

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug-Coated Balloon (DCB) Percutaneous Transluminal Angioplasty Catheter

Device Trade Name: IN.PACT™ Admiral™ Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter

Device Procode: ONU

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

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA Number): P140010/S015
(PMA) Number

Date of FDA Notice of Approval: September 7, 2016

The original PMA (P140010) was approved on December 30, 2014 and is indicated for percutaneous transluminal angioplasty, after pre-dilatation, of *de novo* or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the IN.PACT™ Admiral™ Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter to treat in-stent restenotic (ISR) lesions.

II. INDICATIONS FOR USE

The IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of *de novo*, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

III. CONTRAINDICATIONS

The IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter is contraindicated for use in:

- coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries

- patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
- patients with known allergies or sensitivities to paclitaxel
- women who are breastfeeding, pregnant, or are intending to become pregnant, or men intending to father children. It is unknown whether paclitaxel will be excreted in human milk and whether there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the IN.PACT™ Admiral™ Paclitaxel-coated Percutaneous Transluminal Angioplasty Balloon Catheter labeling.

V. DEVICE DESCRIPTION

The IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter, hereafter referred to as the IN.PACT Admiral DCB, is an over-the-wire balloon catheter with a drug coated balloon at the distal tip (see **Figure 1**).

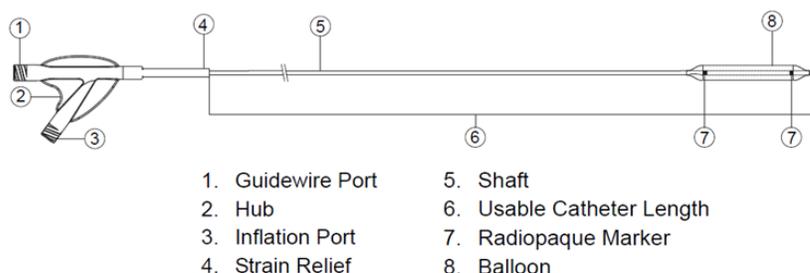


Figure 1: Schematic of the IN.PACT Admiral DCB

PTA Catheter Component

The IN.PACT Admiral DCB will be available in balloon lengths ranging from 20 mm to 150 mm, balloon diameters ranging from 4.0 mm to 7.0 mm, and will be offered in catheter effective lengths of 80 cm and 130 cm. The IN.PACT Admiral DCB is compatible with 0.035” guidewires. Devices are compatible with 5F (for the 4.0 mm balloon diameter), 6F (for the 5.0-6.0 mm balloon diameters), and 7F (for the 7 mm balloon diameter) introducer sheaths. The IN.PACT Admiral DCB product matrix is provided in **Table 1**.

Table 1: IN.PACT Admiral DCB Product Matrix

| Diameter (mm) | Balloon Length (mm) | | | | | | Balloon Wrap |
|---------------|---------------------|----|----|----|-----|-----|--------------|
| | 20 | 40 | 60 | 80 | 120 | 150 | |
| 4.0 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 folds |
| 5.0 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| 6.0 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| 7.0 | ✓ | ✓ | ✓ | ✓ | --- | --- | |

“✓” indicates sizes commercialized with IN.PACT Admiral DCB product in the U.S.
 “---” indicates size not offered with IN.PACT Admiral DCB product.
 All sizes are offered in both 80 cm and 130 cm catheter useable lengths.
 The device is compatible with a 0.035” guide wire.

Drug Components

The IN.PACT Admiral DCB is coated with the FreePac® coating solution, which is a proprietary coating with a nominal drug dose density of 3.5 µg of paclitaxel per mm² of the expanded balloon surface. The FreePac coating contains a hydrophilic excipient (urea) which facilitates the release and transfer of the active pharmaceutical ingredient (paclitaxel) into the arterial vessel wall. Additionally, the FreePac solution contains two solvents, tetrahydrofuran (THF) and pyrogen-free water, which are used during the FreePac formulation process but evaporate off the balloon surface after the FreePac coating is applied.

Based on the nominal drug dose density of 3.5 µg/mm², the total amount of paclitaxel for each balloon size is provided in **Table 2**.

Table 2: Nominal Paclitaxel Content by Balloon Size

| IN.PACT Admiral DCB Balloon Size (mm) | Nominal Paclitaxel Content (µg) |
|--|--|
| 4.0 x 20 | 1089 |
| 4.0 x 40 | 1969 |
| 4.0 x 60 | 2848 |
| 4.0 x 80 | 3728 |
| 4.0 x 120 | 5487 |
| 4.0 x 150 | 6807 |
| 5.0 x 20 | 1454 |
| 5.0 x 40 | 2553 |
| 5.0 x 60 | 3653 |
| 5.0 x 80 | 4752 |
| 5.0 x 120 | 6951 |
| 5.0 x 150 | 8601 |
| 6.0 x 20 | 1850 |
| 6.0 x 40 | 3170 |
| 6.0 x 60 | 4489 |
| 6.0 x 80 | 5809 |
| 6.0 x 120 | 8448 |
| 6.0 x 150 | 10427 |
| 7.0 x 20 | 2279 |
| 7.0 x 40 | 3819 |
| 7.0 x 60 | 5358 |
| 7.0 x 80 | 6897 |

Active Pharmaceutical Ingredient (API) - Paclitaxel

The API of the IN.PACT Admiral DCB is paclitaxel. Paclitaxel is a FDA-approved drug, indicated for the treatment of multiple cancers including breast and ovarian cancer. The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division. The CAS Registry number of paclitaxel is 33069-62-4. The chemical name is (2*a*R-(2*aa*,4*β*,4*aβ*,6*β*,9*a*(*α* R*,*β*S*),11*a*,12*a*,12*ba*))-*β*-(Benzoylamino)-*α*-hydroxybenzenepropanoic acid 6,12*b*-bis(acetyloxy)-12-(benzoyloxy)-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca(3,4)benz(1,2-*b*)oxet-9-yl ester and the chemical formula is C₄₇H₅₁NO₁₄. The chemical structure of paclitaxel is illustrated in **Figure 2** below.

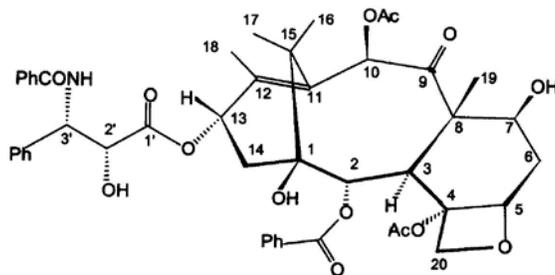


Figure 2: The Chemical Structure of Paclitaxel

Excipient

The FreePac coating contains urea, an excipient used to facilitate the release and transfer of the paclitaxel drug substance from the balloon to the vessel wall upon balloon inflation. The chemical structure of urea is shown in **Figure 3** below.

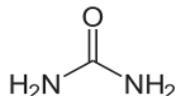


Figure 3: The Chemical Structure of Urea

Mechanism of Action

The IN.PACT Admiral DCB's primary mode of action is mechanical dilatation of *de novo*, restenotic, or in-stent restenotic lesions by means of percutaneous transluminal angioplasty, with a secondary action of inhibition of restenosis (caused by the proliferative response to the PTA) through the application of paclitaxel to the vessel wall.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of *de novo*, restenotic, and in-stent restenotic lesions in the superficial femoral and proximal popliteal arteries:

- Non-invasive (conservative) treatment (risk factor modification, exercise, and/or drug therapy)
- Minimally invasive treatment (balloon angioplasty, bare metal or drug-eluting stent, cutting/scoring balloons, or atherectomy)

- Surgical treatment (surgical bypass)

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

The IN.PACT Admiral DCB received CE Mark on March 12, 2009 and the original PMA (P140010) was approved on December 30, 2014. CE Mark approval was received for the treatment of in-stent restenosis on January 9, 2015. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

The IN.PACT Admiral DCB is commercially available in Afghanistan, Albania, Algeria, Angola, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Bolivia, Bosnia & Herzegovina, Botswana, Brazil, Brunei, Bulgaria, Burundi, Cambodia, Cape Verde, Caribbean Islands, Chad, Chile, Colombia, Comoros, Congo, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Equator Guinea, Estonia, Finland, France, Gambia, Georgia, Germany, Greece, Guatemala, Guinea, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Jordan, Kazakhstan, Kosovo, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lesotho, Libya, Liechtenstein, Lithuania, Luxemburg, Macau, Madagascar, Malawi, Malaysia, Malta, Mauritius, Mexico, Morocco, Mozambique, Myanmar, Namibia, Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Palestine, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Rwanda, Saint Helena, Saudi Arabia, Senegal, Serbia, Seychelles, Singapore, Slovakia, Slovenia, Somali, South Africa, South Korea, Spain, Sudan, Swaziland, Sweden, Switzerland, Syria, Taiwan, Thailand, Togo, Trinidad and Tobago, Tunisia, Turkey, Turkmenistan, Uganda, Ukraine, United Arab Emirates, United Kingdom, United States of America, Uruguay, Venezuela, Vietnam, Yemen, Zambia, and Zimbabwe.

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
- allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (materials, drugs, and excipients)
- amputation/loss of limb
- arrhythmias
- arterial aneurysm
- arterial thrombosis
- arteriovenous (AV) fistula

- death
- dissection
- embolization
- fever
- hematoma
- hemorrhage
- hypotension/hypertension
- inflammation
- ischemia or infarction of tissue/organ
- local infection at access site
- local or distal embolic events
- perforation or rupture of the artery
- pseudoaneurysm
- renal insufficiency or failure
- restenosis of the dilated artery
- sepsis or systemic infection
- shock
- stroke
- systemic embolization
- vessel spasms or recoil
- vessel trauma which requires surgical repair

Potential complications of peripheral balloon catheterization, which may result in adverse effects, include, but are not limited to:

- balloon rupture
- detachment of a component of the balloon and/or catheter system
- failure of the balloon to perform as intended
- failure to cross lesion

Although systemic effects are not anticipated, potential adverse effects not captured above that may be unique to the paclitaxel drug coating include, but are not limited to:

- allergic/immunologic reaction
- alopecia
- anemia
- gastrointestinal symptoms
- hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- hepatic enzyme changes

- histologic changes in the vessel wall, including inflammation, cellular damage, or necrosis
- myalgia/arthralgia
- myelosuppression
- peripheral neuropathy

For the specific adverse events that occurred in the clinical study, please see **Table 9**.

IX. SUMMARY OF NONCLINICAL STUDIES

All the laboratory, animal, shelf life and stability testing previously performed and provided in P140010 and supplements are applicable to and support the use of the IN.PACT Admiral DCB for the treatment of in-stent restenosis in the superficial femoral artery and popliteal arteries. The SSED containing the pre-clinical studies to support the *de novo* and restenotic lesions in native arteries is available on the CDRH website. No changes have been made to the product design or specifications. Confirmatory bench testing was performed on the IN.PACT Admiral DCB to support the use within a stent (constrained environment). An overview of the testing performed specific to in-stent restenosis (ISR) is provided in **Table 3** below.

Table 3: Summary of Testing Performed for ISR on the IN.PACT Admiral DCB

| Test | Testing Summary and/or Objective | Acceptance Criteria (Specification) | Pass/Fail |
|-------------------------------------|--|---|-------------------------------|
| Balloon Rated Burst Pressure | Determine the minimum burst strength of the catheter and calculate the rated burst pressure (RBP) in a constrained environment | Devices will not fail at or below the rated burst pressure of 14 atm. | Pass |
| Balloon Fatigue | Determine that balloons will sustain 10 inflations to RBP in a constrained environment | Samples will withstand 10 cycles at rated burst pressure. | Pass |
| Particulate | Particulate levels measured for the IN.PACT Admiral DCB when deployed within a stent | For characterization only. | N/A (For Information Only) |
| Coating Integrity | Coating Integrity was performed in order to verify no unintended delamination or degradation of the coating | For characterization only. | N/A (For Information Only) |

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous transluminal angioplasty, after appropriate vessel preparation, of in-stent restenotic lesions with lengths up to 180 mm in superficial

femoral or popliteal arteries with reference vessel diameters of 4-7 mm with the IN.PACT Admiral DCB in Europe (Austria, Belgium, Canada, Egypt, Germany, Hungary, Italy, The Netherlands, Poland, Singapore, Slovakia, South Korea, and Switzerland). Data from this clinical study (“DCB ISR Cohort”) were retrospectively compared to standard PTA data (“PTA ISR Comparator”) from 23 US sites employing propensity score adjustments in the IN.PACT Admiral DCB ISR Clinical Evaluation, which were the basis for the Panel Track Supplement approval decision. A summary of this clinical evaluation is presented below.

A. Study Design

For the DCB ISR Cohort, patients were treated in the IN.PACT Global Study between June 6, 2012 and December 16, 2013 at 31 investigational sites outside the U.S. (OUS). A total of 164 DCB subjects from this study met the inclusion criteria of the IN.PACT Admiral DCB ISR Clinical Evaluation, as described below. For the PTA ISR Comparator, patients were treated at 23 participating centers from the Society of Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry between 2011 and 2014. More than 500 patients were screened for eligibility and a total of 153 PTA subjects met the inclusion criteria, as described below.

The clinical evaluation was an observational, propensity score-adjusted, comparative analysis to investigate the safety and effectiveness of the IN.PACT Admiral DCB in subjects with ISR in the superficial femoral artery (SFA) or popliteal artery. The objective of this analysis was to demonstrate that the primary effectiveness endpoint of 12-month target lesion revascularization (TLR) was significantly lower in the DCB ISR Cohort when compared to the PTA ISR Comparator group when treating ISR.

Due to the nature of this non-randomized, retrospective comparison, it was necessary to adjust for expected baseline differences between the subjects in the two groups to ensure objectivity of the clinical evaluation design and the validity of the results. A propensity score analysis was performed using clinically relevant baseline characteristics specified in **Table 6** below. All of the variables listed in this table were included in the propensity score calculation except TASC lesion type, which was excluded due to a missing data rate that exceeded the pre-specified cutoff (20%).

For the primary effectiveness endpoint of 12-month TLR, the treatment (DCB ISR Cohort) and control (PTA ISR Comparator) groups were compared in a superiority format. The hypothesis tested was:

H_0 : 12-month TLR rate in subjects in DCB ISR Cohort (p_T) is equal to or higher than that for subjects in PTA ISR Comparator (p_C).

$$H_0: p_T \geq p_C$$

H_A : 12-month TLR rate in subjects in DCB ISR Cohort (p_T) is lower than that for subjects in PTA ISR Comparator (p_C).

$$H_A: p_T < p_C$$

1. Clinical Inclusion and Exclusion Criteria

For inclusion in the IN.PACT Admiral DCB ISR Clinical Evaluation, subjects in the DCB ISR Cohort were required to meet the following inclusion criteria, as specified in the IN.PACT Global Study Clinical Investigation Plan:

1. Age \geq 18 years or minimum age as required by local regulations.
2. Subject with documented diagnosis of peripheral arterial disease (PAD) in the superficial femoral artery (SFA) and/or popliteal artery (PA) (including P1, P2, P3) classified as Rutherford class 2-3-4.
3. Angiographically documented single or multiple lesions/occlusions (*de novo* or re-stenotic lesion(s) or in-stent restenosis within the target vessels with a minimum lesion length of 2 cm including bilateral disease if both limbs are treated within 35 days.
4. Positive diagnostic indication for PTA with a DCB in accordance with the Instructions For Use (IFU) of the IN.PACT Admiral DCB.
5. Adequate distal run-off to the ankle (at least one native calf vessel [posterior tibial, anterior tibial, or peroneal arteries] is patent, defined as \leq 50% diameter stenosis) either pre-existing or successfully reestablished prior to target lesion treatment.
6. Adequate inflow (\leq 50% diameter stenosis) either pre-existing or successfully re-established prior to target lesion treatment.
7. Female subjects of childbearing potential must have a negative pregnancy test \leq 7 days before enrollment.
8. Signed and dated Patient Informed Consent (PIC) form.
9. Ability and willingness to comply with the clinical investigation plan (CIP).
10. Life expectancy, in the Investigator's opinion, of at least 12 months.

Additional inclusion criteria specific to this analysis included the following:

1. Single-limb and single-lesion treatment during index procedure
2. *De novo* or recurrent ISR
3. Rutherford classification 2, 3, or 4
4. Target lesion in the SFA and/or popliteal artery

For inclusion in the IN.PACT Admiral DCB ISR Clinical Evaluation, subjects in the PTA ISR Comparator were required to meet the following inclusion criteria:

1. Must be a participating center in the VQI and have peripheral vascular intervention (PVI) procedures entered into M2S's PATHWAYS clinical data performance platform (database)
2. Procedures with standard PTA treatment of SFA and/or popliteal artery in one leg only in patients with a history of prior infrainguinal PVI treatment
3. Concomitant treatment of iliac or tibial lesions in same leg as SFA/popliteal treatment is allowed

4. If either or both SFA and popliteal treatments were intervened for ISR, the procedure will be included and subsequent analyses will focus only on the treated leg
 - a) If both SFA and popliteal ISR are treated, subsequent failure of either will be treated as failure of the treatment
 - b) If either one of the SFA or popliteal lesion represent ISR and the other does not, a sub-set analysis can be performed of ISR treatment only, since outcome of each artery segment is categorized separately
 - c) If a patient had previous PTA treatment in both legs, but is only having one leg, not both, re-treated as PVI with PTA, this patient will be included. Only the leg that contains ISR lesion will be included as target leg, and then refer to item #a and #b for event determinations
5. Includes only those patients who have claudication or rest pain
6. The first treatment type must be PTA and the second treatment type may be None, PTA, or Stent

Subjects in the DCB ISR Cohort were not included in the IN.PACT Admiral DCB ISR Clinical Evaluation if they met any of the following exclusion criteria, as specified in the IN.PACT Global Study Clinical Investigation Plan:

1. High probability of non-adherence to CIP follow-up requirements.
2. Failure to successfully cross the target lesion with a guide wire (successful crossing means tip of the guide wire distal to the target lesion in the absence of flow limiting dissections or perforations).
3. Lesion within or adjacent to an aneurysm or presence of a popliteal aneurysm.
4. Acute or sub-acute thrombus in the target vessel.
5. Previous bypass surgery to the target lesion.
6. Target lesion also requires treatment with alternative therapy such as drug-eluting stent (DES), laser, atherectomy, cryoplasty, cutting/scoring balloon, brachytherapy.
7. Plan for surgical or interventional procedure within 30 days after the study procedure (except for bilateral target limb treatment).
8. Known allergies or sensitivities to heparin, aspirin, other anticoagulant/anti-platelet therapies, and/or paclitaxel.

Subjects in the PTA ISR Comparator were not included in the IN.PACT Admiral DCB ISR Clinical Evaluation if they met any of the following exclusion criteria:

1. Procedures with bilateral simultaneous SFA or popliteal treatment
2. Subsequent procedures to treat ISR in the opposite leg of the same patient will be excluded, so that the unit of analysis is the initially treated leg in each patient.

3. Procedures with technical failure of iliac or tibial lesions in same leg as SFA/popliteal treatment (e.g., unsuccessful treatment of inflow or outflow disease due to residual stenosis) will be excluded
 4. Patients who report a history of acute ischemia and who have not been treated in the past
 5. Patients who report they are asymptomatic
 6. Patients who have a history of tissue loss in the target limb
 7. Patients who have not had at least one post-index procedure follow-up visit
2. Follow-up Schedule

Subjects in the DCB ISR Cohort were followed per the IN.PACT Global Study Clinical Investigation Plan protocol requirements (1, 6, and 12 months then annually up to 5 years). Subjects in the PTA ISR Comparator were followed per the standard of care at the centers participating in the SVS VQI Registry.

Preoperative and postoperative evaluations of the DCB ISR cohort are summarized in **Table 4** below.

Table 4: IN.PACT Global Study Follow-up Evaluation Schedule

| Test/ Evaluation | Baseline | Index Procedure | Discharge (or < 48h post- proc.) | 30 days ±14d Phone/ Visit | 6 mo ±30d Visit | 12 mo ±60d Visit | 24 mo ±60 d Visit | 36 mo ±60d Visit | 48 mo ±60d Phone | 60 mo ±60d Phone | Unscheduled Visit (Ischemic events in the target limb) |
|--|----------------|--------------------|---|------------------------------------|-----------------------|------------------------|-------------------------|------------------------|------------------------|------------------------|---|
| Informed Consent | X | | | | | | | | | | |
| Inclusion/ Exclusion Criteria | X ¹ | X | | | | | | | | | |
| Medical History | X ¹ | | | | | | | | | | |
| Physical Examination | X ¹ | | X | X ⁸ | X | X | X | X | | | X |
| Blood Sampling for Routine Lab Testing* | X ¹ | | X | | X | X | X | X | | | X |
| Concomitant Medication** | X ¹ | X | X | X | X | X | X | X | | | X |
| ABI | X ¹ | | X ³ | | X | X | X | X | | | X |
| DUS (Clinical Cohort)* | | | X | | X | X | X | X | | | X |
| DUS (Imaging Cohort) ⁴ | | | | | | X | | | | | X |
| Angiography | | X ⁵ | | | | | | | | | X ⁶ |
| Pregnancy Test (βHCG) | X ² | | | | | | | | | | |
| Rutherford | X ¹ | | | | X | X | X | X | | | X |
| EQ5D / WIQ | X ¹ | | | | X | X | X | X | | | X |
| 6MWT with Vital Signs* | X ¹ | | | | X | X | X | X | | | X |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X |
| Health Economics data ⁷ | | X | | X | X | X | X | X | X | X | X |

(1) Within 14 days prior to index-procedure.

(2) Women of childbearing potential must have a negative pregnancy test within 7 days prior to enrollment.

(3) Post-index procedure ABI may be performed either at discharge or within 30 days, as per institution’s standard of care.

(4) For subjects who are enrolled into the imaging cohort, post-index procedure DUS of all target lesions at 12 months and at the time of re-intervention if it occurs prior to the 12-month follow-up are required.

(5) Copy of the angiography to be submitted to the Sponsor.

(6) Angiography during unscheduled follow-up visits only if required as per institution’s standard of care.

(7) In addition to clinical data elements, the study will collect utilization metrics.

(8) In case the subject reports symptoms suggestive of an embolic event during the 30-day phone call, the subject will be asked to return to the hospital for a physical examination. Failure to conduct a physical exam will result in a protocol deviation.

* Lab testing type, DUS (clinical cohort) and the 6-minute walk test (6MWT) with vital signs are performed per institution’s standard of care. Lab testing should include:

White Blood Count (WBC), Hemoglobin, Hematocrit, Platelet Count, Serum creatinine, Partial Thromboplastin Time (PTT), INR (International Normalized Ratio), HbA1c, Low Density Lipoprotein (LDL) and Thyroid Stimulating Hormone (TSH)).

** Only protocol-required medication need to be collected. NOTE: Periodic test, calibration and maintenance of all the equipment’s used for study assessments are required according to local protocols per Institution’s standards

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

3. Endpoints

With regard to safety and effectiveness, the primary effectiveness endpoint of the powered statistical analysis comparing ISR outcomes in the DCB ISR Cohort and the PTA ISR Comparator was the incidence of TLR through 12 months.

Some of the clinically-relevant secondary endpoints assessed included:

1. All-cause mortality at 30 days, 6 months, and 12 months.
2. Any TVR at 30 days, 6 months, and 12 months.
3. Major target limb amputation at 30 days, 6 months, and 12 months.
4. Time to first TLR through 12 months post-index procedure.
5. Time to all-cause mortality through 12 months post-index procedure.

With regard to success criteria, the study was deemed successful if it demonstrated superiority of the DCB ISR Cohort on the 12-month primary effectiveness endpoint of target lesion revascularization compared to the PTA ISR Comparator

B. Accountability of PMA Cohort

A total of 164 DCB subjects from the IN.PACT Global Study met the inclusion criteria and comprised the DCB ISR Cohort, while a total of 153 PTA subjects from the SVS VQI registry met the inclusion criteria and comprised the PTA ISR Comparator.

Follow-up compliance for the 12-month follow-up visits is presented in **Table 5** for the DCB ISR Cohort subjects. The rate of in-window follow-up visit completion at 12 months was 92.3%.

Table 5: Subject Follow-up Compliance (IN.PACT Global DCB ISR Cohort)

| Subject Compliance Characteristics | DCB ISR Cohort (N=164 Subjects) |
|--|------------------------------------|
| 12-Month Follow-up | |
| Eligible Subjects ^a | 155 |
| Death ^b | 1 |
| Withdrawal ^b | 8 |
| Follow-up Not Done | 7 |
| Follow-up Visit Within Window ^c | 143 |
| Follow-up Visit Out of Window ^c | 5 |
| Follow-up Compliance (%) ^d | 92.3% |

^aEligible subjects are all subjects who either have a follow-up visit form or are past due for their follow-up (beyond upper limit of window on study and did not exit the study before the upper limit of the window)

^bDeath and withdrawal are cumulative

^cWithin window visits are defined as: 12-month ± 60 days.

^dPercentage based on number of subjects who had follow-up visit within window divided by total number of eligible subjects
Site reported data

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for patients with in-stent restenosis in the US. **Table 6** below presents the baseline demographics and clinical characteristics for the 164 DCB ISR Cohort subjects and the 153 PTA ISR Comparator subjects. These 20 baseline variables were pre-specified as the covariates in the propensity score analysis.

Table 6: Baseline Demographics and Clinical Characteristics

| Baseline Characteristics | DCB ISR Cohort (N=164) | PTA ISR Comparator (N=153) | Propensity Score Adjusted p-value [†] |
|--|---------------------------|-------------------------------|---|
| Baseline Demographics | | | |
| Age | | | |
| Mean±SD (N) | 66.95±9.84 (163) | 66.79±11.23 (153) | 0.795 |
| Median (Q1, Q3) | 67.00 (60.00,74.00) | 66.00 (58.00,75.00) | |
| Range (Min, Max) | (39.00,86.00) | (44.00,89.00) | |
| Male | 72.6% (119/164) | 51.6% (79/153) | 0.536 |
| BMI | | | |
| Mean±SD (N) | 26.34±4.39 (164) | 28.21±6.06 (153) | 0.835 |
| Median (Q1, Q3) | 25.94 (23.63,28.57) | 28.00 (24.00,30.00) | |
| Range (Min, Max) | (16.46,43.26) | (13.00,50.00) | |
| Ankle-Brachial Index (ABI) | | | |
| Mean±SD (N) | 0.64±0.22 (147) | 0.70±0.41 (140) | 0.786 |
| Median (Q1, Q3) | 0.65 (0.51,0.77) | 0.64 (0.48,0.81) | |
| Range (Min, Max) | (0.00,1.43) | (0.00,2.00) | |
| Baseline Clinical Characteristics | | | |
| Hypertension | 83.4% (136/163) | 87.6% (134/153) | 0.972 |
| Diabetes | 36.6% (60/164) | 49.0% (75/153) | 0.920 |
| Insulin-dependent Diabetes | 16.5% (27/164) | 22.9% (35/153) | 0.946 |
| On Dialysis | 3.0% (5/164) | 1.3% (2/153) | 0.579 |
| Coronary artery disease | 20.5% (30/146) | 24.2% (37/153) | 0.964 |
| Current smoker | 36.0% (59/164) | 32.7% (50/153) | 0.915 |
| Previous limb amputation (major or minor) | 5.5% (9/164) | 4.6% (7/153) | 0.980 |
| Renal insufficiency (per serum creatinine ≥1.5 mg/dl) | 9.5% (14/147) | 9.9% (15/151) | 0.931 |
| Baseline Lesion and Procedural Characteristics | | | |
| TASC lesion type | | | 0.906 |
| A | 20.2% (21/104) | 30.7% (47/153) | |
| B | 30.8% (32/104) | 27.5% (42/153) | |
| C | 36.5% (38/104) | 30.1% (46/153) | |
| D | 12.5% (13/104) | 11.8% (18/153) | |
| Lesion length | | | |
| Mean±SD (N) | 17.59±10.49 (164) | 13.16±9.61 (151) | 0.735 |
| Median (Q1, Q3) | 16.00 (10.00,27.00) | 10.00 (6.00,20.00) | |
| Range (Min, Max) | (1.00,47.00) | (2.00,47.00) | |
| Total occlusion | 40.9% (67/164) | 68.7% (103/150) | 0.990 |
| Occluded lesion length | | | |
| Mean±SD (N) | 7.47±11.65 (164) | 7.87±9.40 (150) | 0.709 |
| Median (Q1, Q3) | 0.00 (0.00,10.50) | 4.00 (0.00,14.00) | |
| Range (Min, Max) | (0.00,42.00) | (0.00,45.00) | |
| Pre-op aspirin | 95.7% (157/164) | 83.0% (127/153) | 0.422 |
| Indication of Claudication - Rutherford Classification or equivalent | 87.8% (144/164) | 74.5% (114/153) | 0.633 |
| Lesion Location: SFA | 71.3% (117/164) | 86.9% (133/153) | 0.706 |

| Baseline Characteristics | DCB ISR Cohort (N=164) | PTA ISR Comparator (N=153) | Propensity Score Adjusted p-value [†] |
|--------------------------|---------------------------|-------------------------------|---|
| Provisional stent | 15.9% (26/164) | 33.3% (51/153) | 0.814 |

Numbers are % (counts/sample size) unless otherwise stated.
Categorical variables between groups were compared using the chi-squared test or Fisher's exact test as appropriate, and continuous variables were compared using Student's t-test.
Site reported data.
All of the variables in this table were included in the propensity score calculation except TASC lesion type due to a missing data rate that exceeded the pre-specified cutoff of 20%.
[†]The propensity score adjusted p-value was based on all subjects for each baseline variable. For each variable with missing values (<20%), a gender-specific imputation was performed by replacing the missing values of the variable with the gender-specific median observed value within each group.
p-values are not adjusted for multiplicity

D. Safety and Effectiveness Results

1. Primary Effectiveness Endpoint Analysis

The results of the powered statistical analysis comparing the 12-month primary endpoint between the DCB ISR Cohort and the PTA ISR Comparator are shown in **Table 7**.

The primary endpoint of the clinical evaluation was met, demonstrating superiority of the DCB ISR Cohort over the PTA ISR Comparator on the primary effectiveness endpoint of target lesion revascularization (TLR) at 12 months (10.13% vs. 35.92%, p<0.001).

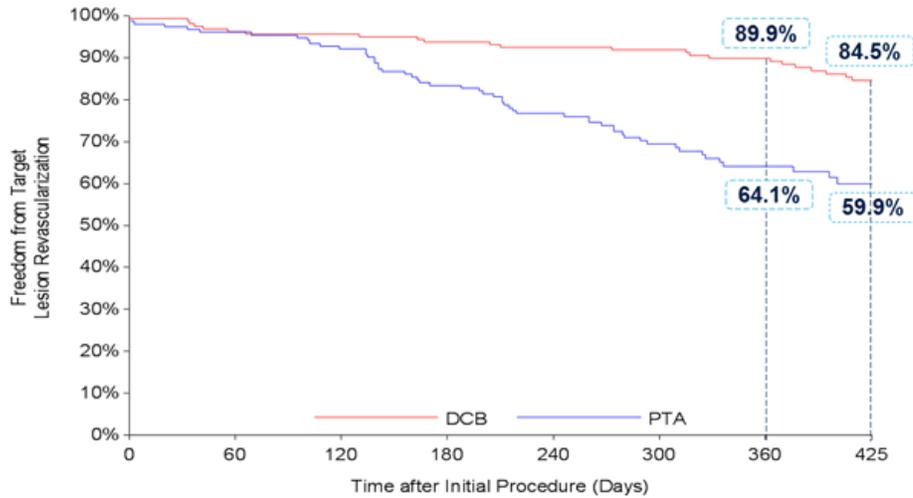
Table 7: Primary Effectiveness Endpoint Results

| Effectiveness Parameters | DCB ISR Cohort (N=164) | PTA ISR Comparator (N=153) | Hazard Ratio [95% CI] | p-value ^a |
|--|---------------------------|----------------------------------|-----------------------|----------------------|
| Target Lesion Revascularization at 12 Months | 10.13% (16) | 35.92% (51) | 0.258 [0.128, 0.517] | <0.001 |

Statistical references:

- Numbers are cumulative incidence % (number of failures) based on Kaplan-Meier method. CI – Confidence Interval
- Analysis sets: The primary analysis set was based on the intent-to-treat (ITT) principle. All subjects enrolled through the selection process specified in Statistical Analysis Plan were included as ITT subjects.
- ^aTo analyze the treatment differences between the DCB ISR Cohort and PTA ISR Comparator groups in the clinical/safety endpoints such as TLR, a propensity-quintile-stratified Cox proportional hazards model was employed, with time to event as the dependent variable and treatment group as the independent variable.

The Kaplan-Meier analysis of this primary effectiveness endpoint, presented as freedom from target lesion revascularization, is shown in **Figure 4**.



| | Target Lesion Revascularization | 0 | 1-60 | 61-120 | 121-180 | 181-240 | 241-300 | 301-360 | 361-425 |
|------------|---------------------------------|--------|--------|--------|---------|---------|---------|---------|---------|
| DCB | | | | | | | | | |
| | # Entered | 164 | 163 | 154 | 152 | 148 | 143 | 141 | 126 |
| | # Censored | 0 | 4 | 1 | 1 | 3 | 0 | 12 | 15 |
| | # Events | 1 | 5 | 1 | 3 | 2 | 1 | 3 | 7 |
| | % Survived | 99.39% | 96.27% | 95.65% | 93.75% | 92.47% | 91.82% | 89.87% | 84.53% |
| PTA | | | | | | | | | |
| | # Entered | 153 | 151 | 144 | 138 | 125 | 113 | 90 | 56 |
| | # Censored | 0 | 3 | 0 | 0 | 2 | 13 | 28 | 17 |
| | # Events | 2 | 4 | 6 | 13 | 10 | 10 | 6 | 3 |
| | % Survived | 98.69% | 96.07% | 92.06% | 83.39% | 76.66% | 69.40% | 64.08% | 59.94% |

Figure 4: Kaplan-Meier Plot - Event-free from Target Lesion Revascularization through 360 and 425 Days

2. Secondary Safety and Effectiveness Endpoints

The results of the secondary endpoints for the IN.PACT Admiral DCB ISR Clinical Evaluation are shown in **Table 8**.

In both the DCB ISR Cohort and the PTA ISR Comparator, there were high rates of acute success. Since the acute success definitions differed, these were not able to be directly compared, but the DCB ISR Cohort had high rates of device success (99.5%), procedural success (99.4%), and clinical success (98.8%), while the PTA ISR Comparator had a high rate of technical success (97.4%). The definitions of each of these endpoints are provided in the footnotes of **Table 8**.

Clinical safety and effectiveness outcomes were reported at 30 days, 6 months, and 12 months. All event rates were low in both groups at 30 days, but lower event rates were observed at 6 months and at 12 months for both the TLR and the target vessel revascularization (TVR) endpoints in the DCB ISR Cohort. The 12-month TVR rate was 11.41% in the DCB ISR Cohort compared to 38.07% in the PTA ISR Comparator.

There were no major target limb amputations in the DCB ISR Cohort and three major target limb amputations in the PTA ISR Comparator within 12 months. Lastly, there

was one death in the DCB ISR Cohort and no deaths in the PTA ISR Comparator within 12 months. One subject in the DCB ISR Cohort experienced a non-cardiac death at day 276 post-index procedure. The independent clinical events committee determined that the death was not device-related and not procedure-related.

Table 8: Secondary Safety and Effectiveness Endpoint Results

| | DCB ISR Cohort (N=164) | PTA ISR Comparator (N=153) |
|--|-----------------------------------|---|
| Effectiveness Parameters | | |
| Device Success ^a | 99.5% (364/366) | NA |
| Procedural Success ^a | 99.4% (163/164) | NA |
| Clinical Success ^a | 98.8% (162/164) | NA |
| Technical Success ^a | NA | 97.4% (149/153) |
| Safety Parameters | | |
| Cumulative complications within 30 days | | |
| Death (all-cause) | 0.00% (0) | 0.00% (0) |
| Target Vessel Revascularization | 0.61% (1) | 2.61% (4) |
| Major Target Limb Amputation | 0.00% (0) | 0.00% (0) |
| Target Lesion Revascularization | 0.61% (1) | 2.61% (4) |
| Cumulative complications within 180 days | | |
| Death (all-cause) | 0.00% (0) | 0.00% (0) |
| Target Vessel Revascularization | 6.88% (11) | 17.28% (26) |
| Major Target Limb Amputation | 0.00% (0) | 1.33% (2) |
| Target Lesion Revascularization | 6.25% (10) | 16.61% (25) |
| Cumulative complications within 360 days | | |
| Death (all-cause) | 0.65% (1) | 0.00% (0) |
| Target Vessel Revascularization | 11.41% (18) | 38.07% (54) |
| Major Target Limb Amputation | 0.00% (0) | 2.08% (3) |
| Other Major Secondary Endpoints at 12 Months (360 Days) | | |
| Time to all-cause mortality (days) | | |
| Mean±SD (N) | 276.00 (1) | -- |
| Median | 276.00 | -- |
| (Min, Max) | (276.00,276.00) | -- |
| Time to first TLR (days) | | |
| Mean±SD (N) | 148.44±115.25 (16) | 182.33±93.53 (51) |
| Median | 146.50 | 187.00 |
| (Min, Max) | (0.00,328.00) | (0.00,335.00) |

Endpoint definitions:

- Device success (assessed for DCB ISR Cohort only) defined as successful delivery, balloon inflation and deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP).
- Procedure success (assessed for DCB ISR Cohort only) defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by visual estimate.
- Clinical success (assessed for DCB ISR Cohort only) defined as procedural success without procedural complications (mortality, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.
- Technical success (assessed for PTA ISR Comparator only) defined as the ability to cross the lesion without resulting in occlusion and having residual stenosis ≤ 30% and resting systolic pressure gradient < 10 mmHg (if measured).

Statistical references:

- Numbers are cumulative incidence % (number of failures) based on Kaplan-Meier method unless otherwise stated.
- ^aNumbers are % (counts/sample size)
- Analysis sets: The primary analysis set was based on the intent-to-treat (ITT) principle. All subjects enrolled through the selection process specified in SAP Section 3.1 were included as ITT subjects.

3. Serious Adverse Events

A serious adverse event was defined in the IN.PACT Global Study protocol as an adverse event that led to death; led to serious deterioration in the health of the subject that resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect.

Table 9 provides a summary of serious adverse event rates by system-organ class (SOC) through 360 days occurring in the DCB ISR Cohort.

Table 9: Serious Adverse Event Rates by SOC and Preferred Term through 360 Days – IN.PACT Global DCB ISR Cohort Subjects

| Serious Adverse Event | DCB ISR Cohort (N=164 Subjects) |
|---|------------------------------------|
| Subjects with One or More Serious Adverse Events | 41.5% (68/164) |
| CARDIAC DISORDERS^a | 2.4% (4/164) |
| ACUTE MYOCARDIAL INFARCTION | 0.6% (1/164) |
| ATRIAL FIBRILLATION | 0.6% (1/164) |
| CONGESTIVE CARDIOMYOPATHY | 0.6% (1/164) |
| CORONARY ARTERY DISEASE | 0.6% (1/164) |
| MYOCARDIAL INFARCTION | 0.6% (1/164) |
| CONGENITAL, FAMILIAL AND GENETIC DISORDERS^a | 0.6% (1/164) |
| CONGENITAL CYSTIC KIDNEY DISEASE | 0.6% (1/164) |
| EYE DISORDERS^a | 1.2% (2/164) |
| CATARACT | 0.6% (1/164) |
| RETINAL ARTERY OCCLUSION | 0.6% (1/164) |
| GASTROINTESTINAL DISORDERS^a | 1.2% (2/164) |
| GASTRITIS | 0.6% (1/164) |
| OESOPHAGEAL HAEMORRHAGE | 0.6% (1/164) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS^a | 1.2% (2/164) |
| DEATH | 0.6% (1/164) |
| DEVICE BREAKAGE | 0.6% (1/164) |
| HEPATOBIILIARY DISORDERS^a | 1.2% (2/164) |
| ACUTE HEPATIC FAILURE | 0.6% (1/164) |
| CHOLECYSTITIS | 0.6% (1/164) |
| CHOLELITHIASIS | 0.6% (1/164) |
| INFECTIONS AND INFESTATIONS^a | 3.0% (5/164) |
| CLOSTRIDIUM DIFFICILE COLITIS | 0.6% (1/164) |
| GANGRENE | 0.6% (1/164) |
| GROIN INFECTION | 0.6% (1/164) |

Table 9: Serious Adverse Event Rates by SOC and Preferred Term through 360 Days – IN.PACT Global DCB ISR Cohort Subjects

| Serious Adverse Event | DCB ISR Cohort (N=164 Subjects) |
|--|------------------------------------|
| PILONIDAL CYST | 0.6% (1/164) |
| PNEUMONIA | 0.6% (1/164) |
| PSEUDOMEMBRANOUS COLITIS | 0.6% (1/164) |
| URINARY TRACT INFECTION | 0.6% (1/164) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS^a | 7.3% (12/164) |
| ARTERIAL RESTENOSIS | 2.4% (4/164) |
| IN-STENT ARTERIAL RESTENOSIS | 4.3% (7/164) |
| IN-STENT CORONARY ARTERY RESTENOSIS | 0.6% (1/164) |
| PERIPHERAL ARTERIAL REOCCLUSION | 0.6% (1/164) |
| VASCULAR PSEUDOANEURYSM | 1.2% (2/164) |
| INVESTIGATIONS^a | 0.6% (1/164) |
| INTERNATIONAL NORMALISED RATIO INCREASED | 0.6% (1/164) |
| METABOLISM AND NUTRITION DISORDERS^a | 1.2% (2/164) |
| DIABETES MELLITUS | 0.6% (1/164) |
| DIABETIC FOOT | 0.6% (1/164) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS^a | 3.7% (6/164) |
| BACK PAIN | 0.6% (1/164) |
| INTERVERTEBRAL DISC PROTRUSION | 0.6% (1/164) |
| MUSCULOSKELETAL DISORDER | 0.6% (1/164) |
| MYOFASCIAL PAIN SYNDROME | 0.6% (1/164) |
| PAIN IN EXTREMITY | 0.6% (1/164) |
| SPINAL COLUMN STENOSIS | 0.6% (1/164) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)^a | 3.7% (6/164) |
| LUNG NEOPLASM | 0.6% (1/164) |
| LUNG NEOPLASM MALIGNANT | 0.6% (1/164) |
| MALIGNANT NEOPLASM PROGRESSION | 0.6% (1/164) |
| NEOPLASM SKIN | 0.6% (1/164) |
| OESOPHAGEAL CARCINOMA | 0.6% (1/164) |
| PROSTATE CANCER RECURRENT | 0.6% (1/164) |
| NERVOUS SYSTEM DISORDERS^a | 2.4% (4/164) |
| CAROTID ARTERY STENOSIS | 0.6% (1/164) |
| CEREBROVASCULAR ACCIDENT | 0.6% (1/164) |
| FACIAL PALSY | 0.6% (1/164) |
| PARAESTHESIA | 0.6% (1/164) |
| RENAL AND URINARY DISORDERS^a | 1.2% (2/164) |

Table 9: Serious Adverse Event Rates by SOC and Preferred Term through 360 Days – IN.PACT Global DCB ISR Cohort Subjects

| Serious Adverse Event | DCB ISR Cohort (N=164 Subjects) |
|--|------------------------------------|
| BLADDER TAMPONADE | 0.6% (1/164) |
| NEPHROLITHIASIS | 0.6% (1/164) |
| RENAL COLIC | 0.6% (1/164) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS^a | 0.6% (1/164) |
| UTERINE POLYP | 0.6% (1/164) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS^a | 1.2% (2/164) |
| DYSPNOEA | 1.2% (2/164) |
| SURGICAL AND MEDICAL PROCEDURES^a | 0.6% (1/164) |
| LEG AMPUTATION | 0.6% (1/164) |
| VASCULAR DISORDERS^a | 25.0% (41/164) |
| ARTERIAL OCCLUSIVE DISEASE | 0.6% (1/164) |
| ARTERIAL STENOSIS LIMB | 0.6% (1/164) |
| ARTERIAL THROMBOSIS | 0.6% (1/164) |
| ARTERIAL THROMBOSIS LIMB | 3.0% (5/164) |
| ARTERIOSCLEROSIS OBLITERANS | 0.6% (1/164) |
| EMBOLISM | 0.6% (1/164) |
| FEMORAL ARTERIAL STENOSIS | 6.7% (11/164) |
| FEMORAL ARTERY OCCLUSION | 4.3% (7/164) |
| HAEMORRHAGE | 0.6% (1/164) |
| HYPERTENSION | 0.6% (1/164) |
| HYPERTENSIVE CRISIS | 0.6% (1/164) |
| INTERMITTENT CLAUDICATION | 3.7% (6/164) |
| PERIPHERAL ARTERIAL OCCLUSIVE DISEASE | 4.3% (7/164) |
| PERIPHERAL EMBOLISM | 0.6% (1/164) |
| PERIPHERAL ISCHAEMIA | 3.0% (5/164) |
| VESSEL PERFORATION | 0.6% (1/164) |
| Total Serious Adverse Events | 123 |

Numbers are % (counts/sample size) unless otherwise stated.

^aEvent verbatim terms are reported by sites. The events listed in this table are then coded using MedDRA version 13.0 and then stratified by System-Organ Class (SOC) and Preferred Term. Patients may be counted in this table more than once by Preferred Term, but are only counted once in the SOC summary line.

Site reported data.

4. Subgroup Analyses

Medtronic has analyzed the clinical evaluation results by the male and female gender subgroups. Both the male and female gender subgroups showed favorable clinical trends on the primary effectiveness endpoint of 12-month TLR (male subgroup: 8.72%

DCB vs. 32.94% PTA, and female subgroup: 14.08% DCB vs. 39.11% PTA). Favorable clinical trends were also noted for the secondary endpoint of 12-month TVR (male subgroup: 10.48% DCB vs. 34.67% PTA, and female subgroup: 14.08% DCB vs. 41.76% PTA).

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 clinical study included 146 investigators of which none were full-time or part-time employees of the sponsor and 3 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
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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 System 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

A. Effectiveness Conclusions

Non-clinical and clinical testing support the expansion of the indications for the treatment of in-stent restenosis. A majority of the preclinical evaluations were leveraged from the original PMA and subsequent supplements. Additional bench testing was performed to demonstrate that this device can be used safely and effectively for in-stent restenosis. The IN.PACT Admiral DCB ISR Clinical Evaluation met its success criteria, demonstrating superiority of the DCB ISR Cohort on the 12-month primary effectiveness endpoint of target lesion revascularization

compared to the PTA ISR Comparator (10.13% vs. 35.92%, $p < 0.001$) in a pre-specified, propensity score-adjusted analysis.

B. Safety Conclusions

Safety information was leveraged from the clinical study conducted to support the original PMA with secondary endpoints from the ISR evaluation further demonstrating the safety of the IN.PACT Admiral DCB in the treatment of ISR, with no major target limb amputations and one death (0.65%) within 12 months in the DCB ISR Cohort.

C. Benefit-Risk Conclusions

The probable benefits of the IN.PACT Admiral DCB for the treatment of ISR lesions are based on the clinical data described above. The probable benefit of the IN.PACT Admiral DCB in improving patients' symptoms and quality of life outweigh the probable risks associated with use of the device for this indication. Additional factors to be considered in determining probable risks and benefits for the IN.PACT Admiral DCB include:

1. The clinical evaluation was well designed and conducted
 - a) Adequate 12-month follow-up was obtained to evaluate safety and effectiveness.
 - b) The propensity score adjustment analysis was developed prospectively, and the results were reviewed by FDA prior to proceeding with the outcome analyses.
 - c) Sensitivity analyses were conducted to assess the impact of missing data.
2. The device is intended for use in patients with peripheral vascular disease of the femoropopliteal artery. The results adequately support general use in the identified population.
3. There are alternative treatments available for this disease, such as percutaneous transluminal angioplasty (PTA) alone, but this treatment has been shown to be more effective than PTA alone with regard to safety and effectiveness.
4. Patient risk is minimized by limiting the use to operators who have the necessary training to use the device safely and effectively. Adherence to the recommended peri-procedural medication regimens is also stressed.

Patient Perspectives

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

In conclusion, given the available information above, the data supports that the probable benefits outweighs the probable risks for percutaneous transluminal angioplasty, after appropriate vessel preparation, of *de novo*, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

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. The available information supports that the probable benefits outweigh the probable risks to support the use of the IN.PACT Admiral DCB for percutaneous transluminal angioplasty, after appropriate vessel preparation, of *de novo*, restenotic, or in-stent restenotic lesions with lengths up to 180 mm in superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on September 7, 2016. The final conditions of approval cited in the approval order are described below.

Post-market Registry: The applicant will support and actively participate as a stakeholder in the Society for Vascular Surgery Patient Safety Organization governed Vascular Quality Initiative and undertake such activities to ensure that surveillance occurs for the IN.PACT Admiral Paclitaxel-Coated Percutaneous Transluminal Angioplasty Balloon Catheter when used to treat in-stent restenotic lesions in the superficial femoral and popliteal arteries in 300 patients.

This surveillance will monitor at 12, 24, and 36 months post-index procedure the following: (1) target lesion revascularization, (2) all-cause mortality, (3) target vessel revascularization, and (4) major target limb amputation. The surveillance will also monitor technical success.

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.