# 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<br><br>Onyx Frontier™ Zotarolimus-Eluting Coronary Stent System |
| Device Procode: | NIQ |
| Applicant's Name and Address: | Medtronic Vascular<br>3576 Unocal Place<br>Santa Rosa, California 95403 |
| Date(s) of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P160043/S058 |
| Date of FDA Notice of Approval: | September 15, 2022 |

The Resolute Onyx Zotarolimus-Eluting Coronary Stent System (Resolute Onyx) PMA (P160043) was previously approved on April 28, 2017. The Onyx Frontier Zotarolimus-Eluting Coronary Stent System (Onyx Frontier) with an alternative delivery system design was approved on May 12, 2022 (P160043/S055). The Resolute Onyx and Onyx Frontier Zotarolimus-Eluting Coronary Stent Systems are 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 and Onyx Frontier Zotarolimus-Eluting Coronary Stent Systems are 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

- P160043/S034:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160043S034

The current supplement was submitted to expand the indication for the Resolute Onyx and Onyx Frontier Zotarolimus-Eluting Coronary Stent Systems (collectively, Onyx DES) to include the treatment of non-left main bifurcation lesions utilizing the provisional bifurcation stenting technique.

## II. INDICATIONS FOR USE

The Resolute Onyx and Onyx Frontier Zotarolimus-Eluting Coronary Stent Systems are 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 and Onyx Frontier Zotarolimus-Eluting Coronary Stent Systems are indicated for treating *de novo* chronic total occlusions and non-left main bifurcation lesions utilizing the provisional bifurcation stenting technique.

## III. CONTRAINDICATIONS

The Onyx DES 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 Onyx DES labeling.

## V. DEVICE DESCRIPTION

The Onyx DES is a combination product consisting of (1) a cobalt alloy and platinum-iridium alloy core stent coated with a polymeric drug carrier containing the antiproliferative drug zotarolimus and (2) the delivery system, either rapid exchange (RX) or over-the-wire (OTW, Resolute Onyx only).

The characteristics of the Onyx DES are described in **Table 1**.

**Table 1. Onyx DES Product Characteristics**

| Characteristic | | Stent Design 1 (Small Vessel) | Stent Design 2 (Medium Vessel) | Stent Design 3 (Large Vessel) | Stent Design 4 (Extra Large Vessel) |
|---|---|---|---|---|---|
| Stent Pattern | | 6.5 crowns per revolution | 8.5 crowns per revolution | 9.5 crowns per revolution | 10.5 crowns per revolution |
| Stent Lengths (mm) | | 8, 12, 15, 18, 22, 26, 30, 34*, 38*<br>*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 Diameters (mm) | | 2.0, 2.25, 2.5 | 2.75, 3.0 | 3.5, 4.0 | (RX Only) – 4.5, 5.0 |
| Stent Strut Thickness (mm) | | 0.081 | 0.081 | 0.081 | 0.091 |
| Stent Material | | A cobalt-based alloy shell conforming to ASTM F562 and a platinum- iridium alloy core conforming to ASTM B684 | | | |
| Drug Component | | A conformal (all surfaces of the stent) coating of polymers loaded with approximately 1.6 µg/mm$^2$ of zotarolimus | | | |
| Delivery System | | Resolute Onyx RX<br>Resolute Onyx OTW<br>Onyx Frontier RX | | | Resolute Onyx RX |
| 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). | | | |

**Table 1. Onyx DES Product Characteristics**

| Characteristic | | Stent Design 1 (Small Vessel) | Stent Design 2 (Medium Vessel) | Stent Design 3 (Large Vessel) | Stent Design 4 (Extra Large Vessel) |
|---|---|---|---|---|---|
| Stent Delivery System Balloon | Resolute Onyx | Single-layer Pebax balloon, wrapped over an inner member tubing with 2 radiopaque marker bands to locate the stent edges. | | | |
| | Onyx Frontier | 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. | | | |
| Guiding Catheter Compatibility | | ≥5 F (min. guide catheter ID of 0.056”/1.42 mm) | | | |
| Balloon Inflation Pressure | | Nominal: 12 atm (1216 kPa)<br>Rated Burst Pressure (2.0 - 4.0 mm): 18 atm (1824 kPa)<br>Rated Burst Pressure (4.5-5.0 mm): 16 atm (1621 kPa) | | | |
| Catheter Shaft Outer Diameter | RX | Distal (Resolute Onyx, 2.0-4.0 mm: 0.0358 in (2.7 F, 0.91 mm)<br>Distal (Onyx Frontier, 2.0-4.0 mm): 0.0362 in (2.8 F, 0.92 mm)<br>Distal (4.5 and 5.0 mm): 0.0421 in (3.2 F, 1.07 mm)<br>Proximal: 0.0271 in (2.1 F, 0.69 mm) | | | |
| | OTW | Proximal: 0.0441 (3.4 F, 1.12 mm)<br>Distal: 0.0358 in (2.7 F, 0.91 mm) | | | |

## A. Device Component Description

The Onyx DES stent is made from a cobalt alloy outer shell with a platinum-iridium alloy core. The stent has four designs that are differentiated by the number of crowns per revolution. The small vessel design with 6.5 crowns per revolution is used for 2.0-2.5 mm diameter stents, the medium vessel design with 8.5 crowns per revolution is used for 2.75-3.0 mm diameter stents, the large vessel design with 9.5 crowns per revolution is used for 3.5-4.0 mm diameter stents, and the extra-large vessel design with 10.5 crowns per revolution is used for 4.5-5.0 mm diameter stents. The stent is formed from a single wire bent into a continuous sinusoid pattern and then laser fused back onto itself. **Figure 1** illustrates an Onyx DES stent.

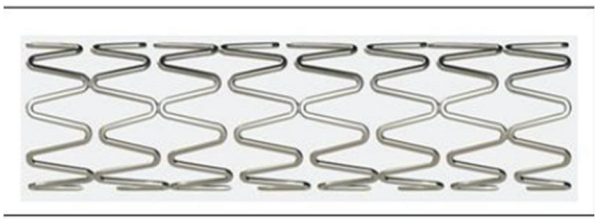

**Figure 1. Onyx DES Stent**

The stent is crimped onto the balloon of one of the available delivery systems: Resolute Onyx RX, Resolute Onyx OTW, or Onyx Frontier RX. The 2.0-4.0 mm sizes of the Resolute Onyx and Onyx Frontier delivery systems are distinguished by differences in the balloon, inner, and outer shaft designs outlined in **Table 1**. The 4.5-5.0 sizes of the Resolute Onyx and Onyx Frontier delivery systems are identical.

## B. Drug Component Description

The Onyx DES stent is conformally coated with a Parylene C primer and a polymer drug coating. The drug matrix is composed of zotarolimus (the active ingredient) and the BioLinx polymer system (the inactive ingredient).

1. Zotarolimus

Zotarolimus is the active pharmaceutical ingredient in the Onyx DES. The zotarolimus chemical name is:

[3S-[3R*[S*(1R*,3S*,4R*)],6S*,7E,9S*,10S*,12S*,14R*,15E,17E,19E, 21R*,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34[a]-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 molecular structure of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2 Da. The chemical structure is provided in **Figure 2**.

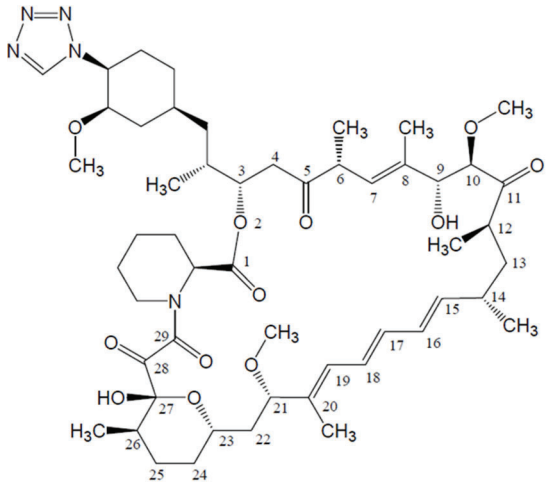

**Figure 2. Chemical Structure of Zotarolimus**

The Onyx DES product matrix and nominal total loaded dose of zotarolimus per nominal stent length/diameter is shown in **Table 2.**

**Table 2. Onyx DES Product Matrix and Drug Content**

| Stent Design | Stent Diameters (mm) | Stent Length (mm) | Zotarolimus Dose RX (µg/stent) | Zotarolimus Dose OTW (µg/stent) |
|---|---|---|---|---|
| Small Vessel | 2.0<br>2.25<br>2.5 | 8 | 51 | 51 |
| | | 12 | 70 | 70 |
| | | 15 | 85 | 85 |
| | | 18 | 104 | 104 |
| | | 22 | 127 | 127 |
| | | 26 | 146 | 146 |
| | | 30 | 168 | 168 |
| | | 34* | 187 | 187 |
| | | 38* | 206 | 206 |
| Medium Vessel | 2.75<br>3.0 | 8 | 67 | 67 |
| | | 12 | 94 | 94 |
| | | 15 | 117 | 117 |
| | | 18 | 140 | 140 |
| | | 22 | 171 | 171 |
| | | 26 | 198 | 198 |
| | | 30 | 225 | 225 |
| | | 34 | 257 | 257 |
| | | 38 | 284 | 284 |
| Large Vessel | 3.5<br>4.0 | 8 | 77 | 77 |
| | | 12 | 108 | 108 |
| | | 15 | 132 | 132 |
| | | 18 | 156 | 156 |
| | | 22 | 186 | 186 |
| | | 26 | 221 | 221 |
| | | 30 | 252 | 252 |
| | | 34 | 282 | 282 |
| | | 38 | 317 | 317 |
| Extra-Large Vessel | 4.5<br>5.0 | 12 | 132 | |
| | | 15 | 158 | |
| | | 18 | 188 | |
| | | 22 | 227 | |
| | | 26 | 265 | |
| | | 30 | 304 | |

*Not available in 2.0 mm diameter

2. Inactive Ingredient: BioLinx polymer

The BioLinx polymer carrier is a blend of the Medtronic proprietary components C10 polymer and C19 polymer, and polyvinyl pyrrolidone (PVP). The ratios are 10% PVP, 27% C10 and 63% C19. The Parylene C primer coating aids in adhesion of the subsequent drug-polymer layer onto the stent surface. The structural formulas of the BioLinx polymer subunits are shown in **Figure 3**.

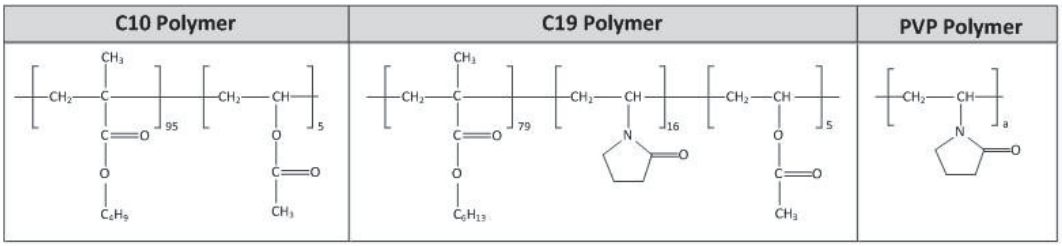


**Figure 3. Chemical Structure of BioLinx Polymer Sub-units**

3. Mechanism of Action of Zotarolimus

Zotarolimus inhibits growth factor-induced proliferation of human coronary artery smooth muscle cells and has also demonstrated binding affinity with FKBP-12 (binding protein) in vitro. 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.

The zotarolimus drug coated on the Onyx DES functions as an anti-proliferative and anti-restenotic agent due to its ability to interrupt smooth muscle cell proliferation.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease. These may include exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of other coronary 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**

Resolute Onyx first received approval on April 28, 2017. Onyx Frontier was approved on May 12, 2022.

**International Marketing/Outside the US (OUS) History**

Resolute Onyx has been in commercial use OUS since 2014. Onyx Frontier is not currently commercially available OUS.

**Table 3** lists countries where Resolute Onyx is currently commercially available. No

Onyx devices have been withdrawn from distribution in any country for any reason related to product safety or effectiveness.

**Table 3. Resolute Onyx Commercial Availability**

| | | | |
|---|---|---|---|
| Albania | El Salvador | Lithuania | Russian |
| Algeria | Estonia | Luxembourg | Rwanda |
| Argentina | Fiji | Malaysia | Saudi Arabia |
| Australia | Finland | Mali | Senegal |
| Austria | France | Malta | Serbia |
| Bahamas | French Guiana | Martinique | Singapore |
| Bahrain | Germany | Mauritius | Slovakia |
| Bangladesh | Ghana | Mexico | Slovenia |
| Barbados | Greece | Montenegro | South Africa |
| Belgium | Guadeloupe | Morocco | Spain |
| Bolivia | Guam | Mozambique | Sri Lanka |
| Bosnia and | Honduras | Myanmar | Sweden |
| Botswana | Hong Kong | Namibia | Switzerland |
| Brazil | Hungary | Nepal | Syrian Arab |
| Brunei | Iceland | Netherlands | Taiwan |
| Bulgaria | India | New Caledonia | Tanzania |
| Cambodia | Indonesia | New Zealand | Thailand |
| Canada | Iran | Nicaragua | Trinidad And |
| Canary Islands | Ireland | Nigeria | Tunisia |
| Cayman Islands | Israel | North | Turkey |
| Chile | Italy | Norway | Turkmenistan |
| Colombia | Japan | Pakistan | Ukraine |
| Costa Rica | Jamaica | Panama | United Arab |
| Cote D'Ivoire | Jordan | Paraguay | United |
| Croatia | Kazakhstan | Peru | United States |
| Curacao | Kenya | Philippines | Uzbekistan |
| Cyprus | Korea, Republic | Poland | Vietnam |
| Czech Republic | Kosovo | Portugal | Virgin Islands, |
| Denmark | Kuwait | Puerto Rico | Virgin Islands, |
| Dominican | Latvia | Qatar | Yemen |
| Ecuador | Lebanon | Reunion | - |
| Egypt | Libya | Romania | - |

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- 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
- 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
- Focal inflammation at the site of stent implantation
- Hemorrhage requiring transfusion
- Hypotension/hypertension
- Infection or fever
- Myocardial infarction (MI)
- Pericarditis
- Peripheral ischemia/peripheral nerve injury
- Renal failure
- Restenosis of the stented artery
- Shock or pulmonary edema
- Stable or unstable angina
- Stroke or transient ischemic attack
- Thrombosis (acute, subacute, or late)

Additional potential adverse effects associated with the administration of zotarolimus include, but are not limited to:

- Anemia
- Diarrhea
- Dry skin
- Headache
- Hematuria (blood in urine)
- Pain (abdominal, joint)
- Rash

For the specific adverse events that occurred in the clinical study, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported non-clinical laboratory studies can be found in the SSED for the original PMA (P160043). Additional non-clinical characterization testing relating to the new indication for "non-left main bifurcation lesions utilizing the provisional bifurcation

stenting technique" is presented here.

In vitro engineering testing was conducted on test samples representative of the Onyx DES in accordance with the following:

- FDA Guidance Document issued on April 18, 2010, *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*
- 21CFR 814.20(b)(6)(i)
- 21 CFR 820.30(f)
- 21 CFR 210/211
- FDA recommendations

**Table 4** summarizes this testing. "Pass" denotes that the test results indicate the devices are capable of being used in non-left main bifurcation lesions utilizing the provisional bifurcation stenting technique.

**Table 4. Summary of Engineering Testing**

| Test | Purpose | Acceptance Criteria | Results |
|---|---|---|---|
| Stress/Strain and Fatigue Analysis | To identify the critical locations and magnitudes of stress or strain on the stent when used in non-left main bifurcation lesions using finite element analysis (FEA). | Acceptable safety factors (>1) | Pass |
| Coating Durability | To assess the durability of the drug coating when subjected to simulated clinical use conditions (deployment in non-left main bifurcation lesion). | Characterization only | Pass |
| Acute Particulate Evaluation – Simulated Use | To measure the particulate matter generated during simulated use of one delivery system through an in vitro model and deploying the stent using the provisional bifurcation stenting technique | Characterization only | Pass |

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study, RESOLUTE ONYX PAS Bifurcation Cohort Primary Analysis (Bifurcation Cohort), to establish a reasonable assurance of safety and effectiveness of the Onyx DES for treatment of non-left main bifurcation lesions utilizing the provisional bifurcation stenting technique in the US, France, Belgium, and Slovakia under IDE #G140178/S010. Data from this clinical study were the basis for the PMA approval decision. A summary of the pivotal Bifurcation Cohort study is presented below.

### A. Study Design

Patients were treated between April 3, 2017 and December 2, 2019. The database for this

PMA reflected data collected through December 2021 and included 205 patients. There were 25 investigational sites.

The study was a multi-center, single-arm clinical study to evaluate the safety and effectiveness of the Onyx DES for the treatment of bifurcation lesions in native coronary arteries amenable to treatment with Onyx stent sizes 2.0 mm – 5.0 mm utilizing the provisional stenting technique. A total of 15 subjects were reconsented from the RESOLUTE ONYX PAS Primary Cohort and 190 subjects were prospectively enrolled.

Assessment of the use of the Onyx DES in treating bifurcated lesions with provisional stenting was based on the primary endpoint of target vessel failure (TVF) at 12 months post-procedure and compared to a performance goal (PG). The PG was based on review of clinical evidence from published literature and was set at 24.5% based on an estimated 16.3% TVF rate and a one-sided 0.05 significance level.

The Bifurcation Cohort utilized an independent angiographic core laboratory and independent clinical events committee (CEC) to evaluate and adjudicate study primary and secondary endpoint data. The core laboratories and CEC were composed of experts in their field.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Bifurcation Cohort was limited to patients who met the following inclusion criteria:

*General Inclusion Criteria:*

- Subject age is ≥ 18 years;
- Subject has symptoms and/or evidence of coronary artery disease; chronic stable angina, silent ischemia, or acute coronary syndromes including non-ST elevation myocardial infarction (non-STEMI) and ST-elevation myocardial infarction (STEMI);
- Subject is an acceptable candidate for treatment with a drug eluting stent;
- Subject is willing and able to cooperate with study procedures and required follow-up evaluations;
- Subject or legal representative has provided written informed consent;
- Subjects of child-bearing potential must have a negative pregnancy test within 7 days before the study procedure;
- Subject requires treatment of one or more target lesion(s) amenable to treatment with a Resolute Onyx 2.0 mm – 5.0 mm stent in up to two separate target vessels.

*Angiographic Inclusion Criteria:*

- Subject requires treatment of a single de novo bifurcated lesion amenable to treatment with provisional stenting technique
    a. All Medina classification types
    b. De novo lesion in native coronary artery
    c. Main branch ≥ 2.25 – 5.0 mm
    d. Side branch ≥ 2.0 mm
    e. Lesion length ≤ 35 mm

- Target lesion(s) must have a stenosis of ≥50% and <100%
- Target vessel(s) must have a Thrombolysis In Myocardial Infarction (TIMI) flow ≥2

Patients were not permitted to enroll in the Bifurcation Cohort if they met any of the following exclusion criteria:

*General Exclusion Criteria:*

- Subjects with known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, thienopyridines, cobalt, nickel, platinum, iridium, chromium, molybdenum, polymer coatings (e.g., BioLinx), anticoagulants, or a sensitivity to contrast media, which cannot be adequately pre-medicated;
- Subjects with a history of an allergic reaction or significant sensitivity to drugs such as zotarolimus, rapamycin, tacrolimus, everolimus, or any other analogue or derivative;
- Subjects 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;
- Subjects with unprotected left main coronary artery disease;
- Subjects with planned PCI of three vessel disease;
- Subjects currently participating in another investigational study that has not completed the primary endpoint or that clinically interferes with the current study endpoints;
- Subjects with planned surgery that would cause interruption in recommended dual antiplatelet therapy (DAPT) duration per current guidelines;
- Subjects with impaired renal function (serum creatinine >2.5 mg/dl or 221 μmol/l) or on dialysis
- Subjects with left ventricular ejection fraction (LVEF) ≤30%

*Angiographic Exclusion Criteria:*

- Subjects with planned two stent technique (main branch and side branch) of a bifurcation;
- Subjects with more than one bifurcation lesion;
- Subjects with trifurcation lesions;
- Subjects with planned treatment of any additional lesion(s) in the bifurcation target vessel(s), inclusive of branches within 12 months;
- Subjects with target lesion(s) located in native vessel(s) within 5 mm distal to anastomosis with a bypass graft and/or with more than 40% diameter stenosis anywhere within the graft.

2. Follow-up Schedule

All patients were scheduled for health status assessments at 30 days, 6 months, 12 months, 2 years, and 3 years post-procedure by telephone, e-mail and/or office visits.

Preoperatively, angina status and LVEF was recorded, routine laboratory tests including

cardiac enzyme assessments were conducted, and 12-lead electrocardiograms were performed. Postoperatively, prior to discharge, patients received another physical examination, cardiac enzymes were drawn (≥3 hours post-procedure and again 4 hours after the first, but prior to 24 hours post-procedure or at discharge, whichever came first), another ECG was performed, and all adverse events were recorded. At follow-up, angina status and any serious adverse events were recorded.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

The primary endpoint was composite of outcomes related to both safety and effectiveness: target vessel failure (TVF) at 12 months, defined as cardiac death, target vessel myocardial infarction (TVMI; MI defined below), or clinically-driven target vessel revascularization (TVR).

With regards to safety, secondary clinical outcomes evaluated at all study timepoints included the following:

- Cardiac death
- TVMI
- Stent thrombosis

With regards to effectiveness, secondary endpoints included the following:

- Acute success (device, lesion, procedure)
- TVR
- Target lesion revascularization (TLR)

With regards to success/failure criteria, comparison of the primary endpoint to a performance goal was planned. An expected event rate of 13.0% was obtained by utilizing the weighted average of outcomes from the RESOLUTE All-Comers (RAC) study in patients with single bifurcations treated with single or double stents (excluding unprotected left main lesions and patients with three vessel disease) and from the provisional stenting arm of the TRYTON study. An upward adjustment of 3.31% was later added to the expected rate to account for the expected difference in MI reporting after the 3rd Universal Definition of MI (UDMI) was adopted (see below regarding the protocol definition of MI). This resulted in an expected event rate of 16.3%. The performance goal of 24.5% is a 50% extension from the updated expected event rate of 16.3%. The original performance goal prior to changing the expected event rate was 19.5%.

Assuming a one-sided alpha level of 0.05 and a true event rate of 16.3%, evaluating a total of 180 patients would yield 85% power to meet the performance goal. To account for loss to follow-up (assumed to be approximately 10%), a total of 200 patients were planned to be enrolled.

The null and alternative hypotheses were:

- $H_0$: $P_{TVF} \geq 24.5\%$
- $H_a$: $P_{TVF} < 24.5\%$

where $P_{TVF}$ is the true primary endpoint rate for the Onyx DES, and 24.5% is the performance goal. The one-sided significance level was 0.05. The number and percentage of patients with 12-month TVF were presented. A one-sided upper bound of the 95% confidence interval of the observed 12-month TVF rate was calculated using the binomial (exact) method. The primary endpoint was evaluated on an intent-to-treat (ITT) basis.

**Protocol Definition of MI:** In June 2019, the protocol definition of MI was changed from the Medtronic Extended Historical definition to the 3rd UDMI. The reason for the change was to account for the decreased use of CK-MB and increasing use of the more sensitive cardiac enzyme troponin (cTn) by study sites. Summaries of the original and updated MI definitions are given below in **Table 5**.

**Table 5. Protocol Definitions of MI**

| MI Definition | Medtronic Extended Historical Definition (Original Protocol) | 3rd UDMI (Modified Protocol) |
|---|---|---|
| Spontaneous MI | A. Recurrent chest pain or ischemic equivalent *and*<br>▪ New pathologic Q waves in ≥2 contiguous ECG leads *and* cardiac enzyme elevation >URL (CK-MB preferred)<br>B. Appropriate cardiac enzyme data (top-down hierarchy):<br>b1. CK ≥2X URL (with confirmation) *or*<br>b2. CK-MB > 3X URL *or*<br>b3. cTn > 3X URL *or*<br>b4. Clinical judgment. | • Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:<br>• Symptoms of ischemia<br>• New significant ST-segment-T wave (ST-T) changes or left bundle branch block (LBBB)<br>• Pathological Q waves<br>• Evidence of loss of viable myocardium or new regional wall motion abnormality<br>• Intracoronary thrombus<br>• Cardiac death before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. |
| Peri-procedural MI | If normal baseline cardiac biomarkers and no acute MI in progress:<br>A. New pathologic Q waves in ≥2 contiguous ECG leads *and* cardiac enzyme elevation >URL (CK-MB preferred)<br>B. Appropriate cardiac enzyme data (top-down hierarchy):<br>b1. CK ≥2X URL (with confirmation) *or*<br>b2. CK-MB >3X URL *or* | Elevation of cTn values (>5 X 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise in cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either<br>(i) symptoms suggestive of myocardial ischemia or<br>(ii) new ischemic ECG changes or<br>(iii) angiographic findings consistent with a procedural complication or |

| | | |
|---|---|---|
| | b3. cTn >3X URL<br><br>Note: URL = upper reference limit, defined as 99th percentile of normal<br><br>If elevated cardiac biomarkers at baseline or acute MI in progress:<br>A. If cardiac biomarker has not yet peaked:<br>• Recurrent chest pain or ischemia equivalent to 20 minutes (or new ECG changes consistent with MI) *and*<br>• CK >2X URL (confirmed) and 50% above previous level *or*<br>• CK-MB or cTn >3X URL and 50% above previous level<br>B. If CK (or CK-MB) has peaked and returned <URL, then any new rise in:<br>• CK >2X URL (confirmed) *or*<br>• CK-MB >3X URL *or*<br>• cTn >3X URL<br>C. If cardiac enzyme has peaked but not returned <URL, a rise in the cardiac enzyme >50% above previous level | (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. |

**B. <u>Accountability of PMA Cohort</u>**

At the time of database lock, of 205 patients enrolled in the PMA study, 99.5% (204) are available for analysis at the completion of the study, the 12-month post-index procedure visit. The disposition of the patients is summarized in **Table 6**.

**Table 6. Patient Disposition**

| **Patient Disposition** | **Total** |
|---|---|
| Number of Patients Enrolled (ITT Population) | 205 |
| Deaths Prior to 12-Month Visit | 2.9% (6/205) |
| Withdrew Consent/Lost to Follow-up/Other | 0.5% (1/205) |
| Missed 12-Month Visit | 0% (0/205) |
| Completed 12 Month Visit | 96.6% (198/205) |
| **Primary Endpoint Evaluable Patients** | 99.5% (204/205) |

The intention-to-treat (ITT) population consisted of all 205 patients enrolled in the study. "Primary-Endpoint Evaluable Patients" are defined as patients 1) experiencing a TVF event within 12 months of the study procedure, or 2) completing clinical follow-up one year after the study procedure.

### C. Study Population Demographics and Baseline Parameters

The demographics of the study population are relatively typical for a coronary stent study performed in the US. **Error! Reference source not found.7** presents demographics for the Bifurcation Cohort ITT population. The mean age of the study patients was 66.6 years and 21.5% were female. Patients were predominantly white (at least 82.4%) and overweight (mean body mass index (BMI) 29.4 kg/m$^2$).

**Table 7. Bifurcation Cohort Baseline Demographics**

| Patient Characteristics | Bifurcation Cohort (N=205 Patients) |
|---|---|
| Age (years) | |
| Mean±SD (N) | 66.6 ± 10.7 (205) |
| Range (min, max) | (37, 87) |
| Sex | |
| Male | 78.5% (161/205) |
| Female | 21.5% (44/205) |
| Ethnicity | |
| Hispanic/Latino | 6.2% (12/194) |
| Race | |
| American Indian or Alaska Native | 0.0% (0/193) |
| Asian | 4.1% (8/193) |
| Black or African American | 5.7% (11/193) |
| Native Hawaiian or other Pacific Islander | 0.0% (0/193) |
| White | 82.4% (159/193) |
| Other | 7.8% (15/193) |
| Unknown | 5.8% (12/205) |
| BMI (kg/m$^2$) | 29.4 ± 5.7 (205) |

**Error! Reference source not found.8** shows the baseline clinical characteristics and medical history of the ITT population. The majority of patients reported prior or current smoking, hypertension and hyperlipidemia. Approximately 30% of patients were diabetic, consistent with previously reported and recent prospective studies.

**Table 8. Baseline Clinical Characteristics**

| Parameter | Bifurcation Cohort (N=205 Patients) |
|---|---|

| | |
|---|---|
| Smoking Status<br>Never Smoked<br>Previous Smoker<br>Current Smoker | <br>48.3% (99/205)<br>37.6% (77/205)<br>14.1% (29/205) |
| History of MI | 19.5% (40/205) |
| Previous PCI | 35.1% (72/205) |
| Previous CABG | 9.3% (19/205) |
| History of Stroke or Transient Ischemic Attack | 6.8% (14/205) |
| Diabetes<br>Type I<br>Type II<br>Insulin Dependent | 30.2% (62/205)<br>3.9% (8/205)<br>26.3% (54/205)<br>7.3% (15/205) |
| Hypertension | 77.1% (158/205) |
| Hyperlipidemia | 74.1% (152/205) |
| Chronic Obstructive Pulmonary Disease | 10.2% (21/205) |
| Cardiac admissions within 30 days prior to index procedure | 11.2% (23/205) |
| Left Ventricular Ejection Fraction (%) | 56.9 ± 11.3 (170) |
| Serum Creatinine (μmol/L) | 96.7 ± 63.0 (205) |

Indications for the index procedure were most often due to stable angina 36.3% (69/190) or unstable angina 36.8% (70/190). Acute coronary syndrome (ACS) was reported in 47.4% (90/190 of patients at the time of the index procedure. Baseline ischemic status is presented in **Table 9**.

**Table 9. Ischemic Status at Baseline**

| **Ischemic Status** | **Bifurcation Cohort (N=205 Patients)** |
|---|---|
| Number of diseased major coronary arteries > 50% stenosed<br>Single<br>Double<br>Triple<br>Quadruple | <br>62.0% (127/205)<br>30.2% (62/205)<br>6.8% (14/205)<br>1.0% (2/205) |
| Canadian Cardiovascular Society (CCS) classification<br>I<br>II<br>III<br>IV | <br>8.3% (14/168)<br>33.9% (57/168)<br>40.5% (68/168)<br>17.3% (29/168) |

| | |
|---|---|
| Clinical Evidence (prompted index procedure) | 92.7% (190/205) |
| Silent Ischemia | 14.2% (27/190) |
| Stable Angina | 36.3% (69/190) |
| Unstable Angina | 36.8% (70/190) |
| Myocardial Infarction | 10.5% (20/190) |
| Within 72 hours | 7.4% (14/190) |
| STEMI | 3.7% (7/190) |
| Non-STEMI | 3.7% (7/190) |
| Within 24 hours | 4.7% (9/190) |
| STEMI | 3.2% (6/190) |
| Non-STEMI | 1.6% (3/190) |
| Within 12 hours | 3.7% (7/190) |
| STEMI | 3.2% (6/190) |
| Non-STEMI | 0.5% (1/190) |
| Acute Coronary Syndrome (ACS) | 47.4% (90/190) |
| Positive Functional Study | 54.1% (111/205) |

**Key Baseline Lesion Characteristics: Table 10** presents baseline lesion characteristics as interpreted by an independent core lab. In Bifurcation Cohort patients, mean reference vessel diameter was 2.65 ± 0.47 mm, mean lesion length was 17.03 ± 9.64 mm, and mean percent stenosis was 65%. The target lesion location distribution is generally reflective of patients presenting for PCI with 64% in the LAD, 33% in the LCX, and 18% in the RCA. The protected left main was treated in 3% of patients. Approximately 96% of lesions were classified as complex (B2/C). Bifurcation lesions represented 78% of lesions treated in the study. Of these, approximately one third represented a "true" bifurcation per Medina classification.

**Table 10. Baseline Lesion Characteristics**

| **Baseline Lesion Characteristics** | **Bifurcation Cohort (N=205 Patients) (N=266 Lesions)** |
|---|---|
| Vessel Location (per patient) | |
| LAD | 64.2% (131/204) |
| LCX | 32.8% (67/204) |
| RCA | 17.6% (36/204) |
| LM | 2.9% (6/204) |
| Lesion Location | |
| Proximal | 42.3% (112/265) |
| Mid | 36.2% (96/265) |
| Distal | 12.1% (32/265) |
| Ostial | 9.4% (25/265) |

| Baseline Lesion Characteristics | Bifurcation Cohort (N=205 Patients) (N=266 Lesions) |
|---|---|
| Modified ACC/AHA Lesion Class | |
| A | 0.4% (1/266) |
| B1 | 3.8% (10/266) |
| B2 | 14.3% (38/266) |
| C | 81.6% (217/266) |
| Calcification | |
| Mild | 66.8% (177/265) |
| Moderate | 15.1% (40/265) |
| Severe | 18.1% (48/265) |
| TIMI Flow | |
| 0 | 0.8% (2/265) |
| 1 | 2.6% (7/265) |
| 2 | 3.0% (8/265) |
| 3 | 93.6% (248/265) |
| Bifurcation (% lesions) | 78.1% (207/265) |
| Medina Classification | |
| 1.1.1 | 22.7% (47/207) |
| 1.1.0 | 23.7% (49/207) |
| 1.0.1 | 3.4% (7/207) |
| 0.1.1 | 6.3% (13/207) |
| 1.0.0 | 15.5% (32/207) |
| 0.1.0 | 26.6% (55/207) |
| 0.0.1 | 0.5% (1/207) |
| "True" bifurcations (1.1.1, 1.0.1, or 0.1.1) | 32.3% (67/207) |
| Stenosis (%) (N) | 64.55±11.92 (265) |
| Side Branch Stenosis (%) (N) | 23.9 ± 30.8 (437) |
| Lesion Length (mm) | |
| Mean±SD (N) | 17.03±9.64 (266) |
| Reference Vessel Diameter (mm) | |
| Mean±SD (N) | 2.65±0.47 (265) |
| Minimal Lumen Diameter (mm) | |
| Mean±SD (N) | 0.94±0.36 (265) |

**Key Procedural Characteristics:** The majority of the Bifurcation Cohort patients had one lesion treated (73%) and one vessel treated (83%). Patients had an average of 1.6 stents implanted. Additional procedural characteristics are presented below in **Table 11**.

**Table 11. Procedural Characteristics**

| Procedural Characteristics | Bifurcation Cohort (N=205 Subjects) (N=266 Lesions) |
|---|---|
| Type of Procedure<br>Index<br>Staged | <br>93.6% (192/205)<br>6.3% (13/205) |
| Number of Lesions Treated per Patient (N)<br>1<br>2<br>3 or more | 1.3 ± 0.6 (205)<br>73.2% (150/205)<br>20.5% (42/205)<br>6.3% (13/205) |
| Vessels Treated<br>Single<br>Multiple | <br>82.8% (169/204)<br>17.2% (35/204) |
| Number of Stents Placed per Patient | 1.59 ± 0.95 (205) |
| Total Procedure Time (min) (N) | 50.86 ± 31.27 (215) |
| Post-Procedure Hospital Length of Stay (days) (N) | 1.2±1.6 (215) |

**D. Safety and Effectiveness Results**

The primary endpoint was a composite that combined measures of both safety and effectiveness.

**Primary Endpoint**: The primary endpoint was met (**Table 12**). The primary endpoint of target vessel failure (TVF; cardiac death, target vessel MI (TVMI), or clinically driven TVR) 12 months following Onyx DES implantation in the intention-to-treat (ITT) group was statistically demonstrated to be below the performance goal.

The 12-month TVF rate was 6.9% in the Bifurcation Cohort, with an upper one-sided confidence interval (CI) of 10.5%. Because the upper bound of this CI is below the pre-specified performance goal of 24.5%, the performance goal was met, and study success may be claimed for the primary endpoint.

The per-protocol (PP) 12-month TVF rate was not meaningfully different at 6.2%.

**Table 12. ITT Analysis of Primary Endpoint at 12 Months**

| | Bifurcation Cohort (N = 205 Patients) | Upper 95% CI | Performance Goal |
|---|---|---|---|
| **TLF** | **6.9% (14/204)** | **10.5%** | **24.5%** |
| Cardiac Death | 1.5% (3/204) | -- | -- |
| TVMI (3rd UDMI) | 2.9% (6/204) | -- | -- |
| Clinically driven TVR | 3.4% (7/204) | -- | -- |

1. Safety Results

The analysis of safety was based on the 204 patients available for the 12-month evaluation as well as the 200 patients available for the 24-month evaluation. Key safety outcomes are presented in **Table 13**.

**Table 13. Summary of Safety Endpoints**

| | Bifurcation Cohort (N=205 Patients) |
|---|---|
| In-Hospital Events | |
| Death | 0.00% (0/205) |
| TVMI (3rd UDMI) | 2.2% (4/179)* |
| Stent Thrombosis** | 0.0% (0/205) |
| Events at 12 Months | |
| 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) |
| Stent Thrombosis** | 0.0% (0/204) |
| Events at 24 Months | |
| 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) |
| Stent Thrombosis** | 0.0% (0/200) |

*25 patients had insufficient cardiac enzymes collected for peri-procedural MI assessment

**Definite or probable

**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 14** presents a comparison of the 3rd UDMI, Extended Historical, and SCAI peri-procedural MI definitions and **Table 15** presents CEC-adjudicated TVMI rates in the Bifurcation Cohort using those definitions.

**Table 14. Comparison of Definitions Used by CEC to Adjudicate Peri-Procedural MI**

| | 3rd UDMI | Extended Historical | SCAI |
|---|---|---|---|
| Relationship to Study | Revised Protocol Definition | Original Definition | Alternative Peri-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<br>>70X URL for troponin |
| Other Required Criteria | Evidence of ischemia (symptoms, angiographic findings, ECG, etc.) | None | None |

**Table 15. TVMI Rates by Definition**

| | 3rd UDMI | Extended Historical | SCAI |
|---|---|---|---|
| TVMI | 2.9% (6/204) | 12.7% (26/204) | -- |
| Peri-procedural | 2.2% (4/179) | 12.8% (23/179) | 5.0% (9/179) |
| Non-Q Wave | 1.7% (3/179) | 12.3% (22/179) | 4.5% (8/179) |
| Spontaneous | 1.0% (2/204) | 1.5% (3/204) | -- |

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 peri-procedural TVMI criteria of >3X URL are much more common than CK-MB elevations meeting the same criteria. Although the Extended Historical definition prefers the use of CK-MB (in other words, if both CK-MB and troponin are available, a site should use CK-MB to adjudicate PPMI), CK-MB was frequently no longer available at Bifurcation Cohort study sites. Approximately 40% of patients in the Bifurcation Cohort did not have CK/CK-MB available at their study site. The Bifurcation Cohort study switched to the 3rd UDMI definition, which prefers troponin, in order to account for this evolution in the standard of care.

**Adverse effects that occurred in the PMA clinical study:**

Adverse events that occurred in the Bifurcation Cohort are presented below in **Table 16**. The scope of adverse event reporting in this study was limited to all serious

adverse events (SAEs) and device deficiencies. Adverse events were reported by sites using MedDRA preferred terms. No unanticipated adverse device effects were reported through 24 months. Only SAEs occurring at a rate of ≥1% are recorded below.

A total of 122 SAEs were reported through the 24-month follow up, with 32% of patients (65/205) experiencing at least one SAE. One device deficiency was reported for one subject in which the Onyx stent was unable to be deployed on the first attempt due to severe calcification in the lesion and was removed intact. The Onyx stent was successfully deployed on the second attempt, and this device deficiency did not lead to an adverse event.

**Table 16. All Serious Adverse Events Occurring in >1% of Patients**

| System Organ Class/Preferred Term | Bifurcation Cohort (N=205 Subjects) |
|---|---|
| **Any Serious Adverse Event to 720 Days** | **31.7% (65/205)** |
| **Cardiac disorders** | **14.6% (30/205)** |
| Acute myocardial infarction | 3.9% (8/205) |
| Angina pectoris | 3.4% (7/205) |
| Atrial fibrillation | 1.5% (3/205) |
| Bradycardia | 1.0% (2/205) |
| Cardiac arrest | 1.0% (2/205) |
| Cardiac failure congestive | 3.4% (7/205) |
| Coronary artery disease | 2.4% (5/205) |
| **Gastrointestinal disorders** | **2.4% (5/205)** |
| Intestinal obstruction | 1.5% (3/205) |
| **General disorders and administration site conditions** | **3.4% (7/205)** |
| Chest pain | 1.0% (2/205) |
| Non-cardiac chest pain | 1.5% (3/205) |
| **Infections and infestations** | **7.3% (15/205)** |
| Pneumonia | 1.5% (3/205) |
| Pulmonary sepsis | 1.0% (2/205) |
| Sepsis | 1.0% (2/205) |
| Urinary tract infection | 1.0% (2/205) |
| **Injury, poisoning and procedural complications** | **2.0% (4/205)** |
| **Investigations** | **1.5% (3/205)** |
| Myocardial necrosis marker increased | 1.5% (3/205) |
| **Metabolism and nutrition disorders** | **1.0% (2/205)** |

| | |
|---|---|
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **2.0% (4/205)** |
| **Nervous system disorders** | **2.9% (6/205)** |
| Cerebrovascular accident | 1.0% (2/205) |
| **Renal and urinary disorders** | **1.0% (2/205)** |
| **Respiratory, thoracic and mediastinal disorders** | **3.4% (7/205)** |
| Chronic obstructive pulmonary disease | 1.0% (2/205) |
| Dyspnoea | 1.0% (2/205) |
| Respiratory failure | 1.0% (2/205) |
| **Surgical and medical procedures** | 1.0% (2/205) |
| **Vascular disorders** | **2.9% (6/205)** |
| Aortic stenosis | 1.0% (2/205) |

2. Effectiveness Results

The analysis of effectiveness was based on the ITT cohort of 204 evaluable patients at the 12-month time point as well as the 200 patients available for the 24-month evaluation. Key effectiveness outcomes are presented in **Table 17**.

Device success was analyzed per lesion and defined as attainment of <30% residual stenosis and TIMI flow 3 after the procedure, using the assigned device only. Lesion success was also analyzed per lesion and defined as attainment of <30% residual stenosis and TIMI flow 3 after the procedure, using any percutaneous method. Procedure success was analyzed per patient and defined as lesion success with no in-hospital major adverse cardiovascular events (MACE). Event rates were reflective of contemporary coronary DES trials.

**Table 17. Summary of Effectiveness Endpoints**

| | **Bifurcation Cohort (N=205 Patients N=266 Lesions)** |
|---|---|
| **Acute Success** | |
| Device Success | 97.3% (257/264) |
| Lesion Success | 98.9% (261/264) |
| Procedure Success | 96.6% (196/203) |
| **In-Hospital Events** | |
| Clinically Driven TLR | 0.0% (0/205) |
| Clinically Driven TVR | 0.0% (0/205) |
| **Events at 12 Months** | |

| | |
|---|---|
| Clinically Driven TLR<br>Clinically Driven TVR | 2.9% (6/204)<br>3.4% (7/204) |
| **Events at 24 Months** | |
| Clinically Driven TLR<br>Clinically Driven TVR | 4.5% (9/200)<br>5.5% (11/200) |

3. Subgroup Analyses

The following pre-operative characteristics were evaluated for potential association with outcomes:

**Sex/Gender**

The Bifurcation Cohort statistical analysis plan prespecified providing principal safety and effectiveness outcomes by sex. **Table 18** presents an analysis of the primary endpoint in male and female patients. The 85% confidence interval was adjusted by stratification using five groups determined by quintile propensity scores, with lesion length, baseline RVD, age, diabetes, history of MI, and worst CCS angina class as the confounding variables.

Female patients in the Bifurcation Cohort were on average older than male patients (71 vs 65 years old), had shorter average lesion lengths (14 mm vs. 18 mm), and were less likely to have prior history of MI (7% vs. 23%).

**Table 18. TVF at 12 Months in Male and Female ITT Patients**

| Male (N=161 Patients) | Female (N=44 Patients) | Difference: Female - Male | Adjusted Difference [85% CI] |
|---|---|---|---|
| 5.6% (9/160) | 11.4% (5/44) | 5.7% | 6.4% [-1.5%, 14.3%] |

Additional secondary endpoint outcomes for male and female patients from the Bifurcation Cohort are also available (**Table 19**).

**Table 19: Secondary Endpoints by Sex/Gender at 24 Months**

| | Male (N=161 Patients N=213 Lesions) | Female (N=44 Patients N=53 Lesions) | Difference [95% CI] |
|---|---|---|---|
| All Death | 2.6% (4/156) | 4.5% (2/44) | -2.0% [-8.6%, 4.7%] |
| Cardiac Death | 0.6% (1/156) | 4.5% (2/44) | -3.9% [-10.2%, 2.4%] |
| TVMI (3rd UDMI) | 3.8% (6/156) | 4.5% (2/44) | -0.7% [-7.6%, 6.2%] |
| Clinically Driven TLR | 4.5% (7/156) | 4.5% (2/44) | -0.1% [-7.0%, 6.9%] |
| Clinically Driven TVR | 5.8% (9/156) | 4.5% (2/44) | 1.2% [-5.9%, 8.4%] |
| Stent Thrombosis | 0.0% (0/160) | 0.0% (0/44) | N/A |
| Lesion Success | 98.6% (208/211) | 100.0% (53/53) | -1.4% [-3.0%, 0.2%] |

| | Male (N=161 Patients N=213 Lesions) | Female (N=44 Patients N=53 Lesions) | Difference [95% CI] |
|---|---|---|---|
| Device Success | 97.2% (205/211) | 98.1% (52/53) | -1.0% [-5.3%, 3.3%] |
| Procedure Success | 96.2% (153/159) | 97.7% (43/44) | -1.5% [-6.8%, 3.8%] |

Female patients represented 22% of those evaluated for the primary endpoint and 19% of treated lesions. This is somewhat below the proportion of female PCI patients in the general U.S. population, estimated in a recent study to be 33% (Alkhouli, et al., 2020).

Although female patients were under-represented, the totality of the data from the Bifurcation Cohort and previous studies of the Onyx DES support that the overall conclusions of the trial regarding the safety and effectiveness of the Onyx DES when used to treat non-left main bifurcation lesions using a provisional stenting technique can be generalized to males and females.

**Age**

The Bifurcation Cohort statistical analysis plan prespecified providing principal safety and effectiveness outcomes by age. **Table 20** presents an analysis of the primary endpoint in patients ≥65 and <65 years old.

**Table 20. TVF at 12 Months in ITT Patients ≥65 and <65 Years Old**

| ≥65 years (N=118 Patients) | <65 years (N=87 Patients) | Difference [95% CI] |
|---|---|---|
| 7.7% (9/117) | 5.7% (5/87) | 1.9% [-4.9%, 8.8%] |

Additional secondary endpoint outcomes for patients ≥65 and <65 years old from the Bifurcation Cohort are also available (**Table 21**).

**Table 21. Secondary Endpoints by Age at 24 Months**

| | Age ≥65 Years (N=118 Patients N=144 Lesions) | Age <65 Years (N=87 Subjects N=123 Lesions) | Difference [95% CI] |
|---|---|---|---|
| Death | 5.2% (6/116) | 0.0% (0/84) | 5.2% [1.1%, 9.2%] |
| Cardiac Death | 2.6% (3/116) | 0.0% (0/84) | 2.6% [-0.3%, 5.5%] |
| TVMI (3rd UDMI) | 3.4% (4/116) | 4.8% (4/84) | -1.3% [-6.9%, 4.3%] |
| Clinically Driven TLR | 3.4% (4/116) | 6.0% (5/84) | -2.5% [-8.6%, 3.5%] |
| Clinically Driven TVR | 4.3% (5/116) | 7.1% (6/84) | -2.8% [-9.5%, 3.8%] |
| Stent Thrombosis | 0.0% (0/116) | 0.0% (0/84) | N/A |

| | Age ≥65 Years (N=118 Patients N=144 Lesions) | Age <65 Years (N=87 Subjects N=123 Lesions) | Difference [95% CI] |
|---|---|---|---|
| Lesion Success[5] | 98.6% (139/141) | 99.2% (122/123) | -0.6% [-3.1%, 1.9%] |
| Device Success[6] | 97.2% (137/141) | 97.6% (120/123) | -0.4% [-4.3%, 3.5%] |
| Procedure Success[7] | 95.7% (111/116) | 97.7% (85/87) | -2.0% [-6.9%, 2.8%] |

All six study deaths through 24 months occurred in the ≥65 years old group. This result is likely due to the number of comorbidities increasing with age. All other outcomes are comparable across groups.

**Race and Ethnicity**

The Bifurcation Cohort statistical analysis plan prespecified providing principal safety and effectiveness outcomes by race. Of the 204 patients completing 12-month follow-up, 158 (77%) identified as white and 12 (6%) were not identified by race. The available race and ethnicity information is too limited to comment on any potential associations. **Table 22** presents outcomes by race and ethnicity.

**Table 22. Primary and Secondary Endpoints by Race and Ethnicity**

| | American Indian or Alaska Native (N=0 Subjects N=0 Lesions) | Asian (N=8 Subjects N=13 Lesions) | Black or African American (N=11 Subjects N=13 Lesions) | Native Hawaiian or Other Pacific Islander (N=0 Subjects N=0 Lesions) | White (N=159 Subjects N=206 Lesions) | Other (N=15 Subjects N=18 Lesions) | Hispanic/ Latino (N=12 Patients N=18 Lesions) |
|---|---|---|---|---|---|---|---|
| **Primary Endpoint** | | | | | | | |
| TVF at 12 Months | NA | 0.0% (0/8) | 9.1% (1/11) | NA | 7.6% (12/158) | 0.0% (0/15) | 8.3% (1/12) |
| **Secondary Outcomes at 24 Months** | | | | | | | |
| Death | NA | 0.0% (0/7) | 0.0% (0/11) | NA | 3.8% (6/157) | 0.0% (0/13) | 0.0% (0/11) |
| Cardiac Death | NA | 0.0% (0/7) | 0.0% (0/11) | NA | 1.9% (3/157) | 0.0% (0/13) | 0.0% (0/11) |
| TVMI | NA | 0.0% (0/7) | 9.1% (1/11) | NA | 4.5% (7/157) | 0.0% (0/13) | 0.0% (0/11) |
| Clinically Driven TLR | NA | 0.0% (0/7) | 9.1% (1/11) | NA | 5.1% (8/157) | 0.0% (0/13) | 18.2% (2/11) |

| | American Indian or Alaska Native (N=0 Subjects N=0 Lesions) | Asian (N=8 Subjects N=13 Lesions) | Black or African American (N=11 Subjects N=13 Lesions) | Native Hawaiian or Other Pacific Islander (N=0 Subjects N=0 Lesions) | White (N=159 Subjects N=206 Lesions) | Other (N=15 Subjects N=18 Lesions) | Hispanic/ Latino (N=12 Patients N=18 Lesions) |
|---|---|---|---|---|---|---|---|
| Clinically Driven TVR | NA | 0.0% (0/7) | 9.1% (1/11) | NA | 5.7% (9/157) | 0.0% (0/13) | 0.0% (0/11) |
| Stent Thrombosis | NA | 0.0% (0/7) | 0.0% (0/11) | NA | 0.0% (0/157) | 0.0% (0/13) | 0.0% (0/11) |
| Device Success | NA | 92.3% (12/13) | 100.0% (13/13) | NA | 98.0% (199/203) | 94.4% (17/18) | 94.4% (17/18) |
| Lesion Success | NA | 100.0% (13/13) | 100.0% (13/13) | NA | 99.0% (201/203) | 94.4% (17/18) | 94.4% (17/18) |
| Procedure Success | NA | 100.0% (8/8) | 100.0% (11/11) | NA | 96.2% (152/158) | 92.9% (13/14) | 91.7% (11/12) |

**Diabetic Patients**

The Bifurcation Cohort statistical analysis plan prespecified providing principal safety and effectiveness outcomes by diabetes status. **Table 23** presents the primary endpoint by diabetes status. The presence of diabetes did not negatively impact outcomes in the Bifurcation Cohort.

**Table 23. TVF Through 12 Months With and Without Diabetes**

| | Diabetes (N=62 Patients N=89 Lesions) | No Diabetes (N=143 Patients N=177 Lesions) | Difference [95% CI] |
|---|---|---|---|
| **TVF at 12 Months** | 3.3% (2/61) | 8.4% (12/143) | -5.1% [-11.5%, 1.3%] |

**True vs Non-True Bifurcations**

The Bifurcation Cohort statistical analysis plan prespecified providing principal safety and effectiveness outcomes by true vs non-true bifurcation status per Medina classification. True bifurcations are those with significant stenosis in both primary

and side branch vessels. **Table 24** presents the primary endpoint and acute success measure by true vs non-true bifurcation status as assessed by the angiographic core lab. There was a slight trend for true bifurcation lesions to experience less lesion and procedure success, but success rates overall were still high.

**Table 24. Outcomes by True vs Non-True Bifurcations**

| | True Bifurcation (N=62 Patients N=88 Lesions) | Non-True Bifurcation (N=120 Patients N=147 Lesions) | Difference [95% CI] |
|---|---|---|---|
| TVF at 12 Months | 8.1% (5/62) | 6.7% (8/119) | 1.3% [-6.8%, 9.5%] |
| **Acute Success** | | | |
| Device Success | 96.6% (85/88) | 97.3% (143/147) | -0.7% [-5.3%, 3.9%] |
| Lesion Success | 96.6% (85/88) | 100.0% (147/147) | -3.4% [-7.2%, 0.4%] |
| Procedure Success | 93.5% (58/62) | 97.5% (117/120) | -4.0% [-10.7%, 2.8%] |

**Provisional Stenting: Single Stent vs Two Stents**

The Bifurcation Cohort enrollment criteria specified that patients with planned two-stent bifurcation approaches were to be excluded. However, provisional stenting does sometimes require the unplanned use of a second stent and a limited number of bifurcation lesions were treated with stents in both the main and side branches in the study. **Table 25** lists outcomes from the 7 patients/13 lesions treated with a two-stent approach vs patients treated with a single stent approach. The TVF event seen in the two-stent approach subgroup was an MI that occurred prior to hospital discharge, which is the same event preventing a 100% procedure success rate.

**Table 25. Outcomes by Single vs Two Stent Approach**

| | Single Stent Approach (N=197 Patients N=250 Lesions) | Two Stent Approach (N=7 Patients N=13 Lesions) | Difference [95% CI] |
|---|---|---|---|
| TVF at 12 Months | 6.6% (13/196) | 14.3% (1/7) | -8.2% [-34.3%, 18.0%] |
| **Acute Success** | | | |
| Device Success | 97.2% (243/250) | 100.0% (13/13) | -2.8% [-4.8%, -0.8%] |
| Lesion Success | 98.8% (247/250) | 100.0% (13/13) | -1.2% [-2.5%, 0.1%] |

| | Single Stent Approach (N=197 Patients N=250 Lesions) | Two Stent Approach (N=7 Patients N=13 Lesions) | Difference [95% CI] |
|---|---|---|---|
| Procedure Success | 96.9% (190/196) | 85.7% (6/7) | 11.2% [-14.8%, 37.3%] |

4. Poolability Analyses

As the Bifurcation Cohort combined patients from the US and Europe, the study protocol prespecified that a poolability analysis be conducted to determine if baseline characteristics were sufficiently homogenous to combine patients from different regions. Assessment of baseline characteristics showed US patients were older and had a higher worst CCS class than patients outside the US (OUS). However, these differences did not impact poolability of the data after propensity score adjustment. **Table 26** shows the difference in the primary endpoint by region. The CI is adjusted by stratification into five groups using quintile propensity scores, based on lesion length, baseline RVD, age, sex, diabetes, history of MI, and worst CCS class as the confounding variables.

**Table 26. TVF at 12 Months for US and OUS Patients**

| US (N=167 Patients) | OUS (N=38 Patients) | Difference: US - EU | Adjusted Difference [85% CI] |
|---|---|---|---|
| 5.4% (9/166) | 13.2% (5/38) | -7.7% | -6.5% [-14.0%, 0.9%] |

While the sample size is small, the OUS TVF rate was higher than the US TVF rate. However, this does not raise a concern for the performance of the Onyx DES in US patients.

A homogeneity analysis across sites was also performed. A logistic regression model with the primary endpoint as the dependent variable and the sites as independent variables showed no issues of poolability between investigational sites for the primary endpoint.

An assessment of the poolability of the 190 prospectively enrolled patients with the 15 qualifying patients re-consented from the larger PAS was also performed. There were no significant differences in baseline characteristics between these two groups. The two groups did differ in TVF rates at 12 months – the prospectively enrolled group had a rate of 7.4%, while the re-consented group had a rate of 0% (no events). However, given the small size of the re-consented group, just one patient experiencing a TVF event would have raised the rate to 6.7%.

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 pivotal clinical study included 210 investigators of which 1 was the spouse of a full-time or part-time employee of the sponsor and 7 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: 1
- Significant payment of other sorts: 10
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: 4

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. 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.

## XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The principal safety and effectiveness information for the Resolute Onyx and Onyx Frontier Zotoralimus-Eluting Coronary Stent Systems is derived from preclinical studies and from the Bifurcation Cohort clinical trial.

Preclinical testing performed during the design and development of the Onyx DES and reviewed under the original PMA confirmed the product design characteristics, specifications, and intended use. New preclinical testing performed to support the use of the stent in non-left main bifurcation lesions treated using a provisional stenting strategy included FEA analysis, coating durability, and acute particulate evaluation.

### A. Effectiveness Conclusions

The results from the Bifurcation Cohort demonstrated that, in patients with non-left main bifurcation lesions treated using a provisional stenting strategy, the rate of target vessel failure (a composite endpoint including both safety and effectiveness outcomes) at 12 months (6.9%) was shown to be below the prespecified performance goal (24.5%).

Other measures of effectiveness were generally in line with expectations for a current generation DES. Clinically driven TVR was 3.4% at one year and 5.5% at two years. Clinically driven TLR was 2.9% at one year and 4.5% at two years. When examining acute success of the stenting procedure, overall measures were also acceptable. Device, lesion, and procedure success rates were high for both true and non-true bifurcation lesions.

These endpoints are clinically meaningful and commonly used in coronary stent trials. The totality of the available effectiveness data supports the conclusion that the Onyx DES is effective for its intended use.

## B. Safety Conclusions

The risks of the Onyx DES are based on non-clinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above.

No safety signals of concern were identified from a review of serious adverse events and CEC-adjudicated events. Serious adverse events were of similar type and frequency to those previously reported for other US-approved coronary stents. No CEC-adjudicated unanticipated device-related adverse events occurred during the Bifurcation Cohort study.

The TVF composite endpoint of the Bifurcation Cohort included two safety outcomes, rates of cardiac death and TVMI at 12 months. The rate of cardiac death at one year was 1.5%, which is slightly higher than rates seen in recent trials (generally <1%) but in line with expectations for the more complex patient population studied. At two years, there were no additional cardiac deaths, and only 2 additional TVMI events. In addition, no probable or definite stent thrombosis events occurred through two years of follow up.

The rate of TVMI (as defined by the 3rd UDMI) was 2.9%, with 50% of TVMI occurring peri-procedurally. The MI definition was changed mid-study by the applicant; using the original Extended Historical definition, the rate of TVMI was 12.7% (26/204) with 88% of TVMI occurring peri-procedurally. The definition change was justified by the applicant's desire to use a definition that accounted for the increased use of troponin by study sites. How to best account for the increased use of more sensitive biomarkers by study sites when conducting interventional trials is an ongoing problem, and the applicant's decision to switch to the 3rd UDMI definition was reasonable, particularly because the clinical significance of the additional events detected by the Extended Historical definition is debated. When examining patient-level data and CEC adjudication decisions, there is no evidence of MI events beyond what would be expected when treating lesions of similar complexity.

## C. Benefit-Risk Determination

The probable benefits of the device when used to treat non-left main bifurcation lesions using a provisional stenting strategy are based on data collected in the RESOLUTE ONYX PAS Bifurcation Cohort study conducted to support PMA Supplement approval as described above.

The probable benefits of the Onyx DES when used to treat non-left main bifurcation lesions are the same as those of coronary stenting in general. Patients treated with the Onyx DES had immediate increases to their coronary luminal diameter. In comparison to treatment with medical therapy, PCI has been shown to reduce the incidence of angina and increase quality of life.

The probable risks of the device are also based on data collected in the RESOLUTE ONYX PAS Bifurcation Cohort study conducted to support PMA Supplement approval as described above. There were no procedure-related risks associated with the use of the Onyx DES for the treatment of bifurcation lesions that would not be expected with any other coronary stent system. Please refer to Section VIII: Potential Adverse Effects of the Device on Health.

Additional factors to be considered in determining probable risks and benefits for the Onyx DES include:

Another factor to be considered is the availability of alternative treatments. Coronary artery disease can be accompanied by symptomatic chest pain or silent ischemia that affects patients' quality of life. Coronary artery disease 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 coronary artery disease include medical therapy, PCI, and coronary artery bypass graft 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.

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 treatment of non-left main bifurcation lesions utilizing the provisional bifurcation stenting technique, 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.

## XIII. CDRH DECISION

CDRH issued an approval order on September 15, 2022.

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

## XIV. 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.

## XV. REFERENCES

Alkhouli, M., Alqahtani, F., Kalra, A., et al. (2020). Trends in Characteristics and Outcomes of Hospital Inpatients Undergoing Coronary Revascularization in the United States, 2003-2016. *JAMA Network Open*, 3(2):e1921326.