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™ AV Paclitaxel-coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter
Device Product Code:	PRC
Applicant's Name and Address:	Medtronic, Inc. 3576 Unocal Place Santa Rosa, CA 95403

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190008

Date of FDA Notice of Approval: November 21, 2019

II. INDICATIONS FOR USE

The IN.PACT™ AV Paclitaxel-coated PTA Balloon Catheter is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm.

III. CONTRAINDICATIONS

The IN.PACT AV Paclitaxel-coated PTA Balloon Catheter is contraindicated for use in the following anatomy and patient types:

- 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 adverse reaction in nursing infants from paclitaxel exposure

IV. WARNINGS AND PRECAUTIONS

A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Inadequate information is available to evaluate the potential mortality

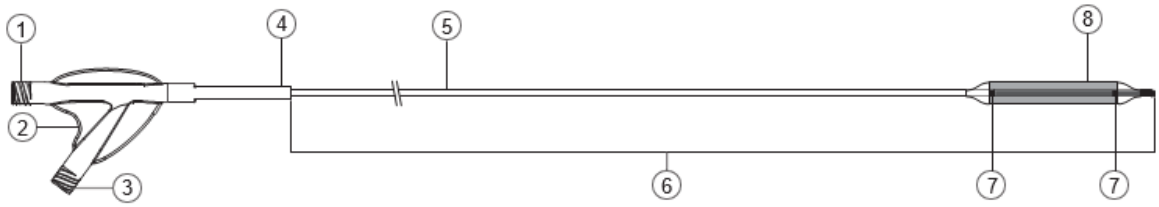
risk associated with the use of paclitaxel-coated devices for the treatment of other diseases/conditions, including this device indicated for use in arteriovenous dialysis fistulae. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options for their specific disease/condition with their patients.

Additional warnings and precautions can be found in the IN.PACT AV Paclitaxel-coated PTA Balloon Catheter labeling.

V. DEVICE DESCRIPTION

The IN.PACT AV Paclitaxel-coated PTA Balloon Catheter (hereinafter referred as IN.PACT AV DCB) is an over-the-wire balloon catheter with a drug-coated balloon at the distal end (see **Figure 1**).

Figure 1: IN.PACT AV Paclitaxel-coated PTA Balloon Catheter



1. Guidewire port
2. Hub
3. Inflation port
4. Strain relief
5. Shaft
6. Usable catheter length
7. Radiopaque marker
8. Drug-coated Balloon

PTA Catheter Component

The IN.PACT AV DCB is available in balloon lengths ranging from 40 to 120 mm, balloon diameters ranging from 4.0 to 12.0 mm, and is offered in catheter effective lengths of 40, 80 and 130 cm. The IN.PACT AV DCB is compatible with 0.035" guidewires. The IN.PACT AV DCB product matrix is provided in **Table 1** and the introducer sheath compatibility for the balloon diameters offered is provided in **Table 2**.

Table 1: IN.PACT AV DCB Product Matrix

Balloon Diameter (mm)	Balloon Length (mm)				
	40	60	80	120	
4.0	x	x	x	x	3 folds
5.0	x	x	x	x	6 folds
6.0	x	x	x	x	
7.0	x	x	x	---	
8.0	x	x	x	---	
9.0	x	x	x	---	
10.0	x	---	---	---	
12.0	x	---	---	---	

Notes:
"---" indicates sizes not offered; "X" indicates
All sizes offered will be available in 40, 80, and 130 cm catheter effective length.

Table 2: Nominal Pressure and Introducer Sheath Compatibility

Balloon Diameter (mm)	Nominal Pressure	Introducer Sheath (F)
4.0	811 kPa / 8 atm	5
5.0		6
6.0		
7.0		7
8.0		
9.0		
10.0	608 kPa / 6 atm	
12.0		9

Drug Components

The IN.PACT AV 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 mm^2 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, tetrahdyrofuran (THF) and pyrogen-free water, which are used during the FreePac formulation process and evaporate off the balloon surface after the FreePac coating is applied. Based on the nominal drug dose density of 3.5 µg/mm^2, the total amount of paclitaxel for each balloon size is provided in **Table 3**.

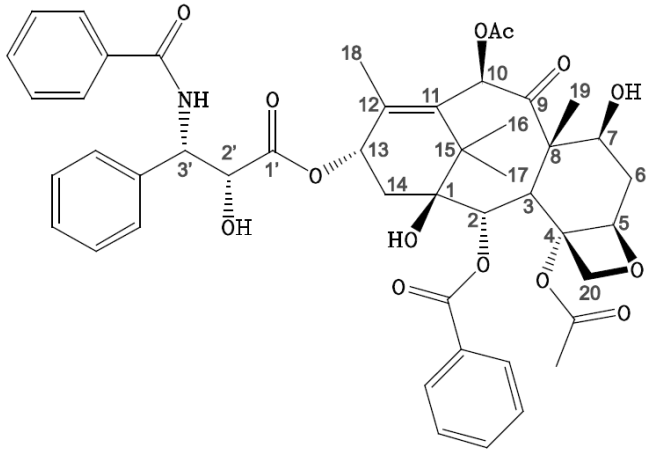
Table 3: Nominal Paclitaxel Content by Balloon Size

Balloon Diameter (mm)	Balloon Length (mm)	Nominal Paclitaxel Content (µg)
4.0	40	1969
4.0	60	2848
4.0	80	3728
4.0	120	5487
5.0	40	2553
5.0	60	3653
5.0	80	4752
5.0	120	6951
6.0	40	3170
6.0	60	4489
6.0	80	5809
6.0	120	8448
7.0	40	3819
7.0	60	5358
7.0	80	6897
8.0	40	4494
8.0	60	6253
8.0	80	8012
9.0	40	5204
9.0	60	7183
9.0	80	9162
10.0	40	5943
12.0	40	7522

Active Pharmaceutical Ingredient (API) - Paclitaxel

The API of the IN.PACT AV DCB is paclitaxel - an 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 Benzenepropanoic acid, ß-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) -2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dhydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-ylester,[2aR-[2aα,4β,4aβ,6β,9α(αR, βS),11α,12α,12aα,12bα]] and the chemical formula is $C_{47}H_{51}NO_{14}$. The chemical structure of paclitaxel is illustrated in **Figure 2** below.

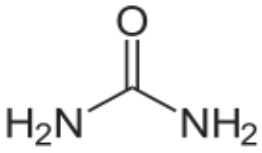
Figure 2: Chemical Structure of Paclitaxel



Excipient (Urea)

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: Chemical Structure of Urea



Mechanism of Action

The IN.PACT AV DCB's primary mode of action is mechanical dilatation of obstructive 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.

Additional details regarding the device can be found in the IN.PACT AV Paclitaxel-coated PTA Balloon Catheter labeling.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other alternatives for the correction of obstructive lesions in the native arteriovenous fistula (AVF):

- percutaneous transluminal angioplasty (PTA),
- endovascular stent graft,
- surgical revision, or
- other drug-coated PTA balloon catheter approved for use in the AVF.

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

Outside of the United States, the IN.PACT™ AV Paclitaxel-coated PTA Balloon Catheter has been marketed for this indication in the European Union (EU) since January 2016. It is also currently marketed in the following countries:

Argentina	India	South Korea
Australia	Indonesia	Taiwan
Bosnia & Herzegovina	Macedonia	Thailand
Colombia	Mexico	Turkey
Costa Rica	Peru	Ukraine
Ecuador	Saudi Arabia	Uruguay
Guatemala	Singapore	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects which may be associated with balloon catherization may include, but are not limited to, the following:

- Abrupt vessel closure
- Allergic reaction
- Arrhythmias
- Arterial or venous aneurysm

- Arterial or venous thrombosis
- Death
- Dissection
- Embolization
- Hematoma
- Hemorrhage
- Hypotension/hypertension
- Infection
- Ischemia or infarction of tissue/organ
- Loss of permanent access
- Pain
- Perforation or rupture of the artery or vein
- Pseudoaneurysm
- Restenosis of the dilated vessel
- Shock
- Stroke
- Vessel spasms or recoil

Potential complications of peripheral balloon catheterization include, but are not limited to, the following:

- Balloon rupture
- Detachment of a component of the balloon and/or catheter system
- Failure of the balloon to perform as intended
- Failure to cross the lesion

These complications may result in adverse effects.

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, the following:

- Allergic/immunologic reaction
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in 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 17** (Table of Serious Adverse Events) in the Clinical Study section (**Section X**) below.

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies related to the IN.PACT AV DCB were performed. These evaluations included biocompatibility studies, *in vitro* bench testing, animal studies, analytical testing, stability testing, shelf life testing, and sterilization.

The IN.PACT AV DCB product is based on the commercially approved IN.PACT Admiral DCB (P140010). In particular, the IN.PACT AV DCB 4.0 - 7.0 mm diameter balloon configurations are leveraged from the IN.PACT

Admiral DCB. The additional 8.0 - 12.0 mm diameter balloon configurations of the IN.PACT AV DCB have the same raw materials, components, component vendors, and manufacturing processes as the commercial IN.PACT Admiral DCB. Due to these similarities, a subset of the IN.PACT Admiral DCB non-clinical laboratory studies are directly applicable to IN.PACT AV DCB. However, since the proposed indication for IN.PACT AV DCB presents a new anatomical condition, performance attributes that are dependent on these anatomical use conditions were tested.

A. Laboratory Studies

Biocompatibility

A biocompatibility evaluation was completed to assess the commonalities between the IN.PACT AV DCB and the commercial IN.PACT Admiral DCB. Results of this evaluation confirmed that the biocompatibility testing performed on IN.PACT Admiral DCB is also applicable to the IN.PACT AV DCB and additional testing was not required. All biocompatibility testing below was leveraged from the IN.PACT Admiral DCB device. Biocompatibility testing performed on IN.PACT Admiral DCB was conducted separately on (1) the balloon with the drug coating, (2) the balloon with the excipient, and (3) the remainder of the balloon catheter. In addition, thrombogenicity and chemical characterization testing was conducted on the balloon catheter with the drug coating to support the overall biocompatibility of the drug-coated balloon. The drug coating was categorized as an implant device with permanent blood contact (> 30 days), and the balloon catheter was categorized as an externally communicating device with limited contact duration (< 24 hours) with circulating blood. A summary of the biocompatibility testing and results can be found in **Table 4**.

All biocompatibility testing was conducted in accordance with:

- Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters (September 8, 2010)
- Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems (April 18, 2010)
  Draft Guidance for Industry: Coronary Drug-Eluting Stents – Nonclinical and Clinical Studies Companion Document (March 2008)

Table 4: Summary of Biocompatibility Testing

Test Name	Test Description	Balloon w/ Excipient (no Drug)	Balloon w/ Drug Coating	Balloon Catheter w/ Excipient (no drug)	Balloon Catheter w/ Drug Coating	Results
Cytotoxicity	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	X	X	X	-	Non-toxic
Sensitization	ISO Guinea Pig Maximization	X	X	X	-	Non-sensitizing
Irritation	ISO Intracutaneous Reactivity	X	X	X	-	Non-irritating
Acute Systemic Toxicity	ISO Systemic Toxicity	X	X	X	-	Non-toxic
Pyrogenicity	USP Material Mediated Pyrogenicity	X	X	X	-	Non-pyrogenic

Test Name	Test Description	Balloon w/ Excipient (no Drug)	Balloon w/ Drug Coating	Balloon Catheter w/ Excipient (no drug)	Balloon Catheter w/ Drug Coating	Results
Hemocompatibility	ASTM Hemolysis (Direct and Indirect Contact)	X	X	X	-	Non-hemolytic
	Complement Activation Assay (C3a and SC5b-9)	X	X	X	-	Not a complement activator
	In vivo Thrombogenicity	-	-	-	X	Non-thrombogenic
Chemical Characterization	Gas Chromatography - Mass Spectroscopy (GC/MS) for volatile and semi-volatile, organic compounds	X	X	-	-	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Inductively Coupled Plasma (ICP) Spectroscopy for metallic compounds	X	X	-	-	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Liquid Chromatography - Mass Spectroscopy (LC/MS) for semi-volatile and non-volatile organic compounds	X	X	-	-	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns

The following permanent implant biocompatibility studies were not conducted on the device: sub-chronic toxicity, chronic toxicity, and muscle implantation. The potential for sub-chronic toxicity, chronic toxicity and implantation were evaluated as part of other *in vivo* studies conducted to evaluate the safety and effectiveness of the device in porcine ilio-femoral artery model, as described in **Section B**, Animal Studies, below. These additional animal studies demonstrated a lack of inflammation and toxicity when the product was used in a clinically-relevant vascular location.

The omission of genotoxicity and carcinogenicity testing were supported by information regarding the starting materials and processing of the finished drug-coated balloon in conjunction with chemical characterization data and toxicity information from the literature.

The information provided demonstrates that the device is biocompatible for its intended use.

In vitro Bench Testing

Table 5 provides an overview of the *in vitro* bench testing supporting the IN.PACT AV DCB. The table includes the tests performed, the objective of the tests, the acceptance criteria (as applicable), and the result of each test.

Table 5: Summary of *In vitro* Bench Testing

<table>
<tr><th>Test</th><th>Testing Summary/ Objective</th><th>Acceptance Criteria (Specification)</th><th>Results</th></tr>
<tr><td>Delivery System Profiles</td><td>To determine the maximum outer diameter (OD) of the catheter shaft and the balloon</td><td>
<table>
<tr><th>Balloon Diameter (mm)</th><th>Maximum Crossing Profile (mm)</th></tr>
<tr><td>4.0</td><td>1.88</td></tr>
<tr><td>5.0</td><td>2.00</td></tr>
<tr><td>6.0</td><td>2.10</td></tr>
<tr><td>7.0</td><td rowspan="4">2.33</td></tr>
<tr><td>8.0</td></tr>
<tr><td>9.0</td></tr>
<tr><td>10.0</td></tr>
<tr><td>12.0</td><td>3.00</td></tr>
</table>
</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Catheter Effective Length (Catheter tip to strain relief)</td><td>To delineate the effective length of the catheter</td><td>40 cm ± 2 cm
80 cm ± 2 cm
130 cm ± 2 cm</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Balloon Working Length at Nominal Pressure</td><td>Determine the balloon length at nominal pressure</td><td>
<table>
<tr><th colspan="3">Balloon Working Length (mm)</th></tr>
<tr><td>Nominal</td><td>Minimum</td><td>Maximum</td></tr>
<tr><td>40.0</td><td>36.0</td><td>44.0</td></tr>
<tr><td>60.0</td><td>56.0</td><td>64.0</td></tr>
<tr><td>80.0</td><td>75.0</td><td>85.0</td></tr>
<tr><td>120.0</td><td>114.0</td><td>126.0</td></tr>
</table>
</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Balloon Preparation</td><td>Demonstrate that the catheter can be safely and reliably prepared, delivered, and retracted using the recommended techniques in the Instructions for Use without damage to the product</td><td>To demonstrate that the catheter can be safely and reliably prepared, delivered, and retracted using the recommended techniques in the Instructions for Use without damage to the product.</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Balloon Rated Burst Pressure</td><td>Determine the minimum burst strength of the balloon and calculate the rated burst pressure (RBP)</td><td>Devices will not fail at or below the rated burst pressure:
<table>
<tr><th>Balloon Diameter (mm)</th><th>Rated Burst Pressure (atm)</th></tr>
<tr><td>4.0</td><td rowspan="4">14</td></tr>
<tr><td>5.0</td></tr>
<tr><td>6.0</td></tr>
<tr><td>7.0</td></tr>
<tr><td>8.0</td><td rowspan="2">10</td></tr>
<tr><td>9.0</td></tr>
<tr><td>10.0</td><td rowspan="2">9</td></tr>
<tr><td>12.0</td></tr>
</table>
</td><td>The device met the established acceptance criteria.</td></tr>
</table>

<table>
<tr><th>Test</th><th>Testing Summary/ Objective</th><th>Acceptance Criteria (Specification)</th><th>Results</th></tr>
<tr><td>Marker Band Spacing</td><td>Determine the marker band spacing at nominal pressure</td><td>The inside edge of the marker band cannot be outside the balloon working length by more than 1.0 mm.
The outside edge of the marker band cannot be inside the balloon working length by more than:
<table><tr><th>Balloon Length (mm)</th><th>Spacing (mm)</th></tr><tr><td>40</td><td>2.0</td></tr><tr><td>60</td><td>2.5</td></tr><tr><td>80</td><td>3.0</td></tr><tr><td>120</td><td>4.0</td></tr></table></td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Balloon Fatigue</td><td>Determine that balloons will sustain 10 inflations to RBP in an unconstrained environment</td><td>Samples will withstand 10 cycles at rated burst pressure.</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Balloon Compliance (Diameter vs. Pressure)</td><td>Evaluate the change in balloon diameter as a function of the inflation pressure</td><td>At nominal pressure balloon diameter must be within:
• ± 0.4 mm for 4.0 mm diameter balloons
• ± 0.5 mm for 5.0-7.0 mm diameter balloons
• ± 0.6 mm for 8.0 and 9.0 mm diameter balloons
• ± 0.7 mm for 10.0 and 12.0 mm diameter balloons</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Balloon Inflation / Deflation Time</td><td>Demonstrate that inflation and deflation of the balloon can be accomplished within clinically acceptable time limits</td><td>Inflation Time:
For characterization only.
Deflation Time:
Deflation time from RBP must be ≤ 60sec</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Tensile Strength</td><td>Determine the tensile strength of the catheter bonds after preconditioning</td><td><table><tr><th colspan="2">Minimum Tensile Strength</th></tr><tr><td>Luer / Bilumen Tube</td><td rowspan="2">≥ 10 N</td></tr><tr><td>Bilumen Tube/ Marker Tube</td></tr><tr><td>Marker Tube / Tip Tube</td><td>≥ 5 N</td></tr><tr><td>Proximal Balloon Weld</td><td>≥ 10 N</td></tr><tr><td>Distal Balloon Weld</td><td>≥ 5 N</td></tr></table></td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Catheter Flexibility and Kink Resistance</td><td>Demonstrate that the catheter will not kink when subjected to flexural forces</td><td>Catheter shaft will not kink at radius of
9.0 mm</td><td>The device met the established acceptance criteria.</td></tr>
<tr><td>Torque Strength</td><td>Demonstrate that the catheter has adequate torque strength after pre-conditioning</td><td>The balloon catheter must
withstand a minimum of 10 x 360-degree rotations inside the representative anatomical models with the distal end fixed and the guide wire in
place</td><td>The device met the established acceptance criteria.</td></tr>
</table>

Analytical Testing

Analytical testing was performed to determine the identity, safety, purity and quality of the drug substance (paclitaxel) of the IN.PACT AV DCB, as seen in **Table 6**.

Table 6: Summary of Analytical Testing

Test	Testing Summary/Objective	Acceptance Criteria	Results
Drug (paclitaxel) Identification	Test the drug substance for identity and to ensure conformity to incoming specifications.	Identity must be confirmed via two different tests	The drug substance met the established acceptance criteria.
Coating Appearance	Visual inspection was conducted to verify that the IN.PACT AV DCB drug coating meets the appearance specification.	Must meet visual standard	The device met the established acceptance criteria.
Drug Content	Quantitative determination of the total amount of paclitaxel on the IN.PACT AV DCB.	USP <905>	The device met the established acceptance criteria.
Content Uniformity	Verification of the content uniformity of the paclitaxel coating from balloon to balloon.	USP <905>	The device met the established acceptance criteria.
Degradants/ Impurities	Quantitative determination of the type and amount of impurities and degradation products of the IN.PACT AV DCB.	ICH Guidance	The device met the established acceptance criteria.
Drug Release	Determination of the *in vitro* release rate of paclitaxel from the IN.PACT AV DCB.	USP <711>	The device met the established acceptance criteria.
Drug Content Circumferential Uniformity	Measure the relative uniformity of the drug content around the balloon circumference of the finished IN.PACT AV DCB.	This testing was performed for characterization only	N/A (For Information Only)
Drug Content Length Uniformity	Measure the relative uniformity of the drug content along the balloon length of the finished IN.PACT AV DCB.	This testing was performed for characterization only	N/A (For Information Only)
Particulate	Particulate levels measured for the IN.PACT AV DCB.	Particulate counts were performed at ≥10 µm, ≥25 µm, ≥50 µm and ≥100 µm using the principles of USP<788>.	N/A (For Information Only)

Test	Testing Summary/Objective	Acceptance Criteria	Results
Particulate Identification	Identification of the particulate for the IN.PACT AV DCB.	This testing was performed for characterization only	N/A (For Information Only)

B. Animal Studies

Previously performed *in vivo* preclinical (animal) testing in porcine ilio-femoral arterial to support IN.PACT Admiral DCB is also applicable to the arteriovenous fistula model. This is due to the similarities in blood flow rate and the corresponding pharmacokinetic response between the porcine ilio-femoral arterial and arteriovenous fistula model. Previously performed studies are provided in the SSED of IN.PACT Admiral DCB (P140010). In addition, Medtronic has conducted *in vivo* preclinical testing in the arteriovenous porcine model to evaluate safety, 3X safety margin and pharmacokinetic profile in the intended clinically relevant vasculature. A summary of these studies is provided in **Table 7** below. In addition to the major endpoints noted for each study, animals were carefully evaluated for general health (i.e. vital signs, behavior, nutritional condition, gait, etc.) and clinical responses to treatment.

Table 7: Summary of Animal Studies

Study	Animal Model	Duration	Test and Control Article	Major Endpoints
FS238 - 60 Day Pharmacokinetic and Downstream Tissue Safety Study*	66 Domestic Farm Swine	PK: 0, 7, 28, 48 and 60 Days; Downstream Tissue Safety: 60 Days	Test: DCB Safety Margin (10.5 μg/mm^2) and Therapeutic (3.5 μg/mm^2) Control: Native AVF tissue	Acute Performance, Angiographic Performance, Histopathology (non-target tissue), Pharmacokinetics
FS241 - 90 Day Safety Evaluation of Treated and Downstream Tissue*	21 Domestic Farm Swine	90 Days	Test: DCB Safety Margin (10.5 μg/mm^2) and Therapeutic (3.5 μg/mm^2) Control: non drug-coated PTA Balloon Catheter	Acute Performance, Angiographic Performance, Histopathology (local and non-target tissue)
PS739 - 28 day Pharmacokinetic and Histological Evaluation of Treated and Downstream Tissue	11 Domestic Farm Swine	28 Days	Test: DCB Safety Margin (10.5 μg/mm^2) and Therapeutic (3.5 μg/mm^2) Histological Control: Native AVF tissue PK Control: non-drug-coated PTA Balloon Catheter	Angiographic Performance, Morphometric Analysis, Histopathology, Pharmacokinetics
* Studies conducted in accordance with FDA 21 CFR Part 58 GLP Regulations. Clinical responses to treatment utilizing the Subjective Objective Assessment Plan (SOAP) methodology were utilized in these studies.				

The porcine arterial and AVF model environments demonstrated that the device performs as intended and did not cause any unexpected histological indications of toxicity resulting from the therapeutic or safety margin doses. The pharmacokinetic and histological indicators of the extended drug activity in arteriovenous tissue provide evidence of effective drug transfer and safety at the intended dose.

AV fistulas are known to mature and arterialize over time, thus presenting clinical similarities to arterial tissue. The effect on local and downstream non-target organ tissue analysis was completed in the 28-, 60- and 90-day studies referenced in **Table 7** which confirms no risk of clinical sequelae using the AVF model. This data combined with the body of safety data provided in the arterial model provided in P140010 to support IN.PACT Admiral DCB indications, presents a strong evaluation of healing out to 365 days.

In addition to the studies listed in Table. 7, Medtronic also conducted two GLP preclinical animal studies (FS236 and FS237) to evaluate the IN.PACT AV DCB in the native femoral veins of healthy swine with timepoints at 28 and 90 days. Histological evaluation from these studies revealed medial smooth muscle loss and fibrin deposition on the luminal surface owing to the absence of atherosclerotic disease in the normal treated veins as well as the lower blood flow velocities and reduced local drug clearance in the venous environment relative to arteries. The treated veins were not compromised as there was no extravasation of blood and the veins maintained patent lumens. No pathologies were recorded in the downstream organs. All treated veins remained patent and exhibited no signs of clinically relevant sequelae during the in-life phase. These findings are not relevant to use in arteriovenous fistulas.

Overall, the preclinical program successfully established the systemic and local tissue exposure including safety margin doses of paclitaxel.

C. Additional Studies

Stability and Shelf Life Studies

Finished product stability studies were developed according to USP and ICH guidelines to establish the shelf life for the IN.PACT AV DCB finished product. The testing includes an evaluation of drug content, impurities, drug release, particulate, sterility, drug content uniformity, residual solvents, urea, water and endotoxins. Appropriate functional tests were also planned and performed on products and packaging to ensure that the IN.PACT AV DCB performed acceptably up to the intended shelf life. The data generated from the stability studies, coupled with the data generated from the shelf life studies, supports a 36-month shelf life for the product.

Sterilization

IN.PACT AV DCB is sterilized using ethylene oxide sterilization and has been validated per ISO 11135:2014 "Sterilization of health care products--Ethylene Oxide--Requirements for development, validation and routine control of a sterilization process for medical devices" and EN 556-1:2001"Sterilization of Medical Devices – Requirements for medical devices to be designated STERILE – Part 1: Requirements for terminally sterilized medical devices". The testing for ethyleneoxide residuals was completed and acceptable per ISO 10993-7:2008. In addition, pyrogenic (LAL) testing was completed per ST72:2011. Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. The amounts of bacterial endotoxin were verified to be within the specification limit.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous transluminal angioplasty, after pre-dilatation, with IN.PACT AV DCB for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm in patients from the US, Japan and New Zealand under IDE # G160242. Data from this IDE clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between April 25, 2017 and May 10, 2018. The database for this PMA reflected data collected through December 6, 2018 and included 330 subjects from 29 investigational sites.

The IN.PACT AV Access study is a prospective, global, multicenter, single-blinded, randomized (1:1) clinical study to evaluate safety and effectiveness of the IN.PACT AV DCB (study group) vs. standard PTA (control group) for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae.

The IN.PACT AV Access study recruited subjects with a *de novo* or non-stented restenotic obstructive lesion located in the native arteriovenous dialysis fistulae. After the informed consent process and screening, subjects were randomized to treatment with IN.PACT AV DCB (study group) or standard PTA balloon (control group) using a 1:1 randomization scheme. The randomization was stratified by lesion type (*de novo* vs restenotic) and study sites. Randomization occurred after successful crossing and pre-dilatation of the target lesion. Subjects who did not meet the protocol-defined criteria after pre-dilation were considered screen failures, treated per standard practice; no further follow-up was required per the protocol.

The data from the IN.PACT AV Access study, with greater than 50% of subjects coming from the U.S. population (204 US subjects, 112 Japan subjects, and 14 New Zealand subjects) comprise the pivotal study data set. This aggregate data provides adequate statistical power for the 30-day primary safety and 6-month primary effectiveness endpoints. The statistical analysis plan included planned primary analysis of the intent to treat (ITT) subjects, as well as a fixed sequential testing procedure for four secondary endpoints through 6 months for the intent to treat (ITT) subjects in the order of cumulative target lesion revascularizations (TLR), number of interventions required to maintain target lesion patency, number of interventions required to maintain access circuit patency, and access circuit primary patency. The ITT population consisted of all randomized subjects, irrespective of the treatment actually delivered.

There were two primary hypotheses for the study, evaluating the primary safety endpoint through 30 days and the primary effectiveness endpoint through 6 months, respectively. Each hypothesis was tested on the ITT subjects at a one-sided significance level of 2.5%, as pre-specified in the Statistical Analysis Plan. The control group is standard percutaneous transluminal angioplasty (PTA).

For the primary safety endpoint, the study and control groups were compared for non-inferiority using the following hypothesis.

H_0: $\pi_T \geq \pi_C + 0.075$

H_A: $\pi_T < \pi_C + 0.075$

where π_T and π_C are the serious adverse event (SAE) rates of the study and control groups, respectively.

For the primary effectiveness endpoint, the study (p_T) and control (p_C) groups were compared for superiority using the following hypothesis:

H_0: $p_T \leq p_C$

H_A: $p_T > p_C$

where p_T and p_C are the target lesion primary patency (TLPP) rates of the study and control groups, respectively.

To control the overall Type I error the study was deemed success only if both primary effectiveness and primary safety endpoints were met.

Once the two primary endpoints were met, the following key secondary endpoints were tested for superiority between treatment groups sequentially by using the ITT analysis set, each at a one-sided significance level of 0.025, in the following order. The testing procedure would stop at the first failure to reject null hypothesis.

1) Cumulative (any) target lesion revascularizations (TLR) measured through 6 months post-procedure;

H_0: $t_T \geq t_C$

H_A: $t_T < t_C$

where t_x refers to the expected cumulative TLR rate through 6 months (x = T for DCB; x = C for PTA). A one-sided Z-test was performed at a significance level of 0.025.

2) Number of interventions required to maintain target lesion patency through 6 months post- procedure;

H_0: $l_T \geq l_C$

H_A: $l_T < l_C$

where l_X refers to the expected number of interventions to maintain target lesion patency through 6 months (x = T for DCB; x = C for PTA). The comparison was performed at a one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.

3) Number of interventions required to maintain access circuit patency through 6 months post- procedure

H_0: $c_T \geq c_C$

H_A: $c_T < c_C$

where c_x refers to the expected number of interventions to maintain access circuit patency through 6 months (x = T for DCB; x = C for PTA). The comparison was performed at a one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.

4) Access circuit primary patency through 6 months post-procedure;

H_0: $a_T \leq a_C$

H_A: $a_T > a_C$

where a_x refers to the expected access circuit primary patency rate through 6 months (x = T for DCB; x = C for PTA). One-sided Z-test will be performed at a significance level of 0.025.

Overview of the study flowchart is provided in **Figure 4** and an overview of the IN.PACT AV Access study design is provided in **Table 8** below.

Figure 4: Study Flowchart

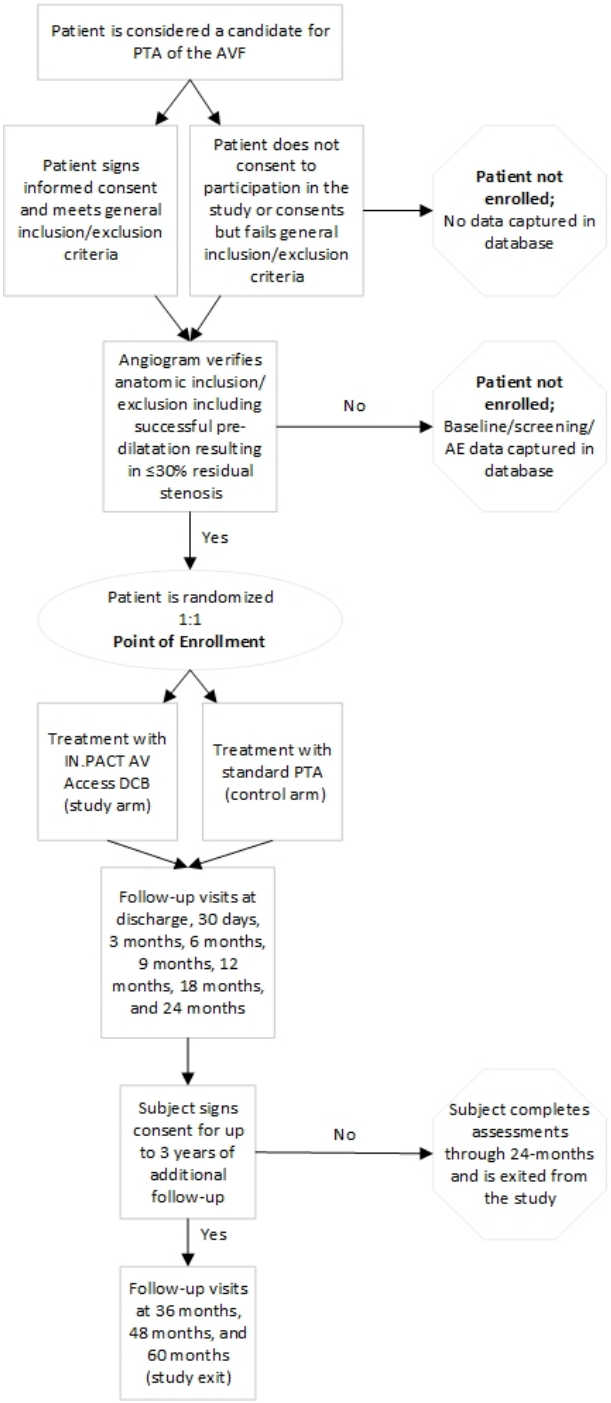


Table 8: IN.PACT AV Access Study Design

Item	Description
Study Design	Prospective, global, multicenter, single-blinded, randomized (1:1) clinical study to evaluate IN.PACT™ AV DCB safety and effectiveness.
Number of Subjects Enrolled	330
Treatment Lesion	Obstructive lesions up to 100 mm in length in native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm
Treatment Device	Study Group: IN.PACT™ AV Paclitaxel-coated PTA Balloon Catheter Control Group: Non-coated standard percutaneous transluminal angioplasty balloon catheter (standard PTA catheter)
Balloon Sizes	Balloon Diameters: 4, 5, 6, 7, 8, 9, 10, and 12 mm Balloon Lengths: 40, 60, 80, and 120 mm in length
Concomitant Medication	Single antiplatelet therapy, at a minimum, (e.g. aspirin, clopidogrel, ticlopidine or Prasugrel) should be administered before the procedure and for a minimum of 4 weeks after the intervention.
Primary Endpoints	*Safety:* Serious adverse event rate (SAE) involving the AV access circuit through 30 days post-procedure. *Effectiveness*: Target Lesion Primary Patency (TLPP) through 6 months.
Randomized Subject Follow-up Schedule	Subjects randomized and enrolled in the study will be followed up to 5 years. Follow-up assessments are scheduled for 30-day, 3, 6, 9, 12, 18, 24, 36, 48 and 60-months post index procedure.* *Angiography*: Unscheduled Visits[1] *Duplex Ultrasound*: 30 days, 6 months, 12 months and unscheduled visits[1]
*Subjects will be contacted via phone for the 3-month, 9-month and 18-month assessments [1]Perform only if clinically warranted or institutional standard	

The IN.PACT AV Access study utilized the following core labs/CROs:

- Clinical Events Committee (CEC): Responsible for adjudicating adverse events and deaths.
- Angiography Core Laboratory: Responsible for reviewing all angiographies
- Duplex Ultrasound Core Laboratory: Responsible for reviewing all duplex exams
- Data Monitoring Committee (DMC): Monitor subject safety and efficacy and evaluate the progress of the study
- Randomization Vendor: Managed the randomization for the study

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the IN.PACT AV Access study was limited to patients who met the following inclusion criteria:

- Patient is ≥ 21 years of age
- Patient has a life expectancy of ≥ 12 months
- Patient has a native AV fistula created ≥ 60 days prior to the index procedure
- The target AV fistula has undergone successful dialysis for at least 8 of 12 sessions during a four-week period
- Patient has a *de novo* and/or non-stented restenotic lesion located between the arteriovenous anastomosis and axillosubclavian junction with ≥50% stenosis
    - *Note:* If the lesion is located in the anastomosis, the treatment may be delivered up to 2 cm upstream on the arterial side
    - *Note:* If the lesion is located in the cephalic arch, the treatment may be delivered up to 2 cm into the subclavian vein
- Patient has a target lesion or a tandem lesion that is ≤ 100 mm in length (by visual estimate)
    - *Note:* Tandem lesions may be enrolled provided they meet <u>all</u> of the following criteria:
        - Separated by a gap of ≤ 30 mm (3 cm)
        - Total combined lesion length, including 30 mm gap, ≤ 100 mm
        - Able to be treated as a single lesion
- Patient has a target vessel diameter of 4.0 – 12.0 mm (by visual estimate)
- Patient underwent successful crossing of the target lesion with the guide wire and pre-dilatation with a high-pressure PTA balloon defined as:
    - Residual stenosis of ≤ 30% AND
    - Absence of a flow limiting dissection (Grade ≥ C) or perforation
- Patient provides written informed consent prior to enrollment in the study
- Patient is willing to comply with all follow-up evaluations at specified times

Patients were <u>not</u> permitted to enroll in the IN.PACT AV Access study if they met any of the following exclusion criteria:

- Women who are breastfeeding, pregnant, or are intending to become pregnant, or men intending to father children
- Patient is receiving immunosuppressive therapy
- Patient is anticipating a kidney transplant within 6 months of enrollment into the study
- Patient with secondary non-target lesion requiring treatment within 30 days post index procedure
- Patient with hemodynamically significant central venous stenoses that cannot be successfully treated prior to treatment of the target lesion
- Patient has undergone prior intervention of access site within 30 days of index procedure
- Patient with anticipated conversion to peritoneal dialysis
- Patient has an infected AV access or systemic infection
- Patient has planned surgical revision of access site

- Patient with target AVF or access circuit which previously had or currently has a thrombosis
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
- Patient with target lesion located central to the axillosubclavian junction
- Patient has significant arterial inflow lesion requiring treatment more than 2 cm upstream from the anastomosis in the AV access
- Patient has presence of pseudoaneurysm or aneurysm requiring treatment at the lesion site
- Patient has presence of a stent located in the target AV access circuit
- Patients with known allergies or sensitivities to paclitaxel
- Patient with known contraindication, including allergic reaction, or sensitivity to contrast material that cannot be adequately pre-treated
- Patient who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patient with clinically significant Steal Syndrome requiring treatment
- Patient is enrolled in another investigational drug, device, or biologic study and has not completed the primary endpoint, or was previously enrolled in this study
- Patient has a co-morbid condition that, in the judgment of the Investigator, may cause him/her to be non-compliant with the protocol or confound the data interpretation

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 6, 12, 24, 36, 48 and 60 months with a telephone follow-up at 3, 9, and 18 months post index procedure. Please see **Table 9** below for the complete procedure and follow-up schedule.

Table 9: Procedure and Follow-up Schedule†

Assessments/ Procedure	**Baseline/ Screening**	**Index Procedure**	**Discharge** (within 7 days post-procedure)	**30 Days** (± 7 days) **6 Months** (180 days ± 30 days) **12 Months** (360 days ± 30 days)	**3 Months*** (90 days ± 15 days) **9 Months*** (270 days ± 30 days) **18 Months*** (540 days ± 30 days)	**24 Months** (720 days ± 30 days) **36 Months** (1,080 days ± 30 days) **48 Months** (1,440 days ± 30 days) **60 Months††** (1,800 days ± 30 days)	**Unscheduled Visit**	**Target AVF Abandonment**
Informed Consent	X[1]							
Medical History	X[2]							
Physical Exam	X[2]						X[4]	
Medication Assessment	X[2]	X	X	X	X	X		
EQ-5D	X[2]			X		X		
Duplex Ultrasound				X			X[6]	
Angiography¥		X[3]					X[4]	
Randomization		X						
Adverse Event	X	X	X	X[5]	X[5]	X[5]	X[5]	X[5]
Abandonment								X

Assessments/ Procedure	Baseline/ Screening	Index Procedure	Discharge (within 7 days post-procedure)	30 Days (± 7 days) 6 Months (180 days ± 30 days) 12 Months (360 days ± 30 days)	3 Months* (90 days ± 15 days) 9 Months* (270 days ± 30 days) 18 Months* (540 days ± 30 days)	24 Months (720 days ± 30 days) 36 Months (1,080 days ± 30 days) 48 Months (1,440 days ± 30 days) 60 Months†† (1,800 days ± 30 days)	Unscheduled Visit	Target AVF Abandonment
eCRF								

†Follow-up dates are calculated based on 30-day months

*Subjects will be contacted by telephone 3 months, 9 months, and 18 months post index procedure to assess adverse events and medications

††After assessments for the 60 months visit are completed, the subject will be exited from the study

¥ Angiograms performed outside of the index procedure and unscheduled visits (e.g. standard of care angiograms at 6 months post index-procedure) should be submitted to the angiographic core laboratory.

[1] Consent process may occur within 14 days prior to enrollment. Signing on the same day as procedure is allowed if allowed by the IRB/EC and source records document that the consent process was conducted and consent was signed pre-procedure

[2] Within 14 days prior to enrollment

[3]Angiogram must include all pre- and post-procedure images.

[4]Repeat at unscheduled visit only if clinically warranted or institutional standard

[5]After the primary endpoints are met (6 months), only SAEs, TLRs, and/or device related events will be collected

[6]Duplex Ultrasounds conducted within 2 years of index procedure should be submitted to the Core Laboratory; after the 24 month assessment DUS exams should no longer be submitted for evaluation

The key timepoints are shown below in **Table 16** and **Table 18** summarizing safety and effectiveness.

3. Clinical Endpoints

   The primary safety endpoint was the serious adverse event rate involving AV access circuit through 30 days post-procedure. The study aimed to demonstrate non-inferiority of the IN.PACT AV DCB to Standard PTA (7.5% non-inferiority margin) for the safety endpoint.

   The primary effectiveness endpoint was Target Lesion Primary Patency (TLPP) through 6 months, defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.

   The study aimed to demonstrate superiority of the IN.PACT AV DCB to Standard PTA for the effectiveness endpoint.

Secondary endpoints included:

- Access Circuit Primary Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure
- Target Lesion Primary Patency through 3 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure
- Cumulative Target Lesion Revascularizations Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure
- Number of Interventions Required to Maintain Target Lesion Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

- Number of Interventions Required to Maintain Access Circuit Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure
- Cumulative Access Circuit Thromboses Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure
- Device, Procedure, and Clinical Success
- Rate of Device and Procedure Related Adverse Events Reported through 30 Days, 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure.

The following endpoints will be assessed annually up to 60 months in addition to the assessment through 24 months where applicable:

- Target Lesion Revascularizations
- Clinically-Driven Target Lesion Revascularizations
- Re-interventions in the access circuit
- Abandonment of Target AVF
- Serious Adverse Events

With regard to success/failure criteria, both the primary safety and effectiveness endpoints had to be met in order for the study to be considered successful.

The long term device safety and effectiveness of the IN.PACT AV DCB for treatment of AVF will be evaluated beyond the pre-specified 30-day (primary safety) and 6-month (primary effectiveness) endpoints.

B. Accountability of PMA Cohort

At the time of database lock (December 6, 2018), of 330 patients enrolled in the PMA study, 95.7% (286/299) of patients completed a 6-month visit.

After successful pre dilatation, subjects were randomized 1:1 to IN.PACT AV DCB (n = 170) and Standard PTA (n = 160). Subject disposition through 6-month follow-up by visit is listed in **Figure 5** and Subject disposition is listed in **Table 10** below.

Figure 5: Subject Disposition through 6-month Follow-up by Visit

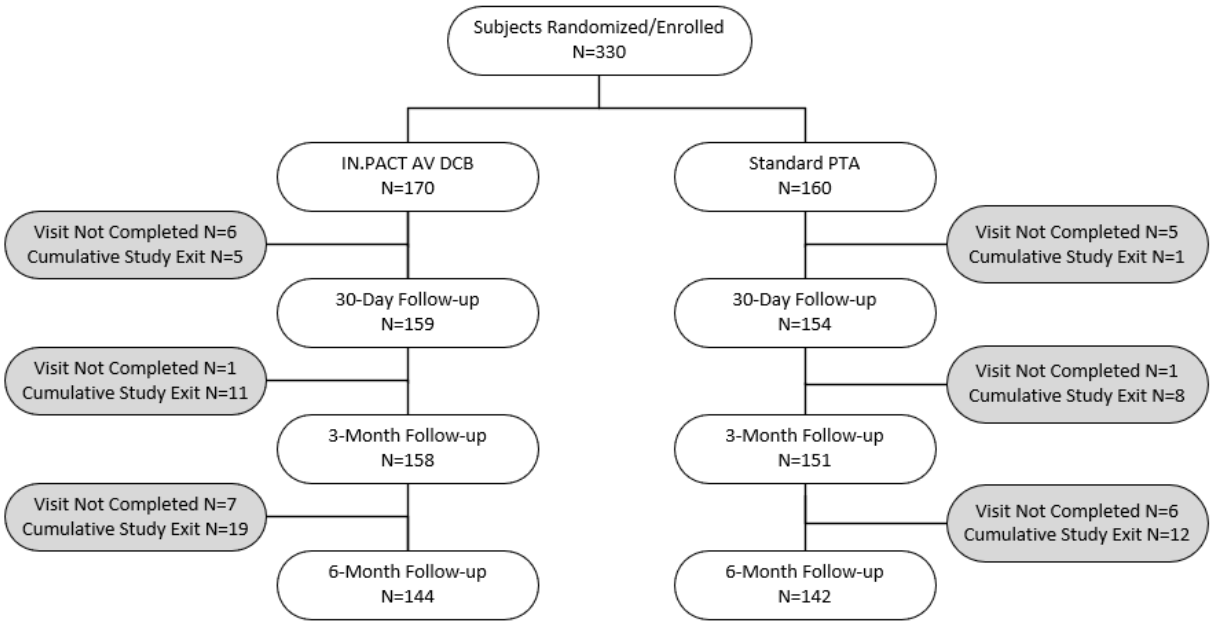


Table 10: Subject Disposition

Description	Randomized (ITT)	30 Day	3 Month	6 Month	9 Month	12 Month
Follow-Up at Time Points	330 (100.0%)	313/330 (94.8%)	309/330 (93.6%)	286/330 (86.7%)	206/330 (62.4%)	120/330 (36.4%)
Discontinued Early[1]	0	6	19	31	43	49
Not Due for Visit[2]	0	0	0	0	79	147
Follow-Up of Eligible[3] Subjects	330 (100.0%)	313/324 (96.6%)	309/311 (99.4%)	286/299 (95.7%)	206/208 (99.0%)	120/134 (89.6%)

Note: The compliance included in- and out-of-window visit.
[1] Study exits are cumulative count. At each follow-up, subjects exited the study for any reasons before the upper limit of the window and had no follow-up visit will be counted.
[2] Not due for visit are cumulative. At each follow-up, a subject is counted as not due for visit if he did not exit the study, had no follow-up visit and did not reach the upper limit of the window (i.e., snapshot date – index procedure date < upper window).
[3] Eligible 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)

Table 11: Evaluable Subjects for Primary Endpoints Analyses (ITT Analysis Set)

Summary	IN.PACT DCB (N=170)	Standard PTA (N=160)
Primary Safety Endpoint (Day 30) % (n)		
Evaluable[1]	97.6% (166)	98.8% (158)
Not Evaluable[2]	2.4% (4)	1.3% (2)
Death before Day 23[3]	0.6% (1)	0.0% (0)
Withdrawal of Consent before Day 23[3]	0.6% (1)	0.6% (1)
Other Discontinued before Day 23[3]	0.6% (1)	0.0% (0)
30-day Visit not done	0.6% (1)	0.6% (1)
TLPP through 6 months (Day 210), %(n)		

Summary	IN.PACT DCB (N=170)	Standard PTA (N=160)
Evaluable[4]	89.4% (152)	92.5% (148)
Not Evaluable[2]	10.6% (18)	7.5% (12)
Death before Day 150[3]	4.1% (7)	1.3% (2)
Abandon AV Circuit before Day 150[3]	0.6% (1)	1.9% (3)
Withdrawal Consent Before Day 150[3]	1.8% (3)	3.1% (5)
Other Discontinued before Day 150[3]	1.8% (3)	1.3% (2)
6-month Visit not done	2.4% (4)	0.0% (0)

[1] Include subjects with at least 23 days of follow-up or with a safety event within 30 days;
[2] The reasons for unevaluable are ordered in hierarchy as applicable: Death > Abandon AV Circuit > Withdrew > Other Discontinuation > Visit Not Done;
[3] Day 23 represents the first day of 1-month (or 30-day visit) clinical window, Day 150 represents first day of 6-month visit window;
[4] Subjects with a clinically driven target lesion revascularization (TLR) or access circuit thrombosis within 210 days or without TLPP failure but had at least 150 days of clinical follow-up were considered evaluable. Subjects had no failure
events but had abandoned AV Access circuit within 150 days were considered not evaluable.

C. Study Population Demographics and Baseline Parameters

Site reported baseline demographic and clinical characteristics for all 330 enrolled subjects are provided in **Table 12** to **Table 14** below. Treatment groups were well balanced in baseline demographics and clinical characteristics between IN.PACT AV DCB and PTA subjects. IN.PACT AV DCB subjects had a mean age of 65.8 years, 65.9% were male, 62.9% had diabetes, and 91.2% had hypertension. Similarly, PTA subjects had a mean age of 65.5 years, 63.1% were male, 68.8% had diabetes, and 94.4% had hypertension. All subjects (100%) reported renal insufficiency, have been receiving hemodialysis for a mean of 4.3 years, and have had their target AVF for a mean of 3.3 years. The most common type of AVF was radiocephalic (50.3% (166/330)), followed by brachiocephalic (36.4% (120/330)), brachiobasilic (9.7% (32/330)), and other (3.6% (12/330)). All subjects (100% (330/330)) presented with clinical symptoms indicating AV access dysfunction at baseline.

Table 12: Baseline Demographics and Clinical Characteristics-ITT Analysis Set

Subject Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Total (N=330 Subjects)	p-value[1]
Age (yrs)				
N	170	160	330	
Mean ± SD	65.8 ± 13.1	65.5 ± 13.4	65.6 ± 13.3	0.837
Median (Q1, Q3)	67.0 (58, 75)	68.0 (57, 75)	67.0 (57, 75)	
Min, Max	29, 94	29, 90	29, 94	
Male	65.9% (112/170)	63.1% (101/160)	64.5% (213/330)	0.646
Ethnicity				
Hispanic/Latino	9.0% (15/167)	8.9% (14/157)	9.0% (29/324)	1.000
Race				0.920
White	24.7% (42/170)	28.8% (46/160)	26.7% (88/330)	
Black or African American	31.8% (54/170)	30.0% (48/160)	30.9% (102/330)	
Asian	37.1% (63/170)	35.6% (57/160)	36.4% (120/330)	
Native Hawaiian or Other Pacific Islander	3.5% (6/170)	2.5% (4/160)	3.0% (10/330)	
American Indian or Alaska Native	0.0% (0/170)	0.0% (0/160)	0.0% (0/330)	
Other	2.9% (5/170)	3.1% (5/160)	3.0% (10/330)	
Hypertension	91.2% (155/170)	94.4% (151/160)	92.7% (306/330)	0.295
Hyperlipidemia	54.1% (92/170)	52.5% (84/160)	53.3% (176/330)	0.825
Diabetes Mellitus	62.9% (107/170)	68.8% (110/160)	65.8% (217/330)	0.297
Type I	2.4% (4/170)	3.8% (6/160)	3.0% (10/330)	0.532
Type II	60.6% (103/170)	65.0% (104/160)	62.7% (207/330)	0.427
Renal Insufficiency	100.0% (170/170)	100.0% (160/160)	100.0% (330/330)	> 0.999
Carotid Artery Disease	4.1% (7/170)	8.8% (14/160)	6.4% (21/330)	0.114
Congestive Heart Failure	22.9% (39/170)	24.4% (39/160)	23.6% (78/330)	0.796
Coronary Heart Disease	35.9% (61/170)	38.8% (62/160)	37.3% (123/330)	0.649
Peripheral Artery Disease	19.4% (33/170)	15.1% (24/159)	17.3% (57/329)	0.312
Current Smoker	11.2% (19/170)	16.3% (26/160)	13.6% (45/330)	0.201
Former Smoker	37.6% (64/170)	28.1% (45/160)	33.0% (109/330)	0.079
AVF Type				0.918
Radiocephalic	50.6% (86/170)	50.0% (80/160)	50.3% (166/330)	
Brachiocephalic	36.5% (62/170)	36.3% (58/160)	36.4% (120/330)	
Brachiobasilic	10.0% (17/170)	9.4% (15/160)	9.7% (32/330)	
Other	2.9% (5/170)	4.4% (7/160)	3.6% (12/330)	
Dominant Arm	22.4% (38/170)	24.4% (39/160)	23.3% (77/330)	0.697
Previous peripheral revascularization	74.1% (126/170)	75.0% (120/160)	74.5% (246/330)	0.900
Years since AVF creation[2]				
N	170	160	330	
Mean ± SD	3.2 ± 3.0	3.5 ± 3.8	3.3 ± 3.4	0.436
Median (Q1, Q3)	2.2 (1, 4)	2.2 (1, 5)	2.2 (1, 5)	
Min, Max	0, 17	0, 28	0, 28	
Years of Hemodialysis History[3]				
N	170	159	329	
Mean ± SD	4.3 ± 5.1	4.2 ± 5.2	4.3 ± 5.1	0.755
Median (Q1, Q3)	2.7 (1, 6)	2.3 (1, 6)	2.6 (1, 6)	
Min, Max	0, 32	0, 41	0, 41	

[1]p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on Cochran-Mantel-Haenszel (CMH) general association test, for ordinal variables were based on CMH score test. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

[2]41 subjects had partial dates and their years since AVF creation was calculated based on the imputed dates using the middle of the month or middle of the year.

[3]51 subjects had partial dates and their years of hemodialysis history was calculated based on the imputed dates using the middle of the month or middle of the year.

Table 13: Site Reported Baseline Lesion Characteristics – ITT Analysis Set

Lesion Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Total (N=330 Subjects)	p-value[1]
Target Arm				0.449
Right Arm	23.5% (40/170)	27.5% (44/160)	25.5% (84/330)	
Left Arm	76.5% (130/170)	72.5% (116/160)	74.5% (246/330)	
Target Lesion Access				0.765
Venous	97.1% (165/170)	96.3% (154/160)	96.7% (319/330)	
Arterial	2.9% (5/170)	3.8% (6/160)	3.3% (11/330)	
Lesion Type				0.905
De Novo	30.0% (51/170)	30.6% (49/160)	30.3% (100/330)	
Restenotic	70.0% (119/170)	69.4% (111/160)	69.7% (230/330)	

[1]p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on CMH general association test, for ordinal variables were based on CMH score test.
Note: Site reported data. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

Table 14: Baseline / Procedural Angiographic Core Lab Characteristics – ITT Analysis Set

Procedural Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[1]
Treated Vessel				
Anastomosis	33.7% (57/169)	31.6% (50/158)	2.1% [-8.8%, 12.9%]	0.724
Arterial Inflow	0.0% (0/169)	0.0% (0/158)	NA	> 0.999
Cephalic Arch	16.6% (28/169)	22.8% (36/158)	-6.2% [-17.0%, 4.6%]	0.166
In Cannulation Zone	26.6% (45/169)	20.9% (33/158)	5.7% [-5.1%, 16.5%]	0.244
Swing Point	19.5% (33/169)	20.9% (33/158)	-1.4% [-12.2%, 9.5%]	0.784
Venous Outflow	3.6% (6/169)	3.8% (6/158)	-0.2% [-11.1%, 10.6%]	1.000
Subjects with Tandem Lesion	12.4% (21/170)	16.3% (26/160)	-3.9% [-14.7%, 6.9%]	0.346
Target Lesion Length (mm)				
N	170	159		
Mean ± SD	46.3 ± 28.1	41.9 ± 25.2	4.4 [-1.4, 10.2]	0.137
Median (Q1, Q3)	42.7 (25, 61)	37.5 (23, 58)		
Min, Max	3, 160	3, 157		
Minimum Lumen Diameter (mm)				
N	170	159		
Mean ± SD	2.7 ± 1.6	2.8 ± 1.7	-0.1 [-0.4, 0.3]	0.731
Median (Q1, Q3)	2.6 (2, 4)	2.4 (1, 4)		
Min, Max	0, 9	0, 9		
Reference Vessel Diameter (mm)				
N	170	159		
Mean ± SD	7.5 ± 2.3	7.7 ± 2.6	-0.2 [-0.7, 0.3]	0.442
Median (Q1, Q3)	7.2 (6, 9)	7.3 (6, 9)		
Min, Max	2, 13	3, 15		
Pre-procedure % Diameter Stenosis				
N	170	159		
Mean ± SD	64.8 ± 13.3	64.8 ± 14.5	0.0 [-3.0, 3.0]	0.986
Median (Q1, Q3)	64.7 (56, 74)	65.6 (55, 76)		
Min, Max	27, 100	2, 100		
Subjects with Occluded Lesions	1.2% (2/169)	0.6% (1/159)	0.6% [-10.3%, 11.4%]	1.000
Length of Occlusion				
N	2	1		
Mean ± SD	37.5 ± 40.5	26.3 ± NA	11.2 [NA, NA]	NA

Procedural Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value[1]
Median (Q1, Q3)	37.5 (9, 66)	26.3 (26, 26)		
Min, Max	9, 66	26, 26		
Dissection	0.0% (0/170)	0.0% (0/159)		NA
Aneurysm	25.3% (43/170)	22.0% (35/159)	3.3% [-7.6%, 14.0%]	0.518
Pseudoaneurysm	0.0% (0/170)	0.0% (0/159)	NA	> 0.999
Perforation	0.0% (0/170)	0.0% (0/159)	NA	> 0.999
Thrombus	0.6% (1/170)	0.6% (1/159)	-0.0% [-10.8%, 10.8%]	1.000
Embolism	0.0% (0/170)	0.0% (0/159)	NA	> 0.999

Core Laboratory reported data.
[1]p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on CMH general association test, for ordinal variables were based on CMH score test. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

Table 15: Treatment Devices Used During Index Procedure – All ITT Subjects

Subject Characteristics	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	p-value[1]
Subjects with			< 0.001
No Balloon	0.0% (0/170)	1.9% (3/160)	
One Balloon	75.3% (128/170)	95.0% (152/160)	
Two Balloons	24.7% (42/170)	3.1% (5/160)	
Three Balloons	0.0% (0/170)	0.0% (0/160)	
More than Three Balloons	0.0% (0/170)	0.0% (0/160)	
Total Balloon Length per Subject (mm)			
N	170	160	
Mean ± SD	73.5 ± 30.6	48.0 ± 18.5	< 0.001
Median (Q1, Q3)	80.0 (40, 100)	40.0 (40, 60)	
Min, Max	40, 160	0, 120	
Number of Treatment Balloons per Subject			
N	170	160	
Mean ± SD	1.2 ± 0.4	1.0 ± 0.2	< 0.001
Median (Q1, Q3)	1.0 (1, 1)	1.0 (1, 1)	
Min, Max	1, 2	0, 2	
Subjects received provisional stents[2]	0.6% (1/170)	0.6% (1/160)	1.000
Number of provisional stents per subject[2]			
N	170	160	
Mean ± SD	0.0 ± 0.1	0.0 ± 0.1	0.966
Median (Q1, Q3)	0.0 (0, 0)	0.0 (0, 0)	
Min, Max	0, 1	0, 1	
Reasons for Provisional Stenting[2, 3]			
Persistent residual stenosis	0.0% (0/169)	0.6% (1/160)	0.486
Major flow-limiting dissection	0.0% (0/169)	0.0% (0/160)	> 0.999

[1]p-values for continuous variables were based on independent t-test, for binary variables were based on Fisher's Exact test, for nominal variables were based on CMH general association test, for ordinal variables were based on CMH score test. The p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.
[2]Provisional stents are not allowed in Japan patients.
[3]One IN.PACT AV DCB study group subject, received provisional stenting for a grade C dissection (not considered flow-limiting) for subject safety, and therefore does not appear in the reasons for provisional stenting.

D. Safety and Effectiveness Results

Results for the primary safety and effectiveness endpoints of the IN.PACT AV Access study are described and summarized below.

1. Safety Results

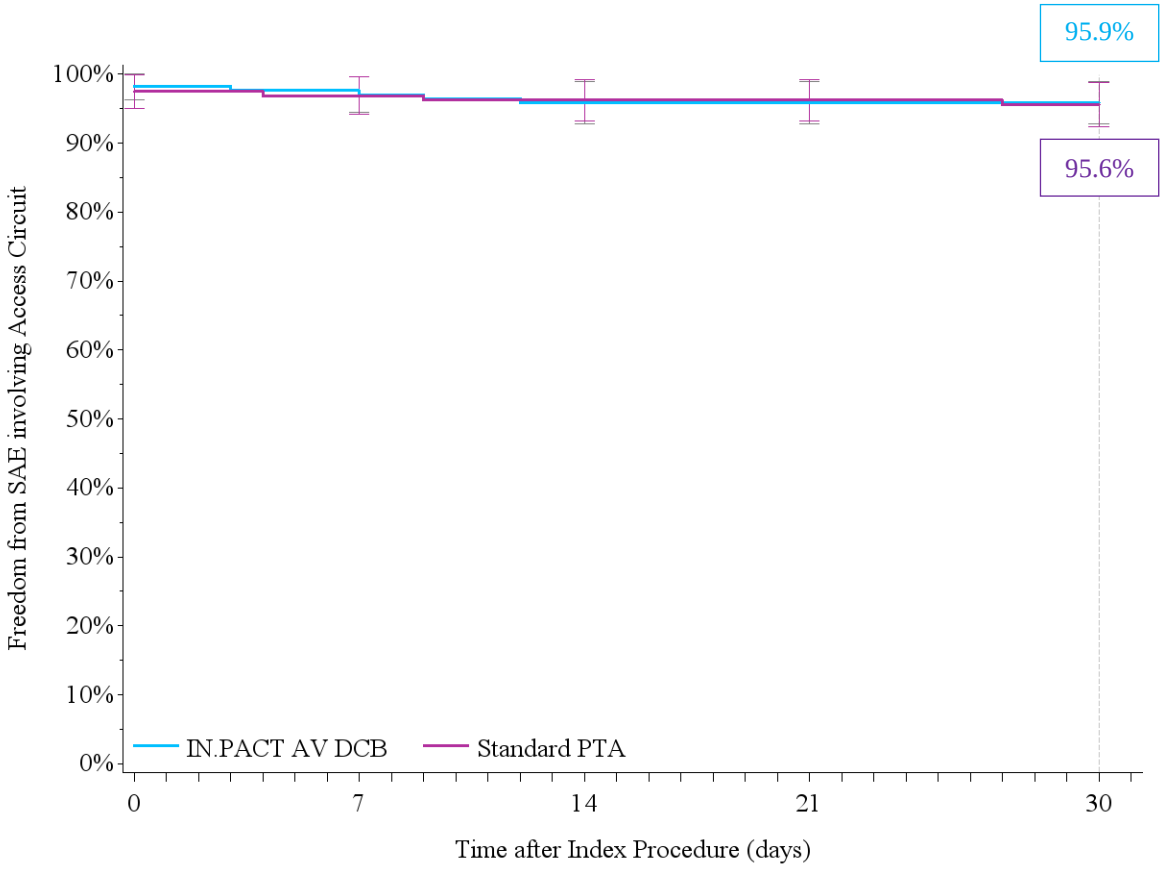
The primary safety endpoint was the rate of Serious Adverse Events (SAE) involving the AV access circuit through 30-day post-procedure. The 30-day SAE rate involving the AV access circuit was 4.2% in the IN.PACT AV DCB study group and 4.4% in the PTA control group (non-inferiority p = 0.002). The upper limit of 95% confidence interval for the risk difference was 5.0%, less than the non-inferiority margin (7.5%), demonstrating that IN.PACT AV DCB was non-inferior to PTA in terms of the primary safety endpoint. The primary safety outcomes for this study are presented below in **Table 16**. A Kaplan-Meier analysis of the primary safety endpoint is shown below in **Figure 6** for all ITT subjects. The Kaplan-Meier survival curve estimate of freedom from SAEs involving the access circuit through 30 days was 95.9% in the IN.PACT AV DCB study group vs. 95.6% in the PTA control group. **Figure 6** provides freedom from SAEs involving the access circuit through 180 days which are also listed in **Table 17**.

Table 16: Primary Safety Endpoint – ITT Analysis Set

	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value†
Primary Safety Endpoint			Non-inferiority Test with 7.5% Margin	
SAE involving the AV access circuit within 30 days	4.2% (7/166)	4.4% (7/158)	-0.2% [-5.5%, 5.0%]	0.002
Arteriovenous Fistula Occlusion	14.3% (1/7)	0.0% (0/7)		
Arteriovenous Fistula Site Complication	71.4% (5/7)	57.1% (4/7)		
Arteriovenous Fistula Thrombosis	14.3% (1/7)	14.3% (1/7)		
Haemodialysis Complication	14.3% (1/7)	0.0% (0/7)		
Vasospasm	0.0% (0/7)	14.3% (1/7)		
Vessel Puncture Site Haematoma	0.0% (0/7)	14.3% (1/7)		

†Non-inferiority p-values for the primary safety endpoint was based on the Farrington-Manning non-inferiority test with a margin of 7.5%.

Figure 6: Kaplan-Meier Plot – Freedom from SAE involving Access Circuit through 30 Days – ITT Analysis Set



From day X To day Y	0 0	1 7	8 14	15 21	22 30
IN.PACT AV Access DCB (N=170 Subjects)					
# Entered	170	166	164	161	159
# Censored	1	0	1	2	1
# Events	3	2	2	0	0
Survival rate [%]	98.2%	97.1%	95.9%	95.9%	95.9%
STANDARD PTA (N=160 Subjects)					
# Entered	160	154	153	152	152
# Censored	2	0	0	0	0
# Events	4	1	1	0	1
Survival rate [%]	97.5%	96.9%	96.2%	96.2%	95.6%
The arrow bars are confidence intervals at each time point. The arrow bars and the log-rank p-value should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified					

Serious Adverse Events

A SAE is an adverse event that a) led to death, b) led to a serious deterioration in the health of the subject, resulting in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. SAEs are summarized in **Table 17**. In total, 62.9% of IN.PACT AV DCB study group subjects experienced one or more serious adverse events and 71.9% of standard PTA control arm subjects experienced one or more serious adverse events within 360 days. All SAEs which led to death were CEC adjudicated as not related to the study device, procedure, or therapy.

Additional analysis on SAEs is presented in Table 18.

Table 17: Number of Subjects with One or More SAEs by MedDRA (Medical Dictionary for Regulatory Activities) System- Within 360 Days – ITT Analysis Set

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
SUBJECTS WITH ONE OR MORE SERIOUS ADVERSE EVENTS	62.9% (107/170)	71.9% (115/160)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1.8% (3/170)	1.3% (2/160)
ANAEMIA	1.2% (2/170)	1.3% (2/160)
LEUKOCYTOSIS	0.6% (1/170)	0.0% (0/160)
THROMBOCYTOPENIA	0.6% (1/170)	0.0% (0/160)
CARDIAC DISORDERS	15.9% (27/170)	14.4% (23/160)
ACUTE CORONARY SYNDROME	0.6% (1/170)	0.0% (0/160)
ACUTE MYOCARDIAL INFARCTION	0.0% (0/170)	1.9% (3/160)
ANGINA PECTORIS	1.8% (3/170)	1.3% (2/160)
ANGINA UNSTABLE	0.6% (1/170)	0.0% (0/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
AORTIC VALVE STENOSIS	0.0% (0/170)	0.6% (1/160)
ATRIAL FIBRILLATION	2.4% (4/170)	2.5% (4/160)
ATRIAL FLUTTER	0.6% (1/170)	0.0% (0/160)
BRADYCARDIA	1.2% (2/170)	0.6% (1/160)
CARDIAC ARREST	2.4% (4/170)	1.9% (3/160)
CARDIAC FAILURE	0.6% (1/170)	0.0% (0/160)
CARDIAC FAILURE CHRONIC	0.6% (1/170)	0.6% (1/160)
CARDIAC FAILURE CONGESTIVE	2.9% (5/170)	3.1% (5/160)
CARDIO-RESPIRATORY ARREST	0.0% (0/170)	0.6% (1/160)
CARDIOMYOPATHY	0.0% (0/170)	0.6% (1/160)
CORONARY ARTERY DISEASE	1.2% (2/170)	1.3% (2/160)
CORONARY ARTERY OCCLUSION	0.6% (1/170)	0.0% (0/160)
CORONARY ARTERY STENOSIS	1.8% (3/170)	1.3% (2/160)
DIASTOLIC DYSFUNCTION	0.6% (1/170)	0.0% (0/160)
ISCHAEMIC CARDIOMYOPATHY	1.2% (2/170)	0.0% (0/160)
MITRAL VALVE INCOMPETENCE	0.6% (1/170)	0.0% (0/160)
MYOCARDIAL ISCHAEMIA	0.0% (0/170)	0.6% (1/160)
PERICARDIAL EFFUSION	1.2% (2/170)	0.6% (1/160)
EAR AND LABYRINTH DISORDERS	0.6% (1/170)	0.0% (0/160)
DEAFNESS NEUROSENSORY	0.6% (1/170)	0.0% (0/160)
EYE DISORDERS	1.8% (3/170)	0.0% (0/160)
CATARACT	1.2% (2/170)	0.0% (0/160)
VITREOUS HAEMORRHAGE	0.6% (1/170)	0.0% (0/160)
GASTROINTESTINAL DISORDERS	4.7% (8/170)	6.9% (11/160)
ASCITES	0.6% (1/170)	0.0% (0/160)
COLITIS ISCHAEMIC	0.6% (1/170)	0.0% (0/160)
DIARRHOEA	0.6% (1/170)	0.0% (0/160)
DIVERTICULUM	0.6% (1/170)	0.0% (0/160)
DYSPHAGIA	0.0% (0/170)	1.3% (2/160)
GASTRIC POLYPS	0.0% (0/170)	0.6% (1/160)
GASTROINTESTINAL HAEMORRHAGE	1.2% (2/170)	1.3% (2/160)
HAEMATEMESIS	0.0% (0/170)	0.6% (1/160)
HAEMORRHOIDS	0.6% (1/170)	0.0% (0/160)
INGUINAL HERNIA	0.0% (0/170)	0.6% (1/160)
LARGE INTESTINAL STENOSIS	0.0% (0/170)	0.6% (1/160)
LOWER GASTROINTESTINAL HAEMORRHAGE	0.0% (0/170)	0.6% (1/160)
MESENTERIC HAEMATOMA	0.6% (1/170)	0.0% (0/160)
NAUSEA	0.6% (1/170)	0.0% (0/160)
PANCREATITIS ACUTE	0.0% (0/170)	0.6% (1/160)
UPPER GASTROINTESTINAL HAEMORRHAGE	0.0% (0/170)	0.6% (1/160)
VOMITING	0.6% (1/170)	0.6% (1/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2.4% (4/170)	3.8% (6/160)
CHEST PAIN	1.8% (3/170)	1.3% (2/160)
COMPLICATION ASSOCIATED WITH DEVICE	0.0% (0/170)	0.6% (1/160)
DEATH	0.0% (0/170)	0.6% (1/160)
MULTIPLE ORGAN DYSFUNCTION SYNDROME	0.6% (1/170)	0.0% (0/160)
PERIPHERAL SWELLING	0.0% (0/170)	0.6% (1/160)
VASCULAR STENT STENOSIS	0.0% (0/170)	0.6% (1/160)
HEPATOBILIARY DISORDERS	4.1% (7/170)	0.0% (0/160)
BILE DUCT STONE	0.6% (1/170)	0.0% (0/160)
CHOLANGITIS	0.6% (1/170)	0.0% (0/160)
CHOLECYSTITIS	0.6% (1/170)	0.0% (0/160)
CHOLECYSTITIS ACUTE	0.6% (1/170)	0.0% (0/160)
CHOLELITHIASIS	0.6% (1/170)	0.0% (0/160)
HEPATIC CIRRHOSIS	0.6% (1/170)	0.0% (0/160)
PORTAL VEIN THROMBOSIS	0.6% (1/170)	0.0% (0/160)
IMMUNE SYSTEM DISORDERS	0.0% (0/170)	0.6% (1/160)
KIDNEY TRANSPLANT REJECTION	0.0% (0/170)	0.6% (1/160)
INFECTIONS AND INFESTATIONS	17.1% (29/170)	11.3% (18/160)
ABDOMINAL ABSCESS	0.6% (1/170)	0.0% (0/160)
ABSCESS LIMB	0.6% (1/170)	0.0% (0/160)
APPENDICITIS	0.6% (1/170)	0.0% (0/160)
BACTERAEMIA	0.6% (1/170)	0.0% (0/160)
BRONCHITIS	0.6% (1/170)	0.0% (0/160)
CELLULITIS	2.4% (4/170)	0.6% (1/160)
CLOSTRIDIUM DIFFICILE COLITIS	0.0% (0/170)	0.6% (1/160)
CLOSTRIDIUM DIFFICILE INFECTION	0.0% (0/170)	0.6% (1/160)
ENDOCARDITIS	0.6% (1/170)	0.0% (0/160)
ENTEROCOCCAL INFECTION	0.0% (0/170)	0.6% (1/160)
ESCHERICHIA BACTERAEMIA	0.6% (1/170)	0.0% (0/160)
GANGRENE	0.6% (1/170)	0.6% (1/160)
GASTROENTERITIS	0.6% (1/170)	0.0% (0/160)
GASTROINTESTINAL INFECTION	0.6% (1/170)	0.0% (0/160)
INFECTED SKIN ULCER	0.6% (1/170)	0.0% (0/160)
INFECTION	0.0% (0/170)	0.6% (1/160)
INFLUENZA	0.0% (0/170)	1.9% (3/160)
LOCALISED INFECTION	0.6% (1/170)	0.0% (0/160)
NECROTISING FASCIITIS	0.0% (0/170)	0.6% (1/160)
OSTEOMYELITIS	1.2% (2/170)	0.0% (0/160)
PNEUMONIA	7.1% (12/170)	3.1% (5/160)
PNEUMONIA STAPHYLOCOCCAL	0.0% (0/170)	0.6% (1/160)
POSTOPERATIVE WOUND INFECTION	0.0% (0/170)	0.6% (1/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
PYELONEPHRITIS	0.6% (1/170)	0.6% (1/160)
SEPSIS	2.4% (4/170)	2.5% (4/160)
SEPTIC SHOCK	0.6% (1/170)	0.0% (0/160)
STAPHYLOCOCCAL BACTERAEMIA	0.6% (1/170)	0.6% (1/160)
SUBCUTANEOUS ABSCESS	0.6% (1/170)	0.0% (0/160)
UPPER RESPIRATORY TRACT INFECTION	0.6% (1/170)	0.6% (1/160)
URINARY TRACT INFECTION	1.2% (2/170)	2.5% (4/160)
URINARY TRACT INFECTION BACTERIAL	0.0% (0/170)	0.6% (1/160)
UROSEPSIS	0.0% (0/170)	0.6% (1/160)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	38.8% (66/170)	57.5% (92/160)
ACETABULUM FRACTURE	0.6% (1/170)	0.0% (0/160)
ARTERIOVENOUS FISTULA ANEURYSM	1.8% (3/170)	3.1% (5/160)
ARTERIOVENOUS FISTULA OCCLUSION	1.8% (3/170)	3.8% (6/160)
ARTERIOVENOUS FISTULA SITE COMPLICATION	31.8% (54/170)	49.4% (79/160)
ARTERIOVENOUS FISTULA SITE HAEMATOMA	0.6% (1/170)	0.6% (1/160)
ARTERIOVENOUS FISTULA SITE HAEMORRHAGE	0.6% (1/170)	1.3% (2/160)
ARTERIOVENOUS FISTULA THROMBOSIS	0.6% (1/170)	2.5% (4/160)
CORONARY ARTERY RESTENOSIS	0.6% (1/170)	0.0% (0/160)
DIALYSIS RELATED COMPLICATION	0.6% (1/170)	0.0% (0/160)
FEMORAL NECK FRACTURE	0.6% (1/170)	0.0% (0/160)
FEMUR FRACTURE	0.0% (0/170)	0.6% (1/160)
HAEMODIALYSIS COMPLICATION	1.8% (3/170)	0.0% (0/160)
HEAD INJURY	0.6% (1/170)	0.0% (0/160)
HIP FRACTURE	0.0% (0/170)	0.6% (1/160)
INCARCERATED INCISIONAL HERNIA	0.0% (0/170)	0.6% (1/160)
LIMB INJURY	0.0% (0/170)	0.6% (1/160)
MULTIPLE FRACTURES	0.0% (0/170)	0.6% (1/160)
OVERDOSE	0.6% (1/170)	0.0% (0/160)
POST PROCEDURAL HAEMORRHAGE	0.0% (0/170)	0.6% (1/160)
RECTAL INJURY	0.6% (1/170)	0.0% (0/160)
SKULL FRACTURE	0.6% (1/170)	0.0% (0/160)
SPINAL COMPRESSION FRACTURE	0.0% (0/170)	1.3% (2/160)
SUBDURAL HAEMATOMA	0.6% (1/170)	0.0% (0/160)
TIBIA FRACTURE	0.0% (0/170)	0.6% (1/160)
TOXICITY TO VARIOUS AGENTS	0.0% (0/170)	0.6% (1/160)
UPPER LIMB FRACTURE	0.0% (0/170)	0.6% (1/160)
INVESTIGATIONS	0.0% (0/170)	0.6% (1/160)
TROPONIN INCREASED	0.0% (0/170)	0.6% (1/160)
METABOLISM AND NUTRITION DISORDERS	5.9% (10/170)	8.1% (13/160)
FLUID OVERLOAD	2.4% (4/170)	1.9% (3/160)
HYPERGLYCAEMIA	0.6% (1/170)	0.6% (1/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
HYPERKALAEMIA	1.8% (3/170)	3.1% (5/160)
HYPERNATRAEMIA	0.0% (0/170)	0.6% (1/160)
HYPERVOLAEMIA	0.6% (1/170)	0.6% (1/160)
HYPOGLYCAEMIA	0.6% (1/170)	0.0% (0/160)
HYPOVOLAEMIA	0.0% (0/170)	0.6% (1/160)
LACTIC ACIDOSIS	0.6% (1/170)	0.6% (1/160)
MALNUTRITION	0.6% (1/170)	0.0% (0/160)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3.5% (6/170)	1.9% (3/160)
ARTHRITIS REACTIVE	0.6% (1/170)	0.0% (0/160)
BACK PAIN	0.6% (1/170)	0.6% (1/160)
CHONDROCALCINOSIS PYROPHOSPHATE	0.6% (1/170)	0.0% (0/160)
COSTOCHONDRITIS	0.6% (1/170)	0.0% (0/160)
FLANK PAIN	0.0% (0/170)	0.6% (1/160)
LUMBAR SPINAL STENOSIS	0.6% (1/170)	0.0% (0/160)
MUSCULAR WEAKNESS	0.0% (0/170)	0.6% (1/160)
SPINAL COLUMN STENOSIS	0.6% (1/170)	0.0% (0/160)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1.8% (3/170)	2.5% (4/160)
ANGIOSARCOMA	0.0% (0/170)	0.6% (1/160)
BLADDER CANCER	0.6% (1/170)	0.0% (0/160)
BREAST ANGIOSARCOMA	0.0% (0/170)	0.6% (1/160)
HEPATIC CANCER	0.6% (1/170)	0.0% (0/160)
LUNG ADENOCARCINOMA	0.0% (0/170)	0.6% (1/160)
METASTASES TO PERITONEUM	0.0% (0/170)	0.6% (1/160)
PROSTATE CANCER METASTATIC	0.6% (1/170)	0.0% (0/160)
RENAL CANCER	0.0% (0/170)	0.6% (1/160)
NERVOUS SYSTEM DISORDERS	3.5% (6/170)	6.9% (11/160)
BRAIN STEM STROKE	0.0% (0/170)	0.6% (1/160)
CAROTID ARTERY STENOSIS	0.0% (0/170)	0.6% (1/160)
CEREBRAL HAEMORRHAGE	0.6% (1/170)	0.0% (0/160)
CEREBROVASCULAR ACCIDENT	1.2% (2/170)	0.0% (0/160)
CERVICAL RADICULOPATHY	0.0% (0/170)	0.6% (1/160)
ENCEPHALOPATHY	0.6% (1/170)	1.3% (2/160)
HEPATIC ENCEPHALOPATHY	0.6% (1/170)	0.0% (0/160)
HYPERTENSIVE ENCEPHALOPATHY	0.0% (0/170)	0.6% (1/160)
ISCHAEMIC STROKE	0.6% (1/170)	0.6% (1/160)
METABOLIC ENCEPHALOPATHY	0.0% (0/170)	1.3% (2/160)
NARCOLEPSY	0.0% (0/170)	0.6% (1/160)
NEUROPATHY PERIPHERAL	0.6% (1/170)	0.0% (0/160)
PRESYNCOPE	0.0% (0/170)	0.6% (1/160)
SYNCOPE	0.0% (0/170)	0.6% (1/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
TRANSIENT ISCHAEMIC ATTACK	0.6% (1/170)	0.0% (0/160)
PSYCHIATRIC DISORDERS	0.6% (1/170)	1.3% (2/160)
DELIRIUM TREMENS	0.6% (1/170)	0.0% (0/160)
MENTAL STATUS CHANGES	0.0% (0/170)	1.3% (2/160)
RENAL AND URINARY DISORDERS	1.2% (2/170)	1.9% (3/160)
END STAGE RENAL DISEASE	0.0% (0/170)	1.3% (2/160)
RENAL CYST	0.6% (1/170)	0.0% (0/160)
RENAL MASS	0.6% (1/170)	0.0% (0/160)
URINARY RETENTION	0.0% (0/170)	0.6% (1/160)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8.2% (14/170)	5.6% (9/160)
ACUTE PULMONARY OEDEMA	0.0% (0/170)	0.6% (1/160)
ACUTE RESPIRATORY FAILURE	1.8% (3/170)	0.6% (1/160)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0.6% (1/170)	0.0% (0/160)
DYSPNOEA EXERTIONAL	0.6% (1/170)	0.0% (0/160)
HYPOXIA	0.6% (1/170)	0.0% (0/160)
PLEURAL EFFUSION	2.9% (5/170)	0.0% (0/160)
PNEUMOTHORAX	0.0% (0/170)	0.6% (1/160)
PULMONARY HYPERTENSION	0.0% (0/170)	0.6% (1/160)
PULMONARY OEDEMA	0.6% (1/170)	1.3% (2/160)
RESPIRATORY ARREST	0.6% (1/170)	0.0% (0/160)
RESPIRATORY FAILURE	1.8% (3/170)	3.8% (6/160)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1.2% (2/170)	1.9% (3/160)
DECUBITUS ULCER	0.0% (0/170)	0.6% (1/160)
DIABETIC FOOT	0.6% (1/170)	0.0% (0/160)
ISCHAEMIC SKIN ULCER	0.0% (0/170)	0.6% (1/160)
PSORIASIS	0.0% (0/170)	0.6% (1/160)
SKIN ULCER	0.6% (1/170)	0.0% (0/160)
SOCIAL CIRCUMSTANCES	0.6% (1/170)	0.0% (0/160)
REFUSAL OF TREATMENT BY PATIENT	0.6% (1/170)	0.0% (0/160)
SURGICAL AND MEDICAL PROCEDURES	0.6% (1/170)	2.5% (4/160)
ARTERIOVENOUS FISTULA OPERATION	0.0% (0/170)	1.3% (2/160)
INTERVERTEBRAL DISC OPERATION	0.0% (0/170)	0.6% (1/160)
PERIPHERAL REVASCULARISATION	0.6% (1/170)	0.0% (0/160)
RENAL TRANSPLANT	0.0% (0/170)	0.6% (1/160)
VASCULAR DISORDERS	7.1% (12/170)	8.8% (14/160)
AORTIC ANEURYSM	0.6% (1/170)	0.0% (0/160)
AORTIC STENOSIS	0.6% (1/170)	0.0% (0/160)
BRACHIOCEPHALIC VEIN STENOSIS	0.0% (0/170)	0.6% (1/160)
HYPERTENSION	0.6% (1/170)	0.0% (0/160)
HYPOTENSION	2.9% (5/170)	1.3% (2/160)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	1.2% (2/170)	2.5% (4/160)

Adverse Event	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)
PERIPHERAL ARTERY OCCLUSION	0.6% (1/170)	0.0% (0/160)
PERIPHERAL ARTERY STENOSIS	0.0% (0/170)	1.3% (2/160)
PERIPHERAL ISCHAEMIA	0.6% (1/170)	0.0% (0/160)
SHOCK HAEMORRHAGIC	0.6% (1/170)	0.0% (0/160)
STEAL SYNDROME	0.6% (1/170)	1.9% (3/160)
SUBCLAVIAN VEIN THROMBOSIS	0.0% (0/170)	0.6% (1/160)
VENOUS STENOSIS	0.0% (0/170)	0.6% (1/160)
VENOUS THROMBOSIS LIMB	0.6% (1/170)	0.0% (0/160)
TOTAL SERIOUS ADVERSE EVENTS	**321**	**350**

Note:
Percentages are calculated as no. of subjects with each event / total no. of subjects in the analysis set.
Event verbatim terms are reported by sites. The events listed in this table are then coded using MedDRA version 19.1 and then stratified by System-Organ Class (SOC) and Preferred Term. Patients are only
counted once in each specific SOC and PT event term.
Site reported data.

Table 18 below provides additional analysis on infections and infestations, and pneumonia. The Kaplan-Meier estimated cumulative incidence of infections and infestations through 180 and 360 days was 10.6% [6.4%, 15.9%], and 18.9% [13.1%, 25.5%] respectively in the IN.PACT AV DCB group and 3.9% [1.6%, 7.9%], and 12.2% [7.6%, 18.1%] respectively in the standard PTA group. The Kaplan-Meier estimated cumulative incidence of pneumonia through 180 and 360 days was 3.8% [1.5%, 7.6%], and 7.9% [4.3%, 13.0%] respectively in the IN.PACT AV DCB group and 1.3% [0.3%, 4.2%] and 4.1% [1.7%, 8.3%] respectively in the standard PTA group. As summarized in **Table 18**, infections and infestations, and pneumonia, are numerically higher in the IN.PACT AV DCB group than in the standard PTA group though 360 days.

Table 18. Number of Subjects with One or More Serious Infections and Infestations or Pneumonia – ITT Analysis Set

Serious Adverse Events	IN.PACT AV DCB (N = 170 Subjects)		Standard PTA (N = 160 Subjects)		Log-rank p-value
	% (n)	95% CI	% (n)	95% CI	
Infections and Infestations through 180 Days	10.6% (17)	6.4%, 15.9%	3.9% (6)	1.6%, 7.9%	0.022
Pneumonia† through 180 Days	3.8% (6)	1.5%, 7.6%	1.3% (2)	0.3%, 4.2%	0.172
Infections and Infestations through 360 Days	18.9% (29)	13.1%, 25.5%	12.2% (18)	7.6%, 18.1%	0.092
Pneumonia† through 360 Days	7.9% (12)	4.3%, 13.0%	4.1% (6)	1.7%, 8.3%	0.164

Note:
Percentages are Cumulative Incidence based on Kaplan-Meier estimate (number of subjects with event)
CI – Confidence Interval
† Include 'Pneumonia' and 'Pneumonia Staphylococcal'
The Log-rank p-values should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

All-cause Mortality

A signal for increased risk of late mortality at 2 years and beyond has been identified for paclitaxel-coated devices used to treat femoropopliteal arterial disease. The magnitude and the mechanism for the late mortality risk is unclear as is the risk for paclitaxel-coated devices indicated for arteriovenous fistulae.

In the IN.PACT AV Access study, Kaplan Meier mortality estimates at 6 and 12 months are 5.5% [2.7%, 9.7%], and 9.4% [5.5%, 14.6%], respectively, for the IN.PACT™ AV DCB treatment device and 2.0% [0.5%, 5.2%] and 9.6% [5.5%, 15.0%], respectively, for the standard PTA control device.

2. Effectiveness results

The primary effectiveness endpoint was target lesion primary patency through 6 months post-procedure. The 6 month target lesion primary patency rate was 82.2% in the IN.PACT AV DCB study group and 59.5% in the PTA control group ($p < 0.001$), showing statistical superiority of the IN.PACT AV DCB study group compared to the PTA control group. Primary effectiveness results are provided in **Table 19** and **Figure 7** show the Kaplan-Meier plot for target lesion primary patency through 210 days. The Kaplan-Meier survival curve shows target lesion primary patency through 210 days (81.4% in the IN.PACT AV DCB study group vs. 59.0% in the PTA control group).

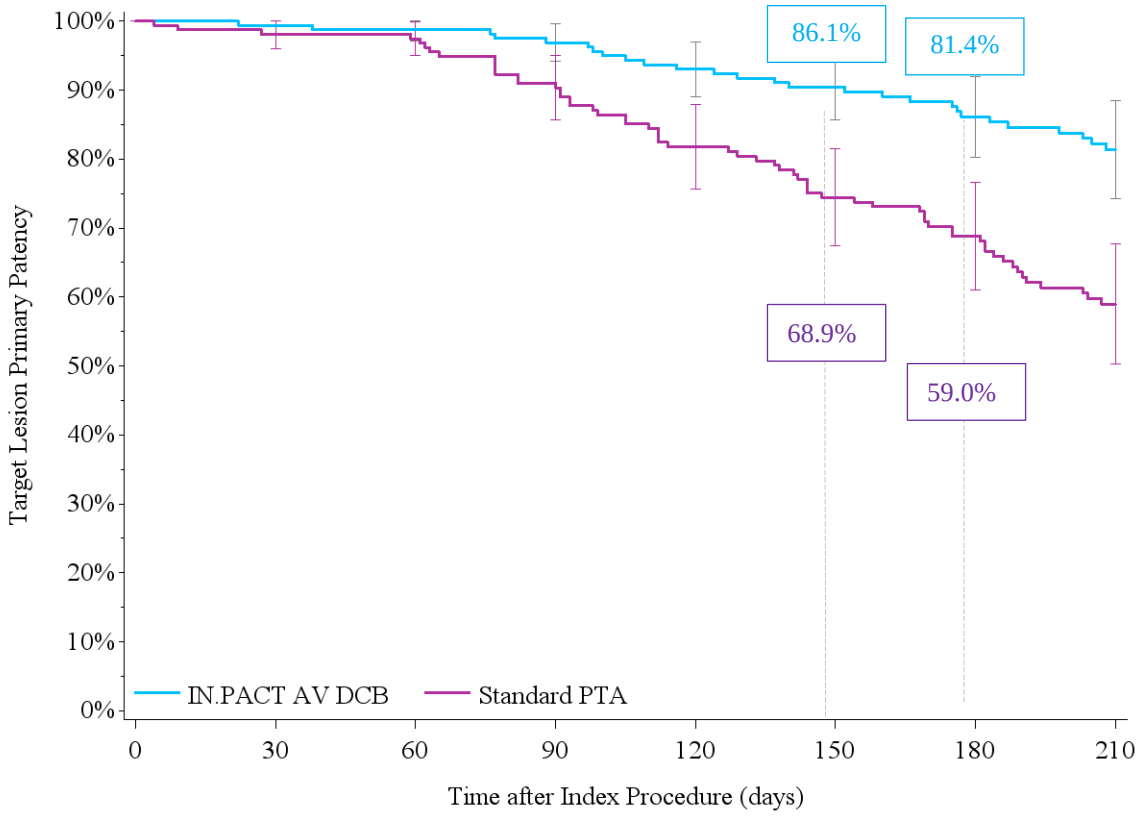
Table 19: Primary Effectiveness Endpoints – ITT Analysis

	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value†
Primary Effectiveness Endpoint				
Target Lesion Primary Patency[1] through 6 Months - freedom from	82.2% (125/152)	59.5% (88/148)	22.8% [12.8%, 32.8%]	< 0.001
CD-TLR	16.4% (25/152)	38.5% (57/148)		
Access circuit thrombosis	2.0% (3/151)	3.4% (5/146)		

[1] Target Lesion Primary Patency (TLPP) is defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis post index procedure.

†p-values for the primary effectiveness endpoint were based on one-sided Z-test.

Figure 7: Kaplan-Meier Plot – Target Lesion Primary Patency through 210 Days – ITT Analysis Set



From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210
IN.PACT AV DCB (N=170 Subjects)								
# Entered	170	169	164	158	152	144	136	115
# Censored	1	4	5	3	2	4	15	14
# Events	0	1	1	3	6	4	6	6
Survival rate [%]	100.0%	99.4%	98.8%	96.9%	93.0%	90.4%	86.1%	81.4%
STANDARD PTA (N=160 Subjects)								
# Entered	160	158	155	152	138	123	111	93
# Censored	2	0	2	3	2	1	10	8
# Events	0	3	1	11	13	11	8	13
Survival rate [%]	100.0%	98.1%	97.5%	90.3%	81.8%	74.4%	68.9%	59.0%

Survival Curves Comparison				
Analysis Method	**Test**	**Chi Square**	**Degr. Freedom**	**P-Value**
Kaplan-Meier Analysis	Log-Rank	18.3761	1	<0.0001

	0	1	31	61	91	121	151	181
From day X To day Y	0	30	60	90	120	150	180	210

The arrow bars are confidence intervals at each time point. The arrow bars and the log-rank p-value should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

The results of key secondary endpoints through 6 months are provided in **Table 20**, which shows superiority of the IN.PACT AV DCB study group results compared to the PTA control group.

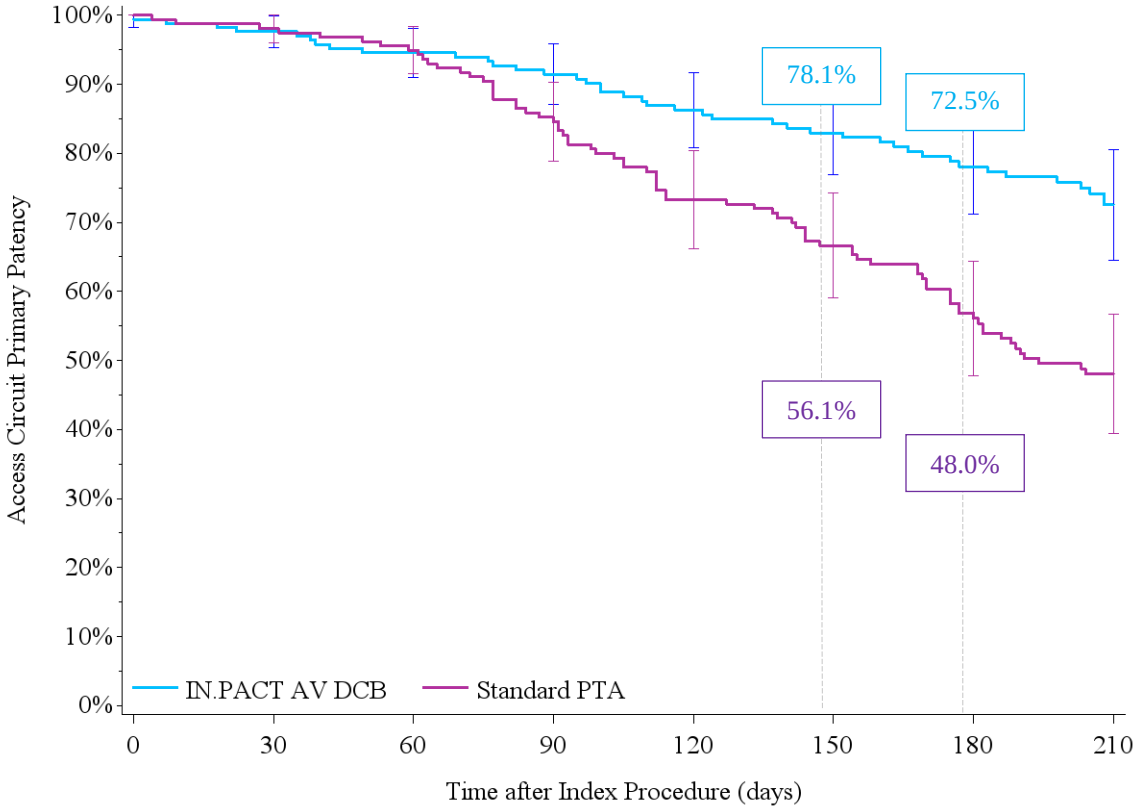
Table 20: Key Secondary Endpoints – ITT Analysis Set

	IN.PACT AV DCB (N=170 Subjects)	Standard PTA (N=160 Subjects)	Difference [95% CI]	p-value†
Key Secondary Endpoints Through 6-months				
Any TLR	16.3% (25/153)	39.9% (59/148)	-23.5% [-33.4%, -13.7%]	< 0.001
Number of interventions required to maintain target lesion patency[1]				
Total number of interventions	40	91		
Subjects with at least one intervention	18.2% (31/170)	43.8% (70/160)		
Number of interventions per subject				< 0.001
N	170	160		
Mean ± SD	0.2 ± 0.6	0.6 ± 0.7	-0.3 [-0.5, -0.2]	
Median (Q1, Q3)	0.0 (0, 0)	0.0 (0, 1)		
Min, Max	0, 4	0, 3		
Number of interventions required to maintain access circuit patency[2]				
Total number of interventions	54	103		
Subjects with at least one intervention	22.9% (39/170)	46.9% (75/160)		
Number of interventions per subject				< 0.001
N	170	160		
Mean ± SD	0.3 ± 0.7	0.6 ± 0.8	-0.3 [-0.5, -0.2]	
Median (Q1, Q3)	0.0 (0, 0)	0.0 (0, 1)		
Min, Max	0, 4	0, 3		
Access circuit primary patency[3] - freedom from	73.2% (112/153)	48.0% (71/148)	25.2% [14.6%, 35.9%]	< 0.001
Re-intervention in access circuit	25.5% (39/153)	50.7% (75/148)		
Access circuit thrombosis	2.0% (3/151)	3.4% (5/146)		

[1] Number of interventions required to maintain target lesion patency is defined as number of TLR post index procedure
[2] Number of interventions required to maintain access circuit patency is defined as number of re-interventions in the target lesion and/or access circuit post index procedure
[3] Access Circuit Primary Patency is defined as freedom from re-intervention in the access circuit or access circuit thrombosis post index procedure
† p-values for the binary key secondary endpoints were based on one-sided Z-test. p-values for the endpoints on number of interventions required were based on one-sided Wilcoxon sum rank test

A Kaplan-Meier analysis of the access circuit primary patency is shown below in **Figure 8** for all ITT subjects. The Kaplan-Meier survival curve shows access circuit primary patency through 210 days (72.5% in the IN.PACT AV DCB study group vs. 48.0% in the PTA control group).

Figure 8. Kaplan-Meier Plot – Access Circuit Primary Patency through 210 Days – ITT Analysis Set.



From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210
IN.PACT AV DCB (N=170 Subjects)								
# Entered	170	168	161	151	143	133	125	106
# Censored	1	4	5	3	2	3	12	13
# Events	1	3	5	5	8	5	7	7
Survival rate [%]	99.4%	97.6%	94.6%	91.4%	86.2%	83.0%	78.1%	72.5%
STANDARD PTA (N=160 Subjects)								
# Entered	160	158	155	148	129	110	99	78
# Censored	2	0	2	3	2	1	6	5
# Events	0	3	5	16	17	10	15	11
Survival rate [%]	100.0%	98.1%	94.9%	84.6%	73.3%	66.6%	56.1%	48.0%

Survival Curve Comparison				
Analysis Method	**Test**	**Chi Square**	**Degr. Freedom**	**P-Value**
Kaplan-Meier Analysis	Log-Rank	18.1873	1	<0.0001

The arrow bars are confidence intervals at each time point. The arrow bars and the log-rank p-value should be interpreted with caution because the analyses were not adjusted for multiplicity and the hypothesis testing was not pre-specified.

3. Subgroup Analyses

The following preoperative characteristic was evaluated for potential association with outcomes:

Gender
Clinical benefit of the IN.PACT AV DCB at 6-months was observed in both male (TLPP: 83.0% DCB vs. 61.7% PTA) and female subjects (TLPP: 80.8% DCB vs. 55.6% PTA). In addition, primary safety events at Day 30 were similar in both males (4.5% DCB vs. 4.0% PTA) and females (3.6% DCB vs. 5.3% PTA).

Table 18: Primary Endpoint Analysis by Gender

Primary Analysis	Gender	AV DCB (N=112 Male, N=58 Female)	Standard PTA (N=101 Male, N=59 Female)	Difference
Primary Safety	Male	4.5% (5/111)	4.0% (4/101)	0.5%
	Female	3.6% (2/55)	5.3% (3/57)	- 1.6%
Primary Effectiveness	Male	83.0% (83/100)	61.7% (58/94)	21.3%
	Female	80.8% (42/52)	55.6% (30/54)	25.2%

Geriatric Use
The IN.PACT AV DCB study had an upper age limit of 94 years, and had predefined study subgroups of ≤ the median age of 67.0 years and > the median age of 67.0 years. Within both subgroups, the IN.PACT AV DCB study group showed improvement on the primary effectiveness endpoints, and no statistically significant difference between treatment groups on the primary safety endpoint. The results of an exploratory analysis indicate that the treatment differences between IN.PACT AV DCB and PTA groups are generally consistent between 2 age groups defined by median age.

4. 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 132 investigators of which none were full-time or part-time employees of the sponsor and one 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: 1
- 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. 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

The primary effectiveness data drawn from the IN.PACT AV Access randomized clinical study demonstrated a reasonable assurance of effectiveness for the IN.PACT AV DCB when used in accordance with the inclusion and exclusion criteria for the indicated patient population. The 6-month target lesion primary patency (TLPP) rate was 82.2% in the IN.PACT AV DCB study group and 59.5% in the PTA control group ($p < 0.001$). The IN.PACT AV DCB study group was statistically superiorto the PTA control group. These results support the effectiveness of the IN.PACT AV DCB for the treatment of dysfunctional arteriovenous fistulae in the upper extremities.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in the clinical study conducted to support PMA approval as described above. The primary safety data drawn from the IN.PACT AV Access randomized clinical study demonstrated a reasonable assurance of safety for the IN.PACT AV DCB when used in accordance with its indication for use. The 30 day SAE rate involving the AV access circuit was 4.2% in the IN.PACT AV DCB study group and 4.4% in the PTA control group. The IN.PACT AV DCB study group met the primary safety endpoint with a pre-defined 7.5% non-inferiority margin. These results support the safety of the IN.PACT AV DCB for the treatment of dysfunctional arteriovenous fistulae in the upper extremities. However, Kaplan-Meier estimated cumulative incidence of infections and infestations through 360 days was 18.9% [13.1%, 25.5%] in the IN.PACT AV DCB group and 12.2% [7.6%, 18.1%] in the standard PTA group (log-rank p-value = 0.092). The Kaplan-Meier estimated cumulative incidence of pneumonia through 360 days was 7.9% [4.3%, 13.0%] in the IN.PACT AV DCB group and 4.1% [1.7%, 8.3%] in the standard PTA group (log-rank p-value = 0.164). While infections and pneumonia rates are typically high in this patient population, the increased rate of infection/infestation and pneumonia in the treatment group requires further monitoring.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The study met the primary effectiveness endpoint for target lesion primary patency, demonstrating superiority of the IN.PACT AV DCB study group compared to the PTA control group. The 6-month target lesion primary patency rate in the ITT population was 82.2% in the IN.PACT AV DCB study group versus 59.5% in the PTA control group ($p < 0.001$), primarily driven by the clinically driven target lesion revascularization (CD-TLR) rate.

As described above, the event-free survival at 30 days was non-inferior to PTA, indicating the probable risks from the IN.PACT AV DCB are similar to standard PTA. Additional factors to be considered in determining probable risks and benefits for the IN.PACT AV DCB included:

- Subject follow-up was adequate and with limited missing data to evaluate safety and effectiveness. Follow-up times for the primary endpoints were 30 days for safety and 6 months for effectiveness, and follow-up will continue for up to 5 years to evaluate the long-term device performance, such as the duration of the benefit and long-term adverse event rates.
- An increased risk of late mortality has been identified at 2 years and beyond for paclitaxel-eluting stents and paclitaxel-coated balloons used to treat femoropopliteal arterial disease[1, 2.] The mortality risk for paclitaxel-coated balloons indicated for arteriovenous fistulae is unknown. However, a trend towards increased mortality over time was not identified in the clinical trial for this device at one year. The device safety will continue to be monitored up to 5 years post-procedure through post-approval studies.
- An increased risk of infections and infestations, specifically incidence of pneumonia, was identified in the treatment group up to one year. Increased rates of pneumonia are expected for this patient population and decreased interventions may reduce the risk of infection over time. The observed increase is noted in the device labeling and will continue to be monitored through postmarket studies.
- This treatment may be preferred by subjects compared to the alternatives as their quality of life may improve due to lesser need for repeat procedures.

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

In conclusion, given the available information above, the clinical data support that the probable benefits outweigh the probable risks for using the device for the treatment of *de novo* or restenotic lesions in native arteriovenous fistulae in the upper extremity, having reference vessel diameter from 4 mm to 12 mm and total lesion lengths up to 100 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 IN.PACT AV DCB was evaluated in this prospective, global, multicenter, single-blinded, randomized study to demonstrate the safety and effectiveness of IN.PACT AV DCB versus standard PTA for the treatment of *de novo* or non-stented restenotic obstructive lesions up to 100 mm in length in the arteriovenous dialysis fistulae.

A total of 330 subjects were enrolled in the study. Baseline and procedural characteristics were well balanced between the study and control groups. Device, procedural and clinical success rates were high and comparable between the study and control groups.

The study met the primary effectiveness endpoint for target lesion primary patency, demonstrating superiority in the IN.PACT AV DCB study group compared to the PTA control group. The 6-month target lesion primary patency rate in the ITT population was 82.2% in the IN.PACT AV DCB study group versus 59.5% in the PTA control group ($p < 0.001$) primarily driven by the CD-TLR rate. The study also met the

primary safety endpoint. The IN.PACT AV DCB study group met the pre-defined 7.5% non-inferiority margin within 30-days post-procedure.

In conclusion, the IN.PACT AV Access study met its success criteria. The IN.PACT AV DCB demonstrated superior effectiveness over PTA and met the non-inferiority safety endpoint within 30 days. These results constitute valid scientific evidence demonstrating reasonable assurance of safety and effectiveness of the IN.PACT AV DCB and an improved benefit-risk profile for the treatment of *de novo* or non-stented restenotic obstructive lesions up to 100 mm in length in the arteriovenous dialysis fistulae**.**

XIII. CDRH DECISION

CDRH issued an approval order on November 21, 2019.

The final conditions of approval cited in the approval order are described below.

1. IDE Cohort Post Approval Study

The IN.PACT AV Access IDE Post Approval Study is a study that was initiated prior to device approval. It was designed as a prospective, global, randomized (1:1), multi-center clinical study that is ongoing at sites in the United States, New Zealand, and Japan. This study will evaluate the long-term safety and effectiveness of the IN.PACT AV DCB for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae. The study has 330 subjects with follow-up assessments scheduled up to 60-months post-index procedure.

The primary safety endpoint is defined as the serious adverse event (SAE) rate involving the AV access circuit through 30 days post-procedure. The primary effectiveness endpoint is defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-index procedure.

Secondary endpoints will be descriptively presented. Secondary endpoints that will be evaluated at 30 days, 3, 6, 9, 12, 18 and 24-months post-index procedure include: access circuit primary patency, target lesion primary patency, cumulative target lesion revascularizations, number of interventions required to maintain target lesion patency, number of interventions required to maintain access circuit patency, cumulative access circuit thromboses, device, procedure and clinical success and the rate of device and procedure and therapy related adverse events. Secondary endpoints that will be evaluated at 30-day, 3, 6, 9, 12, 18, 24, 36, 48, and 60-months post-index procedure include: target lesion revascularizations, CD-TLR, re-interventions in the access circuit, abandonment of target arteriovenous fistula and SAEs.

Data will be analyzed and reported to the Agency annually until completion.

2. New Enrollment Study

The New Enrollment IN.PACT AV Access Post-Approval Study is a prospective, single-arm, multi-center clinical study that will take place at up to 20 investigational sites in the United States and will evaluate the long-term safety of the IN.PACT AV DCB for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae. The study will have two cohorts: a primary cohort with a minimum of 125 patients evaluable at 1-year post-index procedure that meet the inclusion/exclusion criteria of the pre-market study and receive the IN.PACT AV DCB device, and an extended cohort of up to 80 subjects who do not meet the pre-market inclusion/exclusions criteria and receive the IN.PACT AV DCB device. The primary

cohort will be followed for 5-years post-index procedure; the endpoints for this cohort are described below. The extended cohort will be followed for 5-years; the endpoints include infections and infestations, including pneumonia, reported through 1-year and mortality reported through 5-years post-index procedure.

The primary cohort has a primary safety endpoint of site reported incidence of infection and infestation SAEs through 12-months post-index procedure. There is a performance goal of 30%.

The primary cohort secondary safety endpoint is the mortality rate through 1, 2, 3, 4, and 5 years post-index procedure. Additional primary cohort endpoints include: SAEs, target lesion primary patency, access circuit primary patency, cumulative target lesion revascularizations, number of interventions required to maintain target lesion patency, number of interventions required to maintain access circuit patency, cumulative access circuit thromboses, device, procedure and clinical success and the rate of device, procedure and therapy related adverse events at 6-months and 1, 2, 3, 4, and 5 years post-index procedure.

Data will be analyzed and reported to the Agency at 6-months and annually thereafter until completion.

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

1. Katsanos, K., S. Spiliopoulos, P. Kitrou, M. Krokidis, and D. Karnabatidis. 2018. 'Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials', *J Am Heart Assoc*, 7: e011245.
2. Food and Drug Administration June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee. Available Online: https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-19-20-2019-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting.