The Onyx ONE Clear Primary Analysis was conducted to evaluate the performance of the Resolute Onyx stent in selected high bleeding risk (HBR) patients treated with one-month dual antiplatelet therapy (DAPT). Eligible subjects from the Onyx ONE US & Japan trial and the Onyx ONE Global randomized controlled trial (RCT) were pooled to create the Onyx ONE Clear Primary Analysis population.

A summary of the Onyx ONE Clear Primary Analysis is presented below.

A. Study Design

The objective of the Onyx ONE Clear Primary Analysis is to evaluate the safety and effectiveness of the Resolute Onyx stent with use of one-month DAPT following PCI in selected subjects deemed to be at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment.

The Onyx ONE US & Japan Trial oversight was provided throughout the trial by independent committees including a Clinical Events Committee (CEC) and a Data and Safety Monitoring Board (DSMB). Onyx ONE Global RCT oversight was provided throughout the trial by independent committees including a CEC and DSMB.

The Onyx ONE Clear Primary Analysis subject population was derived from the Onyx As-Treated (AT) Population. This study population was formed by pooling eligible subjects enrolled into the Onyx ONE US & Japan Trial (a prospective, multi-center, post-market single-arm trial which enrolled 752 subjects in the United States and Japan) with data from eligible subjects treated with Resolute Onyx only (N=1018[1]) in the Onyx ONE Global RCT (a prospective, multi-center, randomized, single-blind trial which enrolled a total of 1996 subjects globally). From this Onyx AT population, subjects who were 'one-month clear' (as defined below) formed the Onyx ONE Clear Primary Analysis Population (Onyx ONE Clear: N=1506) used to determine the safety and effectiveness of Resolute Onyx stent in high bleeding risk subjects treated with one-month DAPT. See **Figure 3** below.

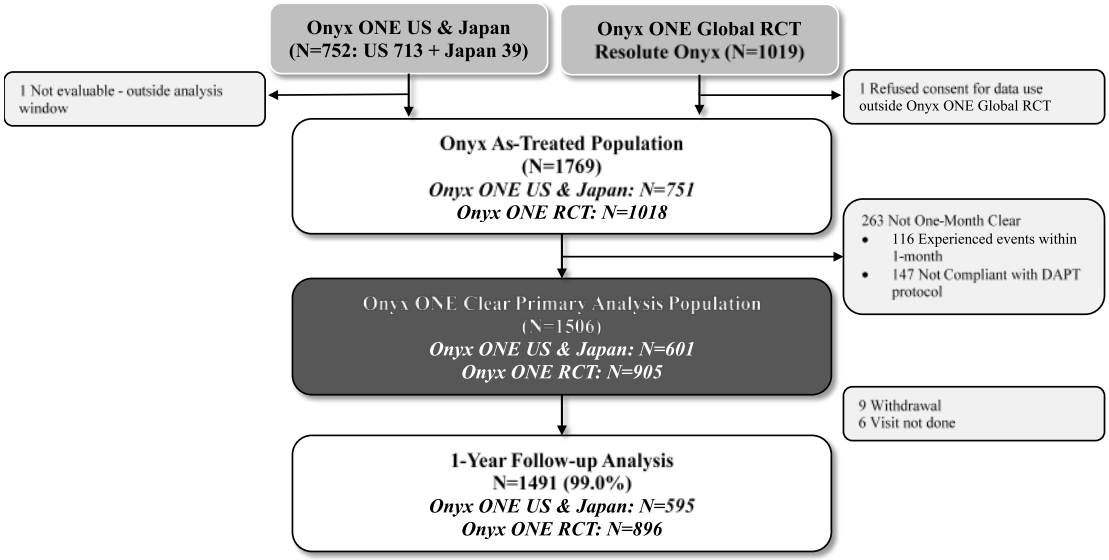

Figure 3: Primary Analysis Population

The one-month clear population excluded the following patient categories:

- Patients who interrupted or discontinued DAPT (greater than 3 cumulative days) within the first one month of procedure,
- Patients who experienced adverse ischemic/thrombotic events that would prohibit them from discontinuing DAPT beyond one month,
- Patients who, due to their own or their physicians' decision, did not plan to transition from DAPT to single antiplatelet therapy (SAPT) one month after procedure. Approximately 20% [(751-601)/751] of subjects from the Onyx

[1] One subject who received the Onyx stent was not consented for data used outside of Onyx ONE Global RCT.

ONE US & Japan group were not eligible for inclusion in the Primary Analysis Population, while 11% [(1018-905)/1018] of subjects from the Onyx ONE RCT group were excluded from the Primary Analysis Population, and

- Patients who were lost to follow-up.

Note: Peri-procedural MIs did not exclude subjects from being considered one-month clear.

Assessment of the use of the Resolute Onyx stent 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, ZEUS, and SENIOR). 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.

1. Clinical Inclusion and Exclusion Criteria

   All subjects who are acceptable candidates for treatment with a DES in accordance with applicable guidelines for percutaneous coronary interventions, per manufacturer's Instructions for Use, who additionally met pre-defined criteria for being high-bleeding risk and/or were candidates for one-month DAPT and in the opinion of the investigator, the potential benefit of one-month DAPT to the subject outweighed the potential risk, were considered. Subjects were at least 18 years of age.

   To qualify as high-bleeding risk and/or a candidate for one-month DAPT, subject must have met at least one of the following criteria:

   - Adjunctive chronic oral anticoagulation treatment planned to continue after PCI
   - Age ≥ 75 years old
   - Baseline Hgb <11 g/dl (or anemia requiring transfusion during the 4 weeks prior to procedure)
   - Any prior documented intracerebral bleed
   - Any documented stroke in the last 12 months
   - Hospital admission for major bleeding during the prior 12 months
   - Active non-skin cancer currently undergoing treatment or surveillance (in lieu of treatment)
   - Planned daily NSAID (other than aspirin) or steroids for ≥30 days after

PCI

- Planned surgery that would require interruption of DAPT (within the next 12 months)
- Renal failure defined as creatinine clearance <40 ml/min
- Thrombocytopenia (PLT <100,000/mm^3)
- Severe chronic liver disease defined as subjects who have developed any of the following: variceal hemorrhage, ascites, hepatic encephalopathy or jaundice
- Expected non-compliance for at least 6 months DAPT for other medical reasons

Patients were not permitted to be enrolled in the study if they met any of the following Exclusion Criteria:

- Pregnant and breastfeeding women
- Subjects requiring a planned PCI procedure after one month of index procedure
- Procedure planned to require non-study stents, stand-alone POBA, or stand-alone atherectomy
- Active bleeding at the time of inclusion
- Cardiogenic shock
- Subject with planned surgery or procedure necessitating discontinuation of DAPT within one month following index procedure
- Subject not expected to comply with long-term single antiplatelet therapy
- A known hypersensitivity or contraindication to aspirin, heparin and bivalirudin, P2Y12 inhibitors, mTOR inhibiting drugs such as zotarolimus, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g., BioLinx®), stainless steel (or other metal ions found in 316L stainless steel), zinc, or a sensitivity to contrast media, which cannot be adequately pre-medicated.
- PCI during the previous 6 months for a lesion other than the target lesion of the index procedure
- Participation in another clinical study within 12 months after index procedure
- Subjects with life expectancy of less than 2 years

2. Follow-up Schedule

   Subjects underwent initial screening and completed the informed consent process prior to any study-related assessments if applicable, i.e., study procedure(s) is not institution's standard of care. Clinic visit health status

assessments were documented at the one-month time point. Subject contact health status assessments were documented at 2 months, 6 months, 1 year, and will be documented at 2 years.

3. Clinical Endpoints

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

Secondary Endpoints
The following secondary endpoints, except acute success which was measured post-procedure, were assessed at 6 months and 1 year in the Onyx ONE Clear population and will be assessed at 2 years:

- Acute success (device, lesion, procedure)
- All deaths, including cardiac death
- Major adverse cardiac event (MACE)
  - Defined as death, myocardial infarction, or clinically driven repeat target lesion revascularization
- Composite of cardiac death and myocardial infarction
- Target vessel failure (TVF)
  - Defined as cardiac death, target vessel myocardial infarction or clinically driven target vessel revascularization
- Target lesion failure (TLF)
  - Defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave), or clinically driven target lesion revascularization (TLR)
- All revascularizations (TLR, TVR and non-TVR)
- Stent thrombosis (def/prob)
- Stroke
- Bleeding per BARC criteria
  - BARC 3 to 5
  - BARC 2 to 5
  - All BARC

B. Accountability of PMA Cohort

Between October 1, 2018 and April 9, 2019, 751[2] subjects were treated in the Onyx ONE US & Japan Trial at 42 US sites and 5 Japan sites. 1018[3] subjects who received the Resolute Onyx stent only in the Onyx ONE Global RCT are also included in the

[2] The last subject enrolled in Japan was consented prior to enrollment closure on April 9, 2019 but did not complete their index procedure until April 17, 2019. This subject was not within their 1-year window at the time of the database lock for the primary endpoint. Therefore, this subject is not included in the primary endpoint analysis but will be included in the 2-year report.
[3] One subject who received the Onyx stent was not consented for data used outside of Onyx ONE Global RCT.

analysis. In total, 1769 subjects constitute the Onyx AT population. 1506 subjects met the one-month clear criteria and formed the primary analysis population (Onyx ONE Clear). 99.0% (1491/1506) of the subjects were evaluable at 1 year, excluding 9 subjects who withdrew and 6 subjects who did not complete the 1-year visit. **Figure 3** above provides an overview of the subject accountability for the primary analysis population through the 1-year follow-up visit.

C. Primary Analysis Population Demographics and Baseline Parameters

Table 4 presents demographics for the primary analysis population. The mean age of the study subjects was 74.0 years, and 32.3% were female. Of the approximately 40% of subjects with available data on race, 65.9% were Caucasian. Subjects were mildly overweight (BMI 28.2).

Table 4. Demographics

Demographics	Onyx ONE Clear (N=1506 Subjects)
Age (years)	74.0±9.5 (1506) (34.0, 95.0)
Gender	
Male	67.7% (1019/1506)
Female	32.3% (487/1506)
Race*	
American Indian/Alaska Native	0% (0/1506)
Asian	2.9% (44/1506)
Black or African American	3.1% (47/1506)
Caucasian	32.9% (495/1506)
Native Hawaiian or other Pacific Islander	0.1% (2/1506)
Other	0.8% (12/1506)
Not Disclosed	60.1% (906/1506)
BMI	28.2±5.7 (1482) (13.6, 70.8)

*Race data were collected only for subjects enrolled in the ONYX ONE US and Japan Trial.

Table 5 shows the baseline clinical characteristics and medical history for the primary analysis population. Thirty-nine percent of subjects had diabetes, 26.3% had prior MI, 22.8% had unstable angina, and 35.6% had a history of atrial fibrillation. Indications for the index procedure were due to one or more of the following: stable angina 40.5% (584/1441), unstable angina 22.8% (328/1441), MI 25.9% (373/1441) (STEMI 4.2% (60/1441) and NSTEMI 21.7% (313/1441)) and/or a positive functional test 4.3% (65/1506).

Table 5. Baseline Clinical Characteristics

Medical History	Onyx ONE Clear (N=1506 Subjects)
Smoking Status	
Current Smoker	9.4% (141/1498)
Former Smoker	41.5% (622/1498)
Never	49.1% (735/1498)
Unknown	0.53% (8/1506)
Current Diabetes Mellitus	39.4% (593/1506)
Type I	0.7% (10/1506)
Type II	38.7% (583/1506)
Insulin Dependent	13.7% (206/1506)
History of Hyperlipidemia	72.4% (1091/1506)
History of Hypertension	84.0% (1265/1506)
Cardiac History	
History of MI	26.3% (396/1506)
Current MI Indication	25.9% (373/1441)
STEMI	4.2% (60/1441)
NSTEMI	21.7% (313/1441)
Current Anginal Status:	
Stable Angina	40.5% (584/1441)
Unstable Angina	22.8% (328/1441)
CCS Class	
1	20.0% (230/1149)
2	31.7% (364/1149)
3	35.2% (405/1149)
4	13.1% (150/1149)
Silent Ischemia	10.8% (156/1441)
History of PCI	30.2% (455/1506)
History of CABG	12.9% (194/1506)
LVEF (%)	52.6+/-12.4 (1123) (12.0, 80.0)
History of Atrial Fibrillation	35.6% (536/1506)
Neurologic History	
History of Cerebrovascular Accidents (Stroke) or TIA	14.1% (212/1506)
Renal History	
Serum Creatinine (µmol/L)	123.5 ± 149.0 (1475) (35.4, 2920.4)
Peripheral History	
History of PVD	10.6% (160/1506)

Key Baseline Lesion Characteristics: The total number of target lesions was 1960. The mean reference vessel diameter was 2.82±0.48 mm, mean lesion length was 20.78±13.02 mm, and mean percent diameter stenosis was 68.31±13.28%. The LAD was treated in 52.5% of the subjects, the LCX was treated in 27.8%, and the RCA

was treated in 34.2%. Moderate or severe calcification was present in 50.0% of subjects. The modified ACC/AHA Lesion Class for B2/C was 78.6%. Additional baseline lesion characteristics can be found in Table 6.

Table 6. Baseline Lesion Characteristics

Vessel and Lesion Characteristics	Onyx ONE Clear (N=1506 Subjects N=1960 Lesions)
Pre-Procedure	
Target Lesion Location	
LAD	52.5% (790/1506)
LCX	27.8% (419/1506)
RCA	34.2% (515/1506)
LM	1.3% (19/1506)
GRAFT	4.1% (62/1506)
Lesion Length (mm)	20.78±13.02 (1889) (2.5, 96.0)
<10 mm	15.8% (299/1889)
10 – 19.9 mm	43.2% (816/1889)
>=20 mm	41.0% (774/1889)
RVD (mm)	2.82±0.48 (1949) (1.74, 5.06)
% Diameter Stenosis	68.31±13.28 (1949) (10.64, 100.0)
Thrombolysis in Myocardial Infarction (TIMI) flow	
0	5.0% (97/1932)
1	0.9% (18/1932)
2	12.2% (235/1932)
3	81.9% (1582/1932)
Lesion Type	
A	4.4% (86/1960)
B1	17.0% (334/1960)
B2	19.0% (372/1960)
C	59.6% (1168/1960)
B2/C	78.6% (1540/1960)
Calcification	
Mild	50.0% (970/1939)
Moderate	19.3% (374/1939)
Severe	30.7% (595/1939)
Vessel Tortuosity	
None/Mild	95.2% (1853/1947)
Moderate	3.1% (60/1947)
Severe	1.7% (34/1947)
Post-Procedure	
Percent diameter stenosis (%)	19.83±9.52 (1948) (-27.66, 100.0)

Key Procedural Characteristics: The total number of target lesions treated per subject was approximately 1.3/patient and the number of Resolute Onyx stents deployed was 1.7/subject (1.2/lesion). The total Resolute Onyx stent length/subject was approximately 36.9 mm. Additional baseline lesion characteristics can be found in Table 7.

Table 7. Procedural Characteristics

Procedure Data	Onyx ONE Clear (N=1506 Subjects N=1960 Lesions)
Procedure Time (min)	41.9±29.8 (1552) (4.0, 213.0)
Subjects with Staged Procedure Planned Within 30 Days	4.4% (66/1506)
Subjects with Staged Procedure Performed	3.3% (49/1506)
Number of Lesions Treated/Subject	1.3±0.6 (1506) (1, 5)
1	74.8% (1126/1506)
2	20.7% (311/1506)
3 or more	4.6% (69/1506)
Number of Vessels Treated/Subject	1.1±0.3 (1487) (1.0, 2.0)
1	81.4% (1226/1506)
2	17.2% (259/1506)
3 or more	1.4% (21/1506)
Number of Resolute Onyx Stents Placed/Subject	1.7±1.0 (1506) (1, 8)
Number of Resolute Onyx Stents Placed/Lesion	1.2±0.5 (2162) (1, 5)
Total Resolute Onyx Stent Length (mm)/Subject	36.9±26.3 (1506) (8, 220)

Numbers are presented as % (count/sample size) or mean ± standard deviation (n) (minimum, maximum).

Site reported lesion characteristics.

HBR Characteristics of Patients Enrolled in Onyx ONE Clear: Table 8 and Table 9 below provide an overview of the study HBR criteria met by the enrolled subjects. The mean number of HBR criteria met per subject was 1.6 ± 0.8. The most common HBR qualifying features were age ≥75 years, present in 59.0% (889/1506) and oral anticoagulation use, present in 41.0% (617/1506). In addition, age ≥ 75 years and oral anticoagulation use were the only HBR criteria met for 26.0% (392/1506) and 15.6% (235/1506), respectively.

Table 8: Subjects Meeting One or More of the HBR Inclusion Criteria

HBR Inclusion Criteria	Onyx ONE Clear (N=1506 Subjects)
Patients satisfying one or more of the following criteria:	
Age ≥ 75 years	59.0% (889/1506)
Oral anticoagulation to continue after PCI	41.0% (617/1506)
Hgb <11 g/dl (or transfusion within 4 weeks before procedure)	14.4% (217/1506)
Creatinine clearance <40 ml/min	12.5% (188/1506)
Non skin cancer diagnosed or treated within 3 years	7.4% (112/1506)
Planned surgery in next 12 months requiring interruption of DAPT	6.6% (100/1506)
At least 6 months non-compliance DAPT	4.2% (64/1506)
NSAID (other than aspirin) or steroids for ≥ 30 days after PCI	3.1% (47/1506)
Hospital admission for major bleeding in prior 12 months	2.8% (42/1506)
Stroke in previous 12 months	2.6% (39/1506)
Prior intracerebral bleed	1.7% (26/1506)
Thrombocytopenia (PLT <100,000/mm^3)	1.7% (26/1506)
Severe chronic liver disease	0.9% (14/1506)

Table 9: Subjects Meeting Only One of the HBR Inclusion Criteria

HBR Inclusion Criteria	Onyx ONE Clear (N=1506 Subjects)
Patients satisfying only one of the following criteria:	
Oral anticoagulation to continue after PCI	15.6% (235/1506)
Age ⩾ 75 years	26.0% (392/1506)
Hgb <11 g/dl (or transfusion within 4 weeks before procedure)	2.0% (30/1506)
Prior intracerebral bleed	0.5% (7/1506)
Stroke in previous 12 months	0.8% (12/1506)
Hospital admission for major bleeding in prior 12 months	0.9% (13/1506)
Non skin cancer diagnosed or treated within 3 years	1.6% (24/1506)
NSAID (other than aspirin) or steroids for ⩾ 30 days after PCI	0.9% (13/1506)
Planned surgery in next 12 months requiring interruption of DAPT	2.2% (33/1506)
Creatinine clearance <40 ml/min	2.3% (34/1506)
Thrombocytopenia (PLT <100,000/mm3)	0.2% (3/1506)
Severe chronic liver disease	0.1% (1/1506)
At least 6 months non-compliance DAPT	2.3% (34/1506)

Antiplatelet and Oral Anticoagulation Medication Usage: The antiplatelet and oral anticoagulation medication usage at procedure, discharge, 30 days, 2 months, 6 months, and 365 days is shown in Table 10 below. Of the subjects included in the Onyx ONE Clear population, 90.0% (1356/1506) were on DAPT at the time of their 30-day visit while 10.0% (150/1506) were maintained on SAPT and an oral anti-coagulant (OAC). At 2 months, 96.9% (1457/1503) of the subjects were on SAPT, of which 37.1% (557/1503) had SAPT with OAC. The rate of SAPT usage at 365 days post index procedure was 89.3% (1255/1406). Only 6.5% (92/1406) of subjects were on DAPT of which 5.7% (80/1406) were on DAPT (excluding triple therapy).

Table 10: Medication to 365 Days

Antiplatelet/Anticoagulant	**Resolute Onyx (N=1506 Subjects)**
Average Duration (days)	
Aspirin	
n[1]	1453
Mean ± SD	218.4 ± 150.6
P2Y12 Inhibitor	
n[1]	1504
Mean ± SD	164.1 ± 149.2
Anticoagulant	
n[1]	638
Mean ± SD	300.8 ± 105.0
At Index Procedure	
Aspirin loading dose administered	66.8% (1006/1506)
P2Y12 loading dose administered	88.4% (1331/1506)
Anticoagulant administered	99.9% (1493/1495)
GP IIb/IIIa receptor blocker	3.3% (50/1506)
DAPT (including triple therapy)	94.3% (1420/1506)
DAPT (excluding triple therapy)	67.7% (1019/1506)
Triple therapy	26.6% (401/1506)
SAPT (with or without OAC)	5.5% (83/1506)
SAPT (aspirin or P2Y12, not both, no OAC)	2.3% (35/1506)
SAPT + OAC (aspirin or P2Y12, not both, with OAC)	3.2% (48/1506)
OAC	29.9% (451/1506)
OAC only, no aspirin, no P2Y12	0.1% (2/1506)
OAC + aspirin, no P2Y12	0.2% (3/1506)
OAC+P2Y12 inhibitor, no aspirin	3.0% (45/1506)
At Discharge (Index Procedure)	

Table 10: Medication to 365 Days

Antiplatelet/Anticoagulant	Resolute Onyx (N=1506 Subjects)
DAPT (including triple therapy)	92.6% (1394/1506)
DAPT (excluding triple therapy)	63.8% (961/1506)
Triple therapy	28.8% (433/1506)
SAPT	7.2% (108/1506)
SAPT (aspirin or P2Y12, not both, no OAC)	0.5% (8/1506)
Aspirin only, no OAC, no P2Y12	0.3% (5/1506)
P2Y12 inhibitor only, no OAC, no aspirin	0.2% (3/1506)
SAPT + OAC (aspirin or P2Y12, not both, with OAC)	6.6% (100/1506)
OAC + P2Y12 only, no aspirin	6.0% (90/1506)
OAC+ aspirin only, no P2Y12	0.7% (10/1506)
OAC only, no aspirin and no P2Y12	0.1% (2/1506)
OAC	35.5% (535/1506)
At 30 Days	
DAPT (including triple therapy)	90.0% (1356/1506)
DAPT (excluding triple therapy)	62.8% (946/1506)
Triple therapy	27.2% (410/1506)
SAPT	10.0% (150/1506)
SAPT (aspirin or P2Y12, not both, no OAC)	0.0% (0/1506)
Aspirin only, no OAC, no P2Y12	0.0% (0/1506)
P2Y12 inhibitor only, no OAC, no aspirin	0.0% (0/1506)
SAPT + OAC (aspirin or P2Y12, not both, with OAC)	10.0% (150/1506)
OAC + P2Y12 only, no aspirin	9.4% (142/1506)
OAC+ aspirin only, no P2Y12	0.5% (8/1506)
OAC only, no aspirin and no P2Y12	0.0% (0/1506)
OAC	37.2% (560/1506)
At 2 months	
DAPT (including triple therapy)	2.9% (44/1503)
DAPT (excluding triple therapy)	2.4% (36/1503)
Triple therapy	0.5% (8/1503)
SAPT	96.9% (1457/1503)
SAPT (aspirin or P2Y12, not both, no OAC)	59.9% (900/1503)
Aspirin only, no OAC, no P2Y12	41.0% (616/1503)
P2Y12 inhibitor only, no OAC, no aspirin	18.9% (284/1503)

Table 10: Medication to 365 Days

Antiplatelet/Anticoagulant	Resolute Onyx (N=1506 Subjects)
SAPT + OAC (aspirin or P2Y12, not both, with OAC)	37.1% (557/1503)
OAC + P2Y12 only, no aspirin	22.4% (336/1503)
OAC+ aspirin only, no P2Y12	14.7% (221/1503)
OAC only, no aspirin and no P2Y12	0.1% (2/1503)
OAC	37.7% (567/1503)
At 6 months	
DAPT (including triple therapy)	5.3% (77/1464)
DAPT (excluding triple therapy)	4.7% (69/1464)
Triple therapy	0.5% (8/1464)
SAPT	93.4% (1368/1464)
SAPT (aspirin or P2Y12, not both, no OAC)	57.2% (838/1464)
Aspirin only, no OAC, no P2Y12	39.5% (579/1464)
P2Y12 inhibitor only, no OAC, no aspirin	17.7% (259/1464)
SAPT + OAC (aspirin or P2Y12, not both, with OAC)	36.2% (530/1464)
OAC + P2Y12 only, no aspirin	21.1% (309/1464)
OAC+ aspirin only, no P2Y12	15.1% (221/1464)
OAC only, no aspirin and no P2Y12	0.8% (11/1464)
OAC	37.5% (549/1464)
At 365 days	
DAPT (including triple therapy)	6.5% (92/1406)
DAPT (excluding triple therapy)	5.7% (80/1406)
Triple therapy	0.9% (12/1406)
SAPT	89.3% (1255/1406)
SAPT (aspirin or P2Y12, not both, no OAC)	54.8% (770/1406)
Aspirin only, no OAC, no P2Y12	38.4% (540/1406)
P2Y12 inhibitor only, no OAC, no aspirin	16.4% (230/1406)
SAPT + OAC (aspirin or P2Y12, not both, with OAC)	34.5% (485/1406)
OAC + P2Y12 only, no aspirin	19.8% (279/1406)
OAC+ aspirin only, no P2Y12	14.7% (206/1406)
OAC only, no aspirin and no P2Y12	3.2% (45/1406)
OAC	38.5% (542/1406)
[1]n = Number of subjects with evaluable data	

D. Safety and Effectiveness Results

Primary Endpoint

The primary endpoint, which is the composite of cardiac death/MI from one month to one year for the Onyx ONE Clear population, was 7.0% (104/1491) with the upper limit of 95% confidence interval of 8.4%. This is below the prespecified performance goal of 9.7%. Therefore, study success may be claimed for the primary endpoint.

Primary endpoint analysis results for the Onyx ONE Clear study are presented below in Table 11.

Table 11: Primary Endpoint Analyses

Primary Endpoint at 1 year[1]	**Onyx ONE Clear (N = 1506 Subjects)**	**Two-side 95% Confidence Interval[2]**	**Performance Goal**	**p-value**	**Primary Objective Met? (Yes/No)**
Primary Analysis					
– Onyx ONE Clear	7.0% (104/1491)	[5.7%, 8.4%]	9.7%	<0.001	Yes
Best Case Analysis[3]					
– Onyx ONE Clear	6.9% (104/1506)	[5.7%, 8.3%]	9.7%	<0.001	Yes
Worst Case Analysis[4]					
– 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 1-year primary endpoint status as no.
[4] Worst case analysis imputed all the missing 1-year primary endpoint status as yes.

1. Safety Results

   The analysis of safety was based on 1491 subjects in the Onyx ONE Clear population available for the 1-year evaluation.

   The 1-year rate for TLF is 8.1% (121/1491), TVF 8.8% (131/1491), MACE 11.7% (174/1491), cardiac death 2.6% (39/1491), TVMI (3rd UDMI) 4.4% (65/1491), clinically driven TLR 3.4% (50/1491), clinically driven TVR 4.3% (64/1491), definite or probable ST (ARC) 0.7% (10/1491), and BARC 3-5 bleeding 4.0% (60/1491). Principal safety and effectiveness results are reported in **Table 12**.

Table 12: Principal safety and effectiveness results

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)
MACE[4]	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)
MACE[4]	11.7% (174/1491)
Cardiac death, MI and definite/probable stent thrombosis	7.0% (104/1491)
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)

Table 12: Principal safety and effectiveness results

Safety and effectiveness measures	RESOLUTE ONYX (N=1506 subjects N=1960 lesions) %(m/n)[1]
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.

2. Effectiveness Results

   Per Table 12, lesion success was reported as 94.6% (1817/1920), device success was reported as 93.3% (1790/1919), and procedure success was reported as 88.5% (1295/1463).

3. Subgroup Analyses

   The following characteristics were evaluated for potential association with outcomes:

Sex/Gender

Although not powered to evaluate safety or effectiveness of the Resolute Onyx Stent in gender-specific subgroups, outcomes for male and female subjects from the Onyx ONE Clear population are available (Table 13).

The composite rate of cardiac death/MI in the Onyx ONE Clear analysis population at 1-year was 7.6% (77/1010) in male subjects and 5.6% (27/481) in female subjects, respectively. Further analysis revealed no statistically significant difference (p=0.191) in the cardiac death/MI rate at 1 year between these two groups.

The ARC definite/probable stent thrombosis rate at 1 year was 0.9% in males and 0.2% in females. The BARC 2-5 bleeding rate was 11.2% in males and 12.9% in females.

Table 13. Onyx ONE Clear Clinical Outcomes by Gender

	Onyx ONE Clear (n=1506)	
Safety Measures (to 365 Days)	**Male (N=1019 Subjects) (N=634 Lesions)**	**Female (N=487 Subjects) (N=634 Lesions)**
TLF	9.0% (91/1010)	6.2% (30/481)
TVF	9.7% (98/1010)	6.9% (33/481)
MACE	12.9% (130/1010)	9.1% (44/481)
Cardiac death, MI, or definite/probable stent thrombosis	7.6% (77/1010)	5.6% (27/481)
Cardiac death or MI	7.6% (77/1010)	5.6% (27/481)
Cardiac death or target vessel MI (TVMI)	7.0% (71/1010)	5.4% (26/481)
Death or TVMI	10.4% (105/1010)	8.1% (39/481)
Death	6.5% (66/1010)	4.8% (23/481)
Cardiac death	3.1% (31/1010)	1.7% (8/481)
Non cardiac death	3.5% (35/1010)	3.1% (15/481)
MI (3rd UDMI)	5.1% (52/1010)	4.2% (20/481)
TVMI (3rd UDMI)	4.6% (46/1010)	4.0% (19/481)
Clinically driven TLR	4.0% (40/1010)	2.1% (10/481)
Clinically driven TVR	5.0% (51/1010)	2.7% (13/481)
Stroke	1.2% (12/1010)	2.1% (10/481)
Stent thrombosis (ARC) definite/probable	0.9% (9/1010)	0.2% (1/481)
Early thrombosis (≤30 days)	0.0% (0/1010)	0.0% (0/481)
Late thrombosis (31-365 days)	0.9% (9/1010)	0.2% (1/481)
Bleeding		
All BARC	12.3% (124/1010)	14.8% (71/481)

	Onyx ONE Clear (n=1506)	
Safety Measures (to 365 Days)	**Male (N=1019 Subjects) (N=634 Lesions)**	**Female (N=487 Subjects) (N=634 Lesions)**
BARC 3-5	3.7% (37/1010)	4.8% (23/481)
BARC 2-5	11.2% (113/1010)	12.9% (62/481)

The overall conclusions of the trial regarding the safety of the Resolute Onyx Stent when used with 1 month of DAPT in patients at high risk of bleeding can be generalized to males and females.

Region

The composite rate of cardiac death/MI in the Onyx ONE Clear analysis population at 1-year was 7.5% (42/559) in US subjects, and 6.7% (62/932) in OUS subjects. Outcomes were not notably different by region.

Age

The composite rate of cardiac death/MI in the Onyx ONE Clear analysis population at 1-year was 7.0% in subjects > 75 years old (55/786) and ⩽ 75 years old (49/705). Outcomes were not notably different by age.

Race and Ethnicity

Due to regional restrictions related to the collection of race data, this variable is only known for subjects enrolled through the Onyx ONE US & Japan trial. Table 14 lists outcomes by race for those subjects. The available race and ethnicity information is too limited to comment on any potential associations.

Table 14. Principal Safety and Effectiveness Results from One Month to 365 Days by Race - (US & Japan Population)

Safety and Effectiveness Measures	**American Indian or Alaska Native (N=0 Subjects) (N=0 Lesions) %(m/n)[1,2]**	**Asian (N=44 Subjects) (N=56 Lesions) %(m/n)[1,2]**	**Black or African American (N=47 Subjects) (N=55 Lesions) %(m/n)[1,2]**	**Native Hawaiian or Other Pacific Islander (N=2 Subjects) (N=2 Lesions) %(m/n)[1,2]**	**White (N=495 Subjects) (N=649 Lesions) %(m/n)[1,2]**	**Other (N=12 Subjects) (N=12 Lesions) %(m/n)[1,2]**
Safety Measures (to 365 days)						
Cardiac death or MI	NA	0.0% (0/43)	8.5% (4/47)	0.0% (0/2)	7.8% (38/490)	0.0% (0/12)
Death	NA	0.0% (0/43)	8.5% (4/47)	0.0% (0/2)	4.5% (22/490)	8.3% (1/12)

Table 14. Principal Safety and Effectiveness Results from One Month to 365 Days by Race - (US & Japan Population)

Safety and Effectiveness Measures	American Indian or Alaska Native (N=0 Subjects) (N=0 Lesions) %(m/n)[1,2]	Asian (N=44 Subjects) (N=56 Lesions) %(m/n)[1,2]	Black or African American (N=47 Subjects) (N=55 Lesions) %(m/n)[1,2]	Native Hawaiian or Other Pacific Islander (N=2 Subjects) (N=2 Lesions) %(m/n)[1,2]	White (N=495 Subjects) (N=649 Lesions) %(m/n)[1,2]	Other (N=12 Subjects) (N=12 Lesions) %(m/n)[1,2]
Cardiac Death	NA	0.0% (0/43)	4.3% (2/47)	0.0% (0/2)	1.2% (6/490)	0.0% (0/12)
Non Cardiac Death	NA	0.0% (0/43)	4.3% (2/47)	0.0% (0/2)	3.3% (16/490)	8.3% (1/12)
MI (3rd UDMI)	NA	0.0% (0/43)	6.4% (3/47)	0.0% (0/2)	6.7% (33/490)	0.0% (0/12)
Stroke	NA	0.0% (0/43)	0.0% (0/47)	0.0% (0/2)	1.6% (8/490)	0.0% (0/12)
Stent Thrombosis (ARC) Definite/Probable	NA	0.0% (0/43)	0.0% (0/47)	0.0% (0/2)	1.0% (5/490)	0.0% (0/12)
Early Thrombosis (≤30 days)	NA	0.0% (0/43)	0.0% (0/47)	0.0% (0/2)	0.0% (0/490)	0.0% (0/12)
Late Thrombosis (31-365 days)	NA	0.0% (0/43)	0.0% (0/47)	0.0% (0/2)	1.0% (5/490)	0.0% (0/12)
Bleeding						
All BARC	NA	11.6% (5/43)	14.9% (7/47)	50.0% (1/2)	19.6% (96/490)	16.7% (2/12)
BARC 3-5	NA	7.0% (3/43)	8.5% (4/47)	0.0% (0/2)	6.3% (31/490)	8.3% (1/12)

[1]Race was unknown for one subject.

[2]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 x (m/n).
Third universal definition of MI was used.

Acute Coronary Syndrome Status

The composite rate of cardiac death/MI in the Onyx ONE Clear analysis population at 1-year was 7.9% (55/694) in patients presenting with acute coronary syndromes (ACS) and 6.0% (44/733) in non-ACS patients.

4. Supplementary Safety and Effectiveness Analysis using the ARC HBR Definition

Using the Academic Research Consortium (ARC) HBR definition, subjects are considered HBR if they had at least 1 major criterion or 2 minor criteria. The consensus definition (ARC) of HBR was published after the initiation of the Onyx ONE RCT and Onyx ONE Clear studies, and therefore not all the ARC HBR criteria were collected. Medtronic used captured data to apply the major/minor criteria categorization defined in ARC HBR. In particular, "any documented stroke in the last 12 months" and "hospital admission for major bleeding during the prior 12 months" could not be simply categorized into major or minor ARC HBR criteria due to the lack of information of the timing of the event occurrence. "Renal failure defined as creatinine clearance <40 ml/min" could not be categorized directly because of the different parameters used to evaluate renal failure as compared to ARC HBR. Therefore, Medtronic proposed two categorization approaches to understand the impact on the outcome (including any stroke or major bleeding within 12 months and Creatinine clearance <40 ml/min as either a minor or major ARC HBR criteria). The application of ARC HBR definition resulted in smaller numbers of eligible subjects because those who met only one minor ARC HBR criterion (e.g., age $\geqslant$ 75 years) were excluded from this analysis. The safety and effectiveness results vary slightly between proposal 1 and 2 but are both comparable to the Onyx ONE Clear study results. The CD/MI rates in ARC HBR subjects at 1 year remain below the performance goal.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation.

The Onyx ONE US & Japan Trial included 387 investigators of which none were full-time or part-time employees of the sponsor and 11 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0; none
- Significant payment of other sorts: 10
- Proprietary interest in the product tested held by the investigator: 0; none
- Significant equity interest held by investigator in sponsor of covered study: 1

The Onyx ONE Global RCT included 660 investigators of which 1 was the spouse of a full-time employee of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described

below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0; none
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: 0; none
- Significant equity interest held by investigator in sponsor of covered study: 0; none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

In addition to the Onyx ONE Clear Primary Analysis, post hoc analyses of the data from the Global RESOLUTE Clinical Program and the optical coherence tomography (OCT) studies of Resolute Onyx and Resolute Integrity also support the high bleeding risk indication for Resolute Onyx.

A. Data from Global RESOLUTE Clinical Program

In a post-hoc analysis of 4,896 patients from the Global RESOLUTE Clinical Program published by Silber et al, 1,069 (21.83%) patients had DAPT interruption and 3,827 patients had no DAPT interruption. Among patients with DAPT interruption, 166 patients interrupted DAPT in the first month, with 6 stent thrombosis events occurring in this group (3.61%). Among 903 patients with DAPT interruption between 1 and 12 months, one stent thrombosis event occurred (0.11%). Among patients without DAPT interruption, 32 stent thrombosis events occurred (0.84%). Kaplan–Meier estimates of the cumulative incidence of stent thrombosis events showed a significant difference between patients who interrupted DAPT in the first month and patients who interrupted between 1 and 12 months (log-rank $P < 0.001$). The rates of CD or TVMI were 6.84% in the <1-month interruption group, 1.41% in the >1–12-month interruption group, and 4.08% in patients with no DAPT interruption. The authors concluded that while randomized clinical trials were needed to corroborate these results, DAPT interruptions between 1 to 12 months after Resolute stent implantation were associated with low rates of ST and adverse cardiac outcomes.

Following the initial analysis published by Silber and colleagues, subsequent analyses were performed assessing additional DAPT interruption timing as well as expanding the dataset from 4,896 to 7,131 patients as data became available from later trials within the Global RESOLUTE Clinical Program. The results from these analyses were consistent with the findings in the original cohort.

B. Data from Optical Coherence Tomography (OCT) Studies

OCT imaging is an accepted high-resolution method to evaluate stent strut coverage and

malapposition once a stent has been implanted. Since incomplete endothelization and positive remodeling has been correlated to the incidence of stent thrombosis, demonstration of early healing is desirable when considering DAPT discontinuation.

OCT imaging in the ORION study showed early healing with Resolute Integrity DES at 2 months (91.6% strut coverage with Resolute compared to 87.2% with BioMatrix, P=0.06) and at 3 months (94.2% vs 87.0%; P=0.004)[4]. In the Onyx 1-Month OCT Study, patients implanted with the Resolute Onyx DES demonstrated an early healing profile with an average of 88% of struts covered by neointima and 92.3% of the total stented area showing complete strut coverage at one month[5].

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of Resolute Onyx is based on the results of preclinical studies leveraged from the original Resolute Onyx PMA, including biocompatibility, *in vivo* pharmacokinetics (generated on the Resolute product); *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing.

The Onyx ONE Clear Primary Analysis evaluated the safety and effectiveness of the Resolute Onyx stent as compared to a PG with the use of one-month DAPT in selected subjects deemed at high risk for bleeding and/or medically unsuitable for more than one-month DAPT treatment. The analysis included subjects who were treated with a Resolute Onyx stent and were one-month clear from two studies: Onyx ONE US & Japan Trial (751 subjects) and the Onyx ONE Global RCT (1018 subjects). The study met the primary endpoint of a composite of cardiac death and myocardial infarction from one month to one year in HBR patients treated with one-month DAPT and supports the safety and effectiveness of the Resolute Onyx stent.

A. Effectiveness Conclusions

Among Onyx ONE Clear patients in the Onyx ONE Clear Primary Analysis, lesion

[4] Stephen L. et al. A Randomized Optical Coherence Tomography Study Comparing Resolute Integrity to Biomatrix Drug-Eluting Stent on the Degree of Early Stent Healing and Late Lumen Loss. Circulation: Cardiovascular Interventions, 2018; 11 (4): 1-10. https://doi.org/10.1161/CIRCINTERVENTIONS.117.006034

[5] Roleder T, Kedhi E, Berta B, et al. Short-term stent coverage of second-generation zotarolimus-eluting durable polymer stents: Onyx one-month optical coherence tomography study. Postepy Kardiol Interwencyjnej. 2019;15(2):143-150. doi:10.5114/aic.2019.86009

success was reported as 94.6% (1817/1920), device success was reported as 93.3% (1790/1919) and procedure success was reported as 88.5% (1295/1463).

B. Safety Conclusions

The primary endpoint for the Onyx ONE Clear Primary Analysis (a composite of cardiac death and myocardial infarction from one month to one year for a one-month clear population) was 7.0% (104/1491) with an upper one-sided 95% CI of 8.4%. This is lower than the prespecified performance goal of 9.7% and therefore meets criteria for success.

The risks associated with use of Resolute Onyx have been evaluated in the clinical studies discussed above along with non-clinical laboratory, animal studies and clinical studies leveraged from the original Resolute Onyx PMA approval. The biocompatibility, in vivo pharmacokinetics (data generated on the Resolute product), and in vivo performance characteristics of the product provide a reasonable assurance of safety for clinical use.

In summary, the leveraged nonclinical data along with the results from the Onyx ONE Clear Primary Analysis, the Global RESOLUTE Clinical Program, and OCT studies demonstrate that Resolute Onyx stent provides reasonable assurance of safety and effectiveness when used according to the proposed indications for the treatment of selected HBR patients who discontinue DAPT after one month.

C. Benefit-Risk Determination

The probable benefits and risks of the device when used with 1 month of DAPT post PCI to treat patients at high bleeding risk are based on data collected in the Onyx ONE Clear Primary Analysis.

Additional factors to be considered in determining probable risks and benefits for the Resolute Onyx stent include characterization of the disease, availability of alternative treatments, quality of the study design and conduct, robustness of analysis of study results, and risk mitigations. Coronary artery disease (CAD) can be accompanied by symptomatic chest pain or silent ischemia, which affects patients' quality of life. CAD is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms and the need for revascularization. Available treatments for CAD include medical therapy, percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. When treatment for coronary artery disease beyond medications and lifestyle changes is warranted, patients often choose stent deployment over surgical revascularization due to shorter recovery times and the less invasive nature of PCI. The risks associated with use of drug eluting stents are already well established, and in comparison to medical therapy, PCI has been shown to reduce the incidence of angina and increase quality of life. Patient tolerance of the Resolute Onyx stent in the Onyx ONE Clear Primary Analysis is in line with expectations. The study did not exclude any typical patient subgroups that would be expected to benefit from treatment.

1. Patient Perspective

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the improvement of coronary luminal diameters in patients, including those with diabetes mellitus *or for patients at 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, including the treatment of *de novo* chronic total occlusions, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the Onyx ONE Clear Primary Analysis, the Global RESOLUTE Clinical Program, and OCT studies support the safety and effectiveness of the Resolute Onyx™ Zotarolimus-Eluting Coronary Stent System for the treatment of patients who are at high bleeding risk.

XIV. CDRH DECISION

CDRH issued an approval order on September 22, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.