

# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

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

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

Device Procode: ONU

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

Date(s) of Panel Recommendation: Not Applicable

Premarket Approval Application: P140010  
(PMA) Number:

Date of FDA Notice of Approval: December 30, 2014

Priority Review: Granted priority review status on June 27, 2014 because the device offers significant advantages over existing approved alternatives

## II. INDICATIONS FOR USE

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

## III. CONTRAINDICATIONS

The IN.PACT Admiral DCB is contraindicated for use in:

- coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
- patients with known allergies or sensitivities to paclitaxel
- women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children. It is unknown whether paclitaxel will be

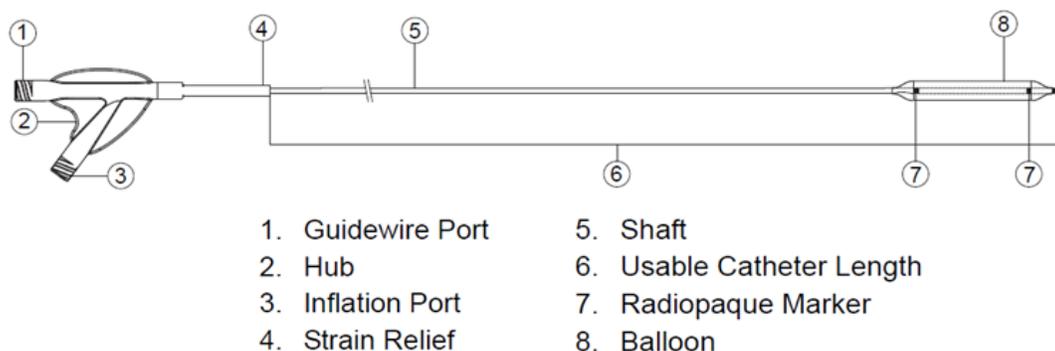
excreted in human milk and whether there is a potential for adverse reaction in nursing infants from paclitaxel exposure.

#### IV. WARNINGS AND PRECAUTIONS

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

#### V. DEVICE DESCRIPTION

The IN.PACT Admiral DCB is an over-the-wire balloon catheter with a drug coated balloon at the distal tip (see **Figure 1**).



**Figure 1: Schematic of the IN.PACT Admiral DCB**

#### PTA Catheter Component

The IN.PACT Admiral DCB will be available in balloon lengths ranging from 20 mm to 120 mm, balloon diameters ranging from 4.0 mm to 7.0 mm, and will be offered in catheter effective lengths of 80 cm and 130 cm. The IN.PACT Admiral DCB is compatible with 0.035” guidewires. Devices are compatible with 5F (for the 4.0 mm balloon diameter), 6F (for the 5.0-6.0 mm balloon diameters), and 7F (for the 7 mm balloon diameter) introducer sheaths. Note that all device sizes proposed for marketing were included in the clinical trials with the exception of the 7 x 120 mm balloon. The IN.PACT Admiral DCB product matrix is provided in **Table 1**.

**Table 1: IN.PACT Admiral DCB Product Matrix**

Diameter (mm)	Balloon Length (mm)					Balloon Wrap
	20	40	60	80	120	
4.0	✓	✓	✓	✓	✓	3 folds
5.0	✓	✓	✓	✓	✓	
6.0	✓	✓	✓	✓	✓	
7.0	✓	✓	✓	✓	---	

*Notes:*  
 “✓” indicates sizes intended for commercialization with IN.PACT Admiral DCB product in the U.S.  
 “---” indicates size not offered with IN.PACT Admiral DCB product.  
 All sizes are offered in both 80 cm and 130 cm catheter useable lengths.  
 The device is compatible with a 0.035” guidewire.

## Drug Components

The IN.PACT Admiral DCB is coated with the FreePac™ coating solution, which is a proprietary coating with a nominal drug dose density of 3.5 µg of paclitaxel per mm<sup>2</sup> of the expanded balloon surface. The FreePac coating contains a hydrophilic excipient (urea) which facilitates the release and transfer of the active pharmaceutical ingredient (paclitaxel) into the arterial vessel wall. Additionally, the FreePac solution contains two solvents, tetrahydrofuran (THF) and pyrogen-free water, which are used during the FreePac formulation process but evaporate off the balloon surface after the FreePac coating is applied.

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

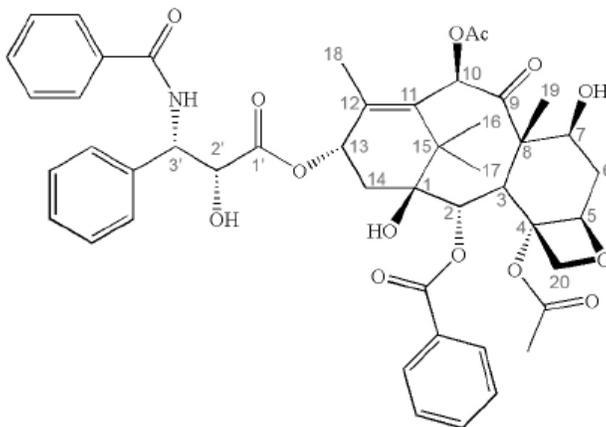
**Table 2: Nominal Paclitaxel Content by Balloon Size**

<b>IN.PACT Admiral DCB Balloon Size (mm)</b>	<b>Nominal Paclitaxel Content (µg)</b>
4.0x20	1089
4.0x40	1969
4.0x60	2848
4.0x80	3728
4.0x120	5487
5.0x20	1454
5.0x40	2553
5.0x60	3653
5.0x80	4752
5.0x120	6951
6.0x20	1850
6.0x40	3170
6.0x60	4489
6.0x80	5809
6.0x120	8448
7.0x20	2279
7.0x40	3819
7.0x60	5358
7.0x80	6897

### Active Pharmaceutical Ingredient (API) - Paclitaxel

The API of the IN.PACT Admiral DCB is paclitaxel. Paclitaxel is a FDA-approved drug, indicated for the treatment of multiple cancers including breast and ovarian cancer. The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division. The CAS Registry number of paclitaxel is 33069-62-4. The chemical name is *(2aR)-(2aα, 4β, 4aβ, 6β, 9α(α R\*, βS\*), 11a, 12a, 12bα))-β-(Benzoylamino)-*

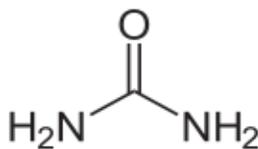
*α*-hydroxybenzenepropanoic acid 6,12*b*-bis(acetyloxy)-12-(benzoyloxy)-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-4,11-dihydroxy-4*a*,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca(3,4)benz(1,2-*b*)oxet-9-yl ester and the chemical formula is C<sub>47</sub>H<sub>51</sub>NO<sub>14</sub>. The chemical structure of paclitaxel is illustrated in **Figure 2** below.



**Figure 2: The Chemical Structure of Paclitaxel**

### Excipient

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



**Figure 3: The Chemical Structure of Urea**

### **Mechanism of Action**

The IN.PACT Admiral DCB's primary mode of action is mechanical dilatation of *de novo* or restenotic lesions by means of percutaneous transluminal angioplasty, with a secondary action of inhibition of restenosis (caused by the proliferative response to the PTA) through the application of paclitaxel to the vessel wall. The primary effect attributed to the device forms the basis for primary regulation under by the Center for Devices and Radiological Health (CDRH) with consultation from the Center for Drug Evaluation and Research (CDER).

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are several other alternatives for the treatment of superficial femoral and popliteal artery atherosclerotic disease, including:

- Non-invasive treatment (risk factor modification, exercise, and/or drug therapy)
- Minimally invasive treatment (balloon angioplasty, bare metal or drug-eluting stent, or plaque debulking by atherectomy)
- Surgical treatment (surgical bypass)

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

The IN.PACT Admiral DCB has been available for distribution in the European Union (EU) since receiving CE mark on March 12, 2009. The IN.PACT Admiral DCB has not been withdrawn from marketing for any reason related to safety or effectiveness. As of October 2014, over 64,700 IN.PACT Admiral DCB units have been sold. The IN.PACT Admiral DCB is available for commercial distribution in 94 countries listed in **Table 3** below.

**Table 3: Commercial Availability of the IN.PACT Admiral DCB**

Afghanistan	Egypt	Kuwait	Serbia
Albania	Estonia	Kyrgyzstan	Singapore
Algeria	Finland	Latvia	Slovakia
Argentina	France	Lebanon	Slovenia
Armenia	Georgia	Libya	Spain
Australia	Germany	Liechtenstein	Sri Lanka
Austria	Ghana	Lithuania	Sweden
Bahrain	Greece	Luxemburg	Switzerland
Barbados	Guatemala	Macau	Taiwan
Belarus	Honduras	Malaysia	Thailand
Belgium	Hong Kong	Malta	Trinidad and Tobago
Bosnia & Herzegovina	Hungary	Mexico	Tunisia
Botswana	Iceland	Netherlands	Turkey
Brazil	India	New Zealand	United Kingdom
Bulgaria	Indonesia	Norway	Ukraine
Caribbean Islands	Iran	Pakistan	United Arab Emirates
Chile	Iraq	Panama	Uruguay
Colombia	Ireland	Paraguay	Venezuela
Costa Rica	Israel	Peru	Vietnam
Croatia	Italy	Philippines	
Cyprus	Jordan	Poland	
Czech Republic	Kazakhstan	Portugal	
Denmark	Kenya	Romania	
Dominican Republic	Korea	Russia	
Ecuador	Kosovo	Saudi Arabia	

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

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

- abrupt vessel closure
- access site pain
- allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (materials, drugs, and excipients)
- amputation/loss of limb
- arrhythmias
- arterial aneurysm
- arterial thrombosis
- arteriovenous (AV) fistula
- death
- dissection
- embolization
- fever
- hematoma
- hemorrhage
- hypotension/hypertension
- inflammation
- ischemia or infarction of tissue/organ
- local infection at access site
- local or distal embolic events
- perforation or rupture of the artery
- pseudoaneurysm
- renal insufficiency or failure
- restenosis of the dilated artery
- sepsis or systemic infection
- shock
- stroke
- systemic embolization
- vessel spasms or recoil
- vessel trauma which requires surgical repair

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

- balloon rupture
- detachment of a component of the balloon and/or catheter system

- failure of the balloon to perform as intended
- failure to cross lesion

These complications may result in adverse events.

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

- allergic/immunologic reaction
- alopecia
- anemia
- gastrointestinal symptoms
- hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- hepatic enzyme changes
- histologic changes in 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 15** in the Clinical Studies section below.

## **IX. SUMMARY OF PRECLINICAL STUDIES**

A series of non-clinical laboratory studies were performed on the IN.PACT Admiral DCB. These evaluations included biocompatibility studies, *in vitro* bench testing, GLP animal studies, analytical testing, stability and shelf life, and sterilization. A summary for each of the evaluations is provided below.

### **A. Laboratory Studies**

#### **Biocompatibility**

Biocompatibility testing for the 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 IN.PACT balloon catheter. In addition, thrombogenicity and chemical characterization testing was conducted *in vivo* on the IN.PACT balloon catheter with the drug coating to support the overall biocompatibility of the drug-coated balloon. The balloon with the drug coating was categorized as an implant device with permanent blood contact (>30 days), and the remainder of the IN.PACT 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 on the IN.PACT Admiral DCB**

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
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
	<i>In vivo</i> 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

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
	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 traditional biocompatibility studies were not conducted on the IN.PACT Admiral DCB: 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 IN.PACT Admiral DCB is biocompatible for its intended use.

### ***In vitro* Bench Testing**

**Table 5** provides an overview of the functional testing performed on the IN.PACT Admiral DCB. The table includes the test performed, the objective of the tests, the acceptance criteria (as applicable), and the result of the test.

**Table 5: Summary of Functional Testing Performed on the IN.PACT Admiral DCB**

Test	Testing Summary and/or Objective	Acceptance Criteria (Specification)		Pass/Fail
<b>Delivery System Profiles</b>	To determine the maximum outer diameter (OD) of the catheter shaft and the balloon	<b>Balloon Diameter (mm)</b>	<b>Maximum Crossing Profile (mm)</b>	Pass
		4.0 (all lengths)	< 1.88	
		5.0 (all lengths)	< 2.00	
		6.0 (all lengths except 120 mm)	< 2.10	
		6.0 mm (120 mm length), 7.0 (all lengths)	< 2.33	

Test	Testing Summary and/or Objective	Acceptance Criteria (Specification)	Pass/Fail																					
<b>Catheter Effective Length (Catheter tip to strain relief)</b>	To delineate the effective length of the catheter	80 cm ± 2 cm 130 cm ± 2 cm	Pass																					
<b>Balloon Working Length at Nominal Pressure</b>	Determine the balloon length at nominal pressure	<table border="1"> <thead> <tr> <th colspan="3">Balloon Working Length (mm)</th> </tr> <tr> <th>Nom.</th> <th>Min.</th> <th>Max.</th> </tr> </thead> <tbody> <tr> <td>20</td> <td>18.5</td> <td>21.5</td> </tr> <tr> <td>40</td> <td>38</td> <td>42</td> </tr> <tr> <td>60</td> <td>57</td> <td>63</td> </tr> <tr> <td>80</td> <td>75</td> <td>85</td> </tr> <tr> <td>120</td> <td>114</td> <td>126</td> </tr> </tbody> </table>	Balloon Working Length (mm)			Nom.	Min.	Max.	20	18.5	21.5	40	38	42	60	57	63	80	75	85	120	114	126	Pass
Balloon Working Length (mm)																								
Nom.	Min.	Max.																						
20	18.5	21.5																						
40	38	42																						
60	57	63																						
80	75	85																						
120	114	126																						
<b>Balloon Preparation</b>	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	The balloon catheter preparation, delivery, balloon inflation/deflation, and catheter retraction procedural steps must not damage the balloon catheter.	Pass																					
<b>Balloon Rated Burst Pressure</b>	Determine the minimum burst strength of the balloon and calculate the rated burst pressure (RBP)	Devices will not fail at or below the rated burst pressure of 14 atm.	Pass																					
<b>Marker Band Spacing</b>	Determine the marker band spacing at nominal pressure	<p>The inside edge of the marker band cannot be outside the balloon working length by more than 1 mm.</p> <p>The outside edge of the marker band cannot be inside the balloon working length by more than:</p> <table border="1"> <thead> <tr> <th>Balloon Length (mm)</th> <th>Maximum (mm)</th> </tr> </thead> <tbody> <tr> <td>20</td> <td>1.0</td> </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> </tbody> </table>	Balloon Length (mm)	Maximum (mm)	20	1.0	40	2.0	60	2.5	80	3.0	120	4.0	Pass									
Balloon Length (mm)	Maximum (mm)																							
20	1.0																							
40	2.0																							
60	2.5																							
80	3.0																							
120	4.0																							
<b>Balloon Fatigue</b>	Determine that balloons will sustain 10 inflations to RBP in an unconstrained environment	Samples will withstand 10 cycles at rated burst pressure.	Pass																					
<b>Balloon Compliance (Diameter vs. Pressure)</b>	Evaluate the change in balloon diameter as a function of the inflation pressure	Balloon Diameter must be within ± 0.4 mm of the nominal diameter for 4 mm diameter balloons and within ± 0.5 mm of the nominal diameter for 5-7 mm diameter balloons.	Pass																					

Test	Testing Summary and/or Objective	Acceptance Criteria (Specification)	Pass/Fail
<b>Balloon Inflation / Deflation Time</b>	Demonstrate that inflation and deflation of the balloon can be accomplished within clinically acceptable time limits	Inflation Time: For characterization only.  Deflation Time: Deflation time from RBP must be $\leq 60$ sec	Pass
<b>Tensile Strength:</b> <b>(a) Luer / Bilumen Tube</b> <b>(b) Bilumen Tube / Marker Tube</b> <b>(c) Marker Tube / Tip Tube</b> <b>(d) Proximal Balloon Weld</b> <b>(e) Distal Balloon Weld</b>	Determine the tensile strength of the catheter bonds after pre-conditioning	(a) (b) (d) minimum strength $\geq 10$ Newton (c) (e) minimum strength $\geq 5$ Newton	Pass
<b>Catheter Flexibility and Kink Resistance</b>	Demonstrate that the catheter will not kink when subjected to flexural forces	Catheter shaft will not kink at radius of 12.5 mm	Pass
<b>Catheter Kink to Failure</b>	Determine the minimum diameter at which catheter will experience kinking	This test is for characterization only	N/A (For Information Only)
<b>Torque Strength</b>	Demonstrate that the catheter has adequate torque strength after pre-conditioning	The balloon catheter must withstand a minimum of 10 full (360 degree) rotations inside the SFA model with the distal end fixed and the guidewire in place.	Pass
<b>Catheter Torque Strength to Failure</b>	To determine the failure point of the catheter after application of torque	This test is for characterization only	N/A (For Information Only)

### Analytical Testing

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

**Table 6: Summary of Analytical Testing Performed on the IN.PACT Admiral DCB**

Test	Description of Test	Acceptance criteria	Results
<b>Drug (paclitaxel) Identification</b>	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.
<b>Coating Appearance</b>	Visual inspection was conducted to verify that the IN.PACT Admiral DCB drug coating meets the appearance specification.	Must meet visual standard	The device met the established acceptance criteria.

<b>Test</b>	<b>Description of Test</b>	<b>Acceptance criteria</b>	<b>Results</b>
<b>Assay (potency)</b>	Quantitative determination of an assay to determine the total amount of paclitaxel on the IN.PACT Admiral DCB	USP <905>	The device met the established acceptance criteria.
<b>Content Uniformity</b>	Verification of the content uniformity of the paclitaxel coating from balloon to balloon	USP <905>	The device met the established acceptance criteria.
<b>Related Substances/ Impurities</b>	Quantitative determination of an assay to determine the type and amount of impurities and degradation products of the IN.PACT Admiral DCB	ICH Guidance	The device met the established acceptance criteria.
<b>In Vitro Elution</b>	Determination of the <i>in vitro</i> release rate of paclitaxel from the IN.PACT Admiral DCB	USP <711>	The device met the established acceptance criteria.
<b>Drug Content Circumferential Uniformity</b>	Measure the relative uniformity of the drug content around the balloon circumference of finished IN.PACT Admiral DCB.	This testing was performed for characterization only	N/A (For Information Only)
<b>Drug Content Length Uniformity</b>	Measure the relative uniformity of the drug content along the balloon length of finished IN.PACT Admiral DCB.	This testing was performed for characterization only	N/A (For Information Only)
<b>Particulate</b>	Particulate levels measured for the IN.PACT Admiral DCB	This testing was performed for characterization only	N/A (For Information Only)
<b>Particulate Identification</b>	Identification of the particulate for the IN.PACT Admiral DCB	This testing was performed for characterization only	N/A (For Information Only)

## **B. Animal Studies**

Medtronic has conducted the following *in vivo* animal testing in a porcine ilio-femoral artery model to evaluate the safety and bioanalytical efficacy of the IN.PACT Admiral DCB. All animal studies were conducted in accordance with 21CFR 58 (Good Laboratory Practices).

In addition to the principal endpoints noted for each study, all animals were carefully evaluated for general health (i.e. vital signs, behavior, nutritional condition, gait, etc.) and clinical responses to treatment, employing the Subjective Objective Assessment Plan (SOAP) methodology for documentation.

- Two pharmacokinetic studies (time points from 0 to 320 days) were completed to evaluate the drug content in plasma, treated ilio-femoral arterial tissue, non-target organ tissue, and downstream muscle specimens.
- One comparative pharmacokinetic study was conducted, to evaluate the residual drug on the balloon and the drug in tissue, utilizing two methods of delivery (contralateral and carotid approach) at an acute time point.
- Six safety studies, including acute (day 1) and chronic (days 7, 28, 90, 180, and 365) durations were completed to provide evidence of drug delivery, tissue response, and safety in the swine ilio-femoral arteries.

A list and description of the animal studies conducted is presented in **Table 7** below.

**Table 7: Summary of *In-Vivo* Animal Studies**

Study ID	No. and Type of Animals	Duration	Drug Dose Evaluated	Balloon Size	Major Endpoints	Endpoints Met
FS201 – 0-180 Day Pharmacokinetic Study	99 Domestic Farm Swine	0, 1, 2, 7, 28, 60, 90, & 180 Days	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> )	Diameter: 5.0 or 6.0 mm Length: 80 mm	Tissue Analysis Plasma Analysis	Yes
FS207 – 0-320 Day Pharmacokinetic Analysis and 365 Day Safety Study	23 (PK) and 8 (Safety) Domestic Farm Swine	PK: 0 & 320 Days	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> )	Diameter: 5.0 or 6.0 mm Length: 80 mm	PK: Tissue Analysis Plasma Analysis	Yes
		Safety: 365 Days	Arm3: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm4: Safety Margin dose (10.5 µg/mm <sup>2</sup> ) Arm5: Untreated vessel		Safety: Angiographic Performance Morphometric Analysis Histopathology	Yes
FS208 – An Acute Pharmacokinetic Comparison of Carotid vs. Contralateral Delivery Approach	9 Domestic Farm Swine	Acute (Day 0)	Therapeutic dose (3.5 µg/mm <sup>2</sup> )	Diameter: 5.0 or 6.0 mm Length: 80 mm	Comparison of residual drug on balloon Comparison of drug in tissue	Yes

<b>Study ID</b>	<b>No. and Type of Animals</b>	<b>Duration</b>	<b>Drug Dose Evaluated</b>	<b>Balloon Size</b>	<b>Major Endpoints</b>	<b>Endpoints Met</b>
FS206 – A 24 Hour Safety Study	25 Yucatan mini Swine	24 Hours	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> ) Arm3: Control POBA	Diameter: 5.0 or 6.0 mm Length: 80 mm	Acute Performance Angiographic Performance Morphometric Analysis Histopathology SEM Analysis	Yes
FS205 – A 7 Day Safety Study	25 Yucatan mini Swine	7 Days	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> ) Arm3: Control POBA	Diameter: 5.0 or 6.0 mm Length: 80 mm	Acute Performance Angiographic Performance Morphometric Analysis Histopathology	Yes
FS203 – A 28 Day Safety Study	21 Yucatan mini Swine	28 days	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> ) Arm3: Control POBA	Diameter: 5.0 or 6.0 mm Length: 80 mm	Acute Performance Angiographic Performance Morphometric Analysis Histopathology SEM Analysis	Yes
FS204 – A 90 Day Safety Study	22 Yucatan mini Swine	90 Days	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> ) Arm3: Control POBA	Diameter: 5.0 or 6.0 mm Length: 80 mm	Acute Performance Angiographic Performance Morphometric Analysis Histopathology SEM Analysis	Yes
FS202 – A 180 Day Safety Study	23 Yucatan mini Swine	180 Days	Arm1: Therapeutic dose (3.5 µg/mm <sup>2</sup> ) Arm2: Safety Margin dose (10.5 µg/mm <sup>2</sup> ) Arm3: Control POBA	Diameter: 5.0 or 6.0 mm Length: 80 mm	Acute Performance Angiographic Performance Morphometric Analysis Histopathology SEM Analysis	Yes

The preclinical studies conducted demonstrate and confirm the safety, effective drug uptake, and utility after treatment with the IN.PACT Admiral DCB. The acute (day 1) and chronic (days 7, 28, 90, 180, and 365 day) GLP safety evaluation studies of IN.PACT Admiral DCB demonstrated favorable safety parameters as defined by the following:

- Successful delivery of the test device to the target treatment location without major procedural or device related complications such as death, artery perforation or flow-limiting dissection/thrombosis in  $\geq 90\%$  of animals.
- A frequency of major device-related complications during the treatment procedures and in-life phases of the experiments with less than 10% procedural and post-operative animal mortality related to device complications.
- Angiographic flow and angiographic percent stenosis in vessels receiving the test articles (therapeutic dose) is similar to vessels receiving the control (uncoated balloon).
- Comparable performance by quantitative morphometric analysis in tissue sections treated with the test articles (therapeutic dose) when compared to tissue sections treated with the uncoated control or untreated vessels.
- Comparable histological indicators of vessel wall healing such as: injury, inflammation and the extent of endothelial coverage as determined by light microscopy and scanning electron microscopy (SEM) in tissue sections treated with the test articles (therapeutic dose) when compared to control tissue sections.
- Absence of significant vascular response to non-target tissues.

The two nonclinical pharmacokinetic studies (up 320 days, 80 mm balloons) demonstrated effective drug delivery and uptake into the arterial tissues at the therapeutic dose density ( $3.5 \mu\text{g}/\text{mm}^2$ ) as follows:

- Successful delivery of the balloons in the iliofemoral arteries without incident.
- Low peak plasma paclitaxel concentration ( $C_{\text{max}} = 1.6 \text{ ng/mL}$ ), which rapidly declined and was undetectable after 48 hours.
- Rapid uptake into the target arteries, with peak paclitaxel levels at  $35.4 \text{ ng/mL}$  immediately post implantation, followed by a steady decline to undetectable levels after 180 days.

Though higher drug exposures in both the plasma and target tissues were observed for balloons coated with a high drug dose density ( $10 \mu\text{g}/\text{mm}^2$ ), the histopathology data demonstrated an acceptable drug dose safety margin for the intended therapeutic dose of  $3.5 \mu\text{g}/\text{mm}^2$ .

### **C. Additional Studies**

#### **Stability and Shelf Life Studies**

Finished product stability studies were conducted according to USP and ICH guidelines and are currently ongoing to establish the shelf life for the IN.PACT Admiral DCB finished product. The testing includes an evaluation of potency, impurities, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents, urea and endotoxins. Appropriate functional tests were also performed on aged product and compared to baseline to ensure that the IN.PACT Admiral DCB performed acceptably. The data generated from the stability studies, coupled with the data generated from the shelf life studies, currently supports a 12-month label claim and associated shelf life for

the product. The expiration date/shelf life of the finished product will be evaluated and extended as additional stability/shelf life data becomes available.

### **Sterilization**

IN.PACT Admiral DCB is sterilized using ethylene oxide sterilization, and has been validated per AAMI/ISO 11135-1:2007 “Sterilization of health care products-Ethylene Oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices” and EN556-1:2002 “Sterilization of Medical Devices – Requirements for medical devices to be designated STERILE – Part 1: Requirements for terminally sterilized medical devices”. The testing for ethylene-oxide 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 for IN.PACT Admiral DCB.

## **X. SUMMARY OF PRIMARY CLINICAL STUDIES**

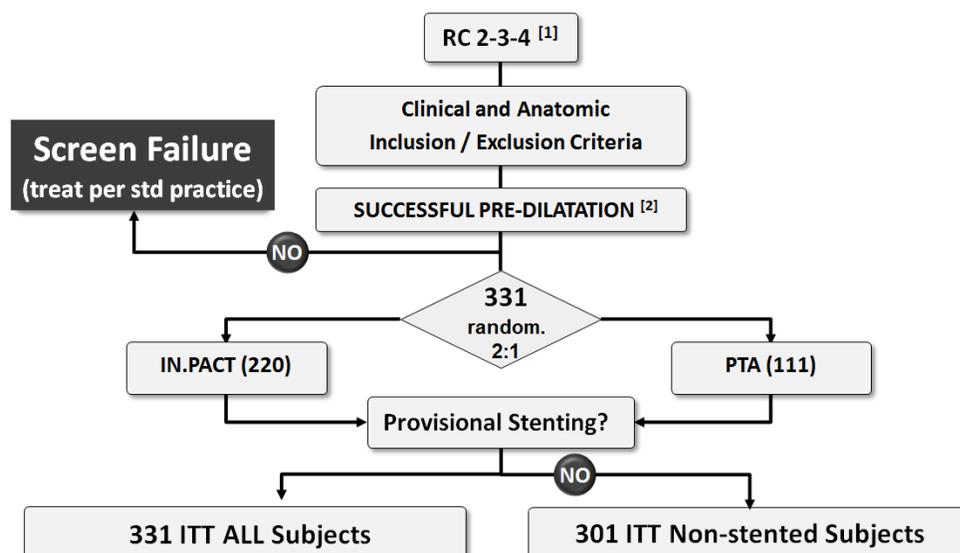
### ***IN.PACT SFA Trial***

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous balloon angioplasty, after predilatation, of de novo and restenotic lesions in native superficial femoral and popliteal arteries with the Medtronic DCB in Europe (SFAI - Austria, Belgium, Germany, Italy, and Switzerland) and the US (SFAII) under IDE # G110200. Data from this clinical study were the basis for the PMA approval decision. A summary of the pivotal study is presented below.

#### **A. Study Design**

Patients were treated between September 2, 2010 and April 28, 2011 for the SFAI trial and between April 9, 2012 and January 8, 2013 for the SFAII trial. The database for this PMA (P140010) reflected data collected through February 10, 2014 and included 331 patients. There were 57 investigational sites.

The study was a two-phase, multicenter, single-blind, randomized (2:1 IN.PACT Admiral DCB to PTA) trial to investigate the safety and effectiveness of the IN.PACT Admiral DCB in subjects with claudication and/or rest pain and with a positive diagnostic finding of *de novo* stenosis and/or non-stented restenotic lesions in the SFA and/or PPA. A subject was randomized once they had been consented, met eligibility criteria, and underwent successful pre-dilatation (for the SFA II Trial), as seen in **Figure 4**.



1. With symptoms of claudication and/or rest pain and angiographic evidence of SFA/PPA stenosis
2. Pre-dilatation mandatory for all subjects in IN.PACT SFA II phase only

**Figure 4: Study Flow Chart**

The data from the IN.PACT SFA Trial, with greater than 50% of subjects coming from the U.S. population (150 subjects Europe and 181 subjects U.S.), have been pooled and comprise the pivotal trial data set. This aggregate data provides statistical power for the 12-month primary safety and effectiveness endpoints. The statistical analysis plan included planned primary analysis of all non-stented patients, as well as a secondary analysis of the intent to treat (ITT) population. The demographics and results provided are for the ITT population, which demonstrated similar results as the all non-stented patient population.

There were two hypotheses for the trial. One was for the primary safety endpoint at 12 months and one was for the primary effectiveness endpoint at 12 months. Each hypothesis was tested first on the all ITT non-stented subjects followed by the all ITT subjects, as pre-specified in the Statistical Analysis Plan.

For the primary safety endpoint, the treatment ( $\pi_T$ ) and control ( $\pi_C$ ) groups were compared in a non-inferiority format under the following hypothesis.

$$H_0: \pi_T \leq \pi_C - 0.1$$

$$H_A: \pi_T > \pi_C - 0.1$$

For the primary effectiveness endpoint, the treatment ( $p_T$ ) and control ( $p_C$ ) groups were compared in a superiority format under the following hypothesis:

$$H_0: p_T = p_C$$

$$H_A: p_T > p_C$$

The IN.PACT SFA I/II Trial was designed as a single-blind trial to maximize the quality and integrity of the data. In this randomized trial design, the subjects, those involved in data analysis, the Core Laboratories, and the Clinical Events Committee (CEC) were blinded. Subjects and those that the sponsor involved in data analysis remained blinded

through the completion of all 12-month (primary endpoint) evaluations. The Core Laboratories and CEC will remain blinded for the duration of the trial. Along with the CEC, a Data Monitoring Committee (DMC) was created to review the overall safety data and make recommendations for continuation of the study. The DMC was not blinded in order to perform their core function.

#### 1. Clinical Inclusion and Exclusion Criteria

Enrollment in the IN.PACT SFA Trial was limited to the following inclusion criteria:

- $\geq 18$  years and  $\leq 85$  years of age;
- Documented ischemia with Rutherford classification 2, 3, or 4;
- Life expectancy, in the Investigator's opinion, of at least 12 months;
- Target lesion is in the SFA and/or PPA down to the P1 segment;
- Adequate distal run-off through the foot;
- Reference vessel diameter  $\geq 4$  mm and  $\leq 7$  mm by visual estimate; and
- Angiographic evidence that target lesion consists of a single *de novo* or non-stented restenotic lesion (or tandem lesions or a combination lesion as defined below) that is:
  - 70% - 99% occluded with total lesion length  $\geq 40$  mm and  $\leq 180$  mm (by visual estimate); or
  - 100% occluded with total lesion length  $\leq 100$  mm (by visual estimate).

Note: Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that (1) the combined lesion length is  $\geq 40$  mm and  $\leq 180$  mm and (2) the totally occluded segment is not greater than 100 mm in length. Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria:

- Separated by a gap of  $\leq 30$  mm (3 cm);
- Total combined lesion length meets requirements (including 30 mm gap); and
- Able to be treated as a single lesion.

Patients were not permitted to enroll in the IN.PACT SFA Trial if they met any of the following exclusion criteria:

- Stroke or STEMI within 3 months prior to enrollment;
- Known allergies or sensitivities to heparin, aspirin, other anticoagulant/antiplatelet therapies, and/or paclitaxel;
- Chronic renal insufficiency with serum creatinine  $> 2.5$  mg/dL
- Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the contralateral SFA/PPA) planned within 30 days post index procedure;
- Presence of a second lesion in the target vessel that requires treatment but does not meet the definition of "tandem lesions";
- Failure to successfully cross the target lesion with a guidewire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations); and

- Target lesion is an in-stent restenosis, a post-DCB restenosis, or has been previously treated with bypass surgery.

## 2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 6, 12, 24 and 36 months with a telephone follow-up at 48 and 60 months postoperatively. A subgroup of patients was subjected to a pharmacokinetics substudy for collection of a blood sample at post-procedure and 1 month follow-up.

Preoperatively, a screening was performed. A peri-procedure assessment was also performed. **Table 8** below summarizes the objective parameters and key timepoints of the IN.PACT SFA Trial.

**Table 8: IN.PACT SFA Trial Follow-up Evaluation Schedule**

Test Evaluation	Screening	Peri- Procedure	Discharge	30 days ±7 Days*	6 months ±30 Days	12 months ±30 Days	24 months ±30 Days	36 months ±30 Days	48 months ±60 Days (Phone)	60 months ±60 Days (Phone)	Unscheduled Visit (for ischemic events)
Informed Consent	X										
Physical Exam <sup>†</sup> and Medical History	X		X	X	X	X	X	X			X
Rutherford	X			X	X	X	X	X			X
Hematology	X		X	X		X					X
CMP	X		X	X		X					X
WIQ and EQ5D	X			X	X	X	X	X			X
6MWT with vital signs <sup>‡</sup>	X			X	X	X	X	X			X
Pregnancy Test	X										
ABI/TBI	X			X	X	X	X	X			X
Angiogram		X									X
Activated clotting time (ACT) <sup>‡</sup>		X									
DUS Scan				X	X	X	X	X			X
AE Assessment		X	X	X	X	X	X	X	X	X	X
* IN.PACT SFA I Phase required a telephone follow-up at 30 days to assess medical history and adverse events. <sup>†</sup> Physical Exam was inclusive of a lower extremity exam in IN.PACT SFA II phase only <sup>‡</sup> 6MWT was only conducted in the IN.PACT SFA II phase <sup>‡</sup> ACT was only measured in the IN.PACT SFA II phase											

## 3. Clinical Endpoints

- With regards to safety, the primary endpoint was:
  - Freedom from device- and procedure-related death through 30 days post-index procedure and freedom from target limb major amputation and

clinically-driven target vessel revascularization (TVR)<sup>a</sup> within 12 months post-index procedure

<sup>a</sup> Clinically-driven TVR is defined as any re-intervention within the target vessel due to symptoms or drop of ABI/TBI of  $\geq 20\%$  or  $> 0.15$  when compared to post-procedure baseline ABI/TBI

- With regards to effectiveness, the primary endpoint was:
  - Primary Patency within 12 months post-index procedure, defined as freedom from clinically-driven target lesion revascularization (TLR)<sup>b</sup> and freedom from restenosis as determined by duplex ultrasound (DUS)<sup>c</sup> peak systolic velocity ratio (PSVR)  $\leq 2.4$ <sup>d</sup>
    - <sup>b</sup> Clinically-driven TLR is defined as any re-intervention at the target lesion due to symptoms or drop of ABI/TBI of  $\geq 20\%$  or  $> 0.15$  when compared to post-procedure baseline ABI/TBI
    - <sup>c</sup> Post-index procedure DUS (intended to establish a post-treatment baseline) does not contribute to the primary endpoint determination
    - <sup>d</sup> Restenosis determined by either PSVR  $> 2.4$  as assessed by an independent DUS core laboratory or  $> 50\%$  stenosis as assessed by an independent angiographic core laboratory
  
- The secondary endpoints for the IN.PACT SFA Trial are listed below.
  - Major Adverse Events (MAE) through 60 months. MAE are defined as all-cause death, clinically-driven TVR, major target limb amputation, and thrombosis at the target lesion site
  - Death of any cause within 30 days, 6, 12, 24, 36, 48 and 60 months
  - TVR within 6, 12, 24, 36, 48 and 60 months
  - TLR within 6, 12, 24, 36, 48 and 60 months
  - Time to first clinically-driven target lesion revascularization (TLR) through 60 months post-index procedure
  - Major target limb amputation within 6, 12, 24, 36, 48 and 60 months
  - Thrombosis at the target lesion site within 6, 12, 24, 36, 48 and 60 months
  - Primary sustained clinical improvement at 6, 12, 24, 36 months post-procedure
  - Secondary sustained clinical improvement at 6, 12, 24, 36 months post-procedure
  - Duplex-defined binary restenosis (PSVR  $> 2.4$ ) of the target lesion at 6, 12, 24 and 36 months or at the time of the re-intervention prior to any pre-specified timepoint
  - Duplex-defined binary restenosis (PSVR  $> 3.4$ ) of the target lesion at 6, 12, 24 and 36 months or at the time of the re-intervention prior to any pre-specified timepoint

- Quality of life assessment by EQ5D questionnaire at 6, 12, 24, 36 months as change from baseline
- Walking distance as assessed by 6 Minute Walk Test at 30 days and at 6, 12, 24, 36 months as change from baseline (IN.PACT SFA II phase only)
- Walking capacity assessment by walking impairment questionnaire (WIQ) at 30 days and at 6, 12, 24, 36 months
- Device success defined as successful delivery, balloon inflation and deflation and retrieval of the intact study device without burst below the rated burst pressure (RBP)
- Procedural success defined as residual stenosis of  $\leq 50\%$  (non-stented subjects) or  $\leq 30\%$  (stented subjects) by core laboratory (if core laboratory was not available then the site-reported estimate was used)
- Clinical success defined as procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge
- Days of hospitalization due to the index lesion from procedure through 6, 12, 24, 36 months

## B. Accountability of PMA Cohort

At the time of database lock, of 220 DCB patients and 111 PTA patients enrolled in the PMA study, 93.1% and 90.7% patients, respectively, were available for analysis at the completion of the study, the 12 month post-operative visit. Follow-up compliance through the 12-month follow-up visit is presented in **Table 9** below.

**Table 9: Subject Follow-up Compliance at 12-Months**

	<b>IN.PACT DCB (N=220 Subjects)</b>	<b>PTA (N=111 Subjects)</b>
Eligible Subjects <sup>a</sup>	202	108
Death <sup>b</sup>	5	0
Withdrawal <sup>b</sup>	13	3
Follow-up Not Done	5	4
Follow-up Visit Within Window <sup>c</sup>	188	98
Follow-up Visit Out of Window <sup>c</sup>	9	6
Follow-up Compliance (%) <sup>d</sup>	93.1%	90.7%
<sup>a</sup> 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) <sup>b</sup> death and withdrawal are cumulative <sup>c</sup> Within window visits are defined as: 12-month $\pm$ 30 days <sup>d</sup> Percentage based on number of subjects who had follow-up visit within window divided by total number of eligible subjects Site reported data.		

### C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral vascular disease study performed in the US and Europe. Subject demographics, medical history, and risk factors of the 331 subjects are summarized in **Table 10** below, which shows similarity between subjects enrolled in both the IN.PACT Admiral DCB and PTA groups.

**Table 10: Baseline Demographics and Medical History**

	<b>IN.PACT DCB (N=220 Subjects)</b>	<b>PTA (N=111 Subjects)</b>	<b>p-value</b>
Age (yr)	67.5 ± 9.5	68.0 ± 9.2	0.612
Male Gender	65.0% (143/220)	67.6% (75/111)	0.713
Race*			
White	78.3% (94/120)	83.3% (50/60)	0.435
Black	14.2% (17/120)	11.7% (7/60)	
Asian	5.8% (7/120)	3.3% (2/60)	
Native Hawaiian or Other Pacific Islander	1.7% (2/120)	0.0% (0/60)	
American Indian or Alaska Native	0.0% (0/120)	0.0% (0/60)	
Other	0.0% (0/120)	1.7% (1/60)	
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	27.7% (61/220)	25.2% (28/111)	
Diabetes Mellitus	40.5% (89/220)	48.6% (54/111)	0.161
Hypertension	91.4% (201/220)	88.3% (98/111)	0.431
Hyperlipidemia	84.5% (186/220)	82.0% (91/111)	0.637
Current Smoker	38.6% (85/220)	36.0% (40/111)	0.719
Coronary Heart Disease	57.0% (122/214)	55.0% (60/109)	0.813
Carotid Artery Disease	34.9% (73/209)	31.7% (32/101)	0.610
Renal Insufficiency (baseline serum creatinine ≥ 1.5 mg/dL)	8.3% (18/217)	6.4% (7/109)	0.662
Below-the-knee Vascular Disease of Target Leg (Stenotic/Occluded)	40.9% (90/220)	53.2% (59/111)	0.036
ABI / TBI <sup>#</sup> (mmHg ratio)	0.769 ± 0.228 (209)	0.744 ± 0.189 (106)	0.308
Rutherford Category			
2	37.7% (83/220)	37.8% (42/111)	0.898
3	57.3% (126/220)	55.9% (62/111)	
4	5.0% (11/220)	5.4% (6/111)	
5	0.0% (0/220)	0.9% (1/111)	
Numbers are % (counts/sample size) unless otherwise stated.			
*Race and ethnicity data was not collected in IN.PACT SFA I phase (Europe).			
<sup>#</sup> TBI was not measured in IN.PACT SFA I phase.			
Site reported data.			

The baseline lesion characteristics, as reported by the sites and the angiographic core laboratories, have been provided in **Table 11**. The total target lesion length was similar between groups (IN.PACT Admiral DCB 8.94 cm, PTA 8.81 cm; p=0.815). Occluded lesions comprised 25.8% of IN.PACT Admiral DCB subject lesions and 19.5% of PTA subject lesions (p=0.222).

**Table 11: Lesion Characteristics**

	<b>IN.PACT DCB</b>	<b>PTA</b>	<b>p-value</b>
<b>Baseline Lesion Characteristics<sup>a</sup></b>	<b>(N=220 Subjects)</b>	<b>(N=111 Subjects)</b>	
Lesion Type			
<i>De novo</i>	95.0% (209/220)	94.6% (105/111)	0.875
Restenotic (non-stented)	5.0% (11/220)	5.4% (6/111)	
<b>Lesion Location<sup>b, c</sup></b>	<b>(N=221 Lesions)</b>	<b>(N=113 Lesions)</b>	
Superficial Femoral Artery	97.7% (216/221)	94.7% (107/113)	0.193
Proximal Popliteal Artery	6.8% (15/221)	7.1% (8/113)	1.000
<b>Angiographic Lesion Characteristics<sup>b</sup></b>	<b>(N=221 Lesions)</b>	<b>(N=113 Lesions)</b>	
Lesion Length (cm)	8.94 ± 4.89	8.81 ± 5.12	0.815
Reference Vessel Diameter (RVD) (mm)	4.647 ± 0.841	4.681 ± 0.828	0.728
Minimum Lumen Diameter (MLD) (Pre-procedure) (mm)	0.900 ± 0.776	0.933 ± 0.771	0.711
Diameter Stenosis (Pre-procedure)	81.1% ± 15.5	81.3% ± 13.7	0.946
Occluded Lesions (100% stenosis)	25.8% (57/221)	19.5% (22/113)	0.222
TASC Lesion Type			
A	56.6% (125/221)	62.8% (71/113)	0.275
B	30.8% (68/221)	26.5% (30/113)	
C	12.2% (27/221)	10.6% (12/113)	
D	0.5% (1/221)	0.0% (0/113)	
Calcification	59.3% (131/221)	58.4% (66/113)	0.907
Severe Calcification	8.1% (18/221)	6.2% (7/113)	0.662
# Run-off Vessels Occluded			
0	41.5% (88/212)	35.7% (40/112)	0.042
1	41.5% (88/212)	33.0% (37/112)	
2	13.7% (29/212)	26.8% (30/112)	
3	3.3% (7/212)	4.5% (5/112)	
Dissections (Post-procedure)			
0 (no dissection)	36.2% (80/221)	38.9% (44/113)	0.360
A-C	63.8% (141/221)	60.2% (68/113)	
D-F	0.0% (0/221)	0.9% (1/113)	
Minimum Lumen Diameter (MLD) (Post-procedure) (mm)	3.903 ± 0.750	3.862 ± 0.732	0.632
Diameter Stenosis (Post-procedure)	19.9 ± 10.4	19.1 ± 10.3	0.535
<b>Procedural Characteristics<sup>a</sup></b>	<b>(N=220 Subjects)</b>	<b>(N=111 Subjects)</b>	

	<b>IN.PACT DCB</b>	<b>PTA</b>	<b>p-value</b>
Pre-dilatation	96.4% (212/220)	85.6% (95/111)	<0.001
Post-dilatation	26.8% (59/220)	18.9% (21/111)	0.135
Provisional Stenting	7.3% (16/220)	12.6% (14/111)	0.110

Numbers are % (counts/sample size) or mean ± standard deviation.  
<sup>a</sup> Site reported data.  
<sup>b</sup> Core laboratory reported data. All lesions within artery segment are counted. Numbers are % (counts/# of lesions) unless otherwise stated.  
<sup>c</sup> All lesions within artery segment are counted.  
Note that four subjects in the trial were assessed by sites as having tandem lesions treated during the index procedure and were assessed by the angiographic core laboratory as having two target lesions treated during the index procedure

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the all ITT cohort of 331 patients available for the 12 month evaluation. The primary safety endpoint of the study, a composite of freedom from device- and procedure-related death through 30 days, freedom from target limb major amputation within 12 months and freedom from clinically-driven target vessel revascularization within 12 months, was 95.7% in the IN.PACT Admiral DCB group and 76.6% in the PTA group (p<0.001). The IN.PACT Admiral DCB group met the pre-defined 10% non-inferiority margin and showed superiority against the PTA group using a sequential analysis approach, as seen in **Table 12**. The Kaplan-Meier Plot for primary safety is shown in **Figure 5**. Principal safety results can be seen in **Table 13**. Serious adverse events are reported in **Table 14**.

**Table 12: Primary Safety Endpoint**

<b>Outcome</b>	<b>IN.PACT DCB (N=220)</b>	<b>PTA (N=111)</b>	<b>Difference [95% CI]</b>	<b>p-value <sup>α</sup></b>
Primary Safety Endpoint	95.7% (198/207)	76.6% (82/107)	19.0% [10.5%, 27.5%]	< 0.001

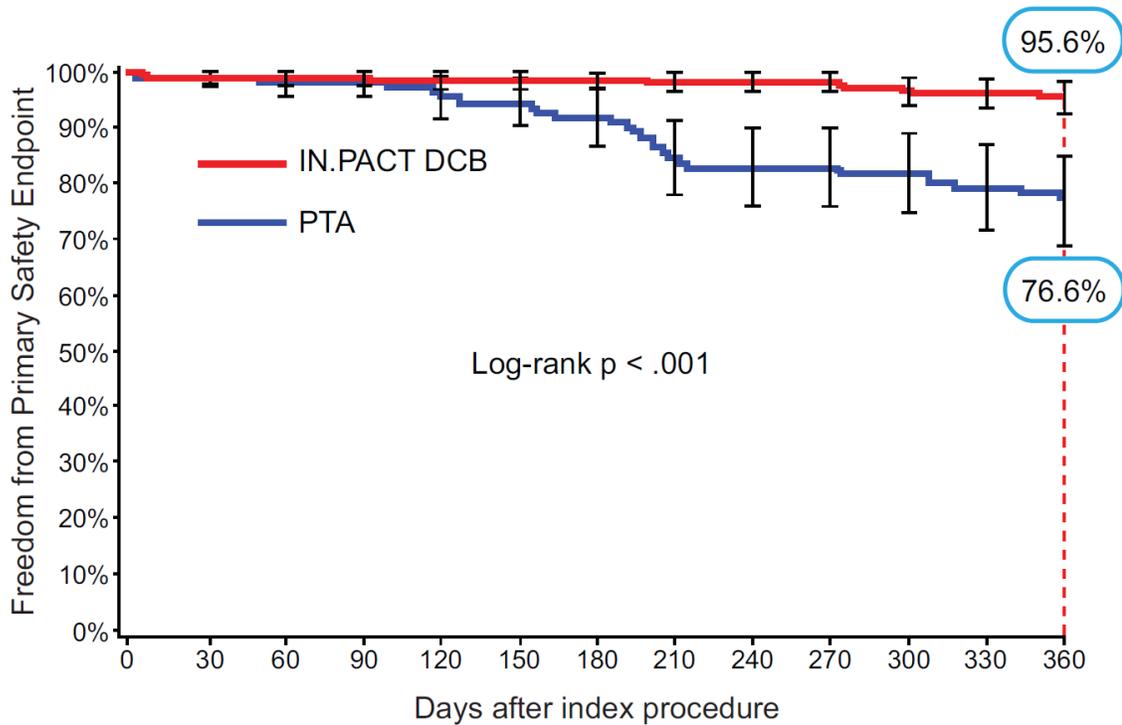
- Primary safety endpoint defined as freedom from device- and procedure-related death through 30 days, target limb major amputation within 360 days, and clinically-driven TVR within 360 days

**Statistical references:**

- CI – Confidence Interval
- Analysis set: All randomized subjects experiencing at least one component for the safety endpoint or with follow-up of at least 330 days post-procedure, i.e. the denominator was adjusted for missing data.
- Non-inferiority on the primary safety endpoint was tested using the Farrington-Manning approach. The non-inferiority margin of 10% was met, however, the results shown above are for superiority testing.

<sup>α</sup> all alpha are one-sided with significance of 0.024995 required.

**Data sources:**  
All events were adjudicated by the independent Clinical Events Committee and all duplex ultrasound and angiographic measures were made by the independent core laboratories.



From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210	211 240	241 270	271 300	301 330	331 360
<b>IN.PACT DCB (N=220 Subjects)</b>													
# Entered	220	220	215	214	214	212	210	208	206	205	203	197	195
# Censored	0	3	1	0	1	2	2	1	1	2	3	1	50
# Events	0	2	0	0	1	0	0	1	0	0	3	1	1
Event-free [%]	100.0%	99.1%	99.1%	99.1%	98.6%	98.6%	98.6%	98.1%	98.1%	98.1%	96.7%	96.2%	95.6%
Greenwood SE [%]	0.0%	0.6%	0.6%	0.6%	0.8%	0.8%	0.8%	0.9%	0.9%	0.9%	1.2%	1.3%	1.4%
<b>PTA (N=111 Subjects)</b>													
# Entered	111	111	109	108	108	105	104	101	91	89	89	88	84
# Censored	0	1	0	0	0	0	0	2	0	0	0	1	24
# Events	0	1	1	0	3	1	3	8	2	0	1	3	2
Event-free [%]	100.0%	99.1%	98.2%	98.2%	95.5%	94.6%	91.8%	84.4%	82.6%	82.6%	81.7%	78.9%	76.6%
Greenwood SE [%]	0.0%	0.9%	1.3%	1.3%	2.0%	2.2%	2.6%	3.5%	3.6%	3.6%	3.7%	3.9%	4.1%
<b>Survival Curves Comparison</b>													
<b>Analysis Method</b>	<b>Test</b>			<b>Chi Square</b>				<b>Degr. Freedom</b>			<b>p-value</b>		
Kaplan-Meier Analysis	Log-Rank			27.3314				1			<0.001		
All events were adjudicated by the independent Clinical Events Committee.													

**Figure 5: Kaplan-Meier Plot: Event-free from Primary Safety Endpoint (360 Days)**

### Principal Safety Results

A summary of the principal safety results, including major secondary endpoints, are shown below in **Table 13**. From this data, it can be seen that the difference in the

primary safety endpoint was primarily driven by a dramatic reduction in the clinically-driven target vessel revascularization (CD-TVR) rate.

**Table 13: Principal Safety Results**

	<b>IN.PACT DCB (N=220 Subjects)</b>	<b>PTA (N=111 Subjects)</b>	<b>Difference [95% CI]</b>	<b>p-value<sup>a</sup></b>
Primary Safety Composite Endpoint – Freedom from:	95.7% (198/207)	76.6% (82/107)	19.0% [10.5%, 27.5%]	< 0.001
- Device- and Procedure-related Death through 30 Days	0.0% (0/218)	0.0% (0/111)	NA	> 0.999
Target Limb Major Amputation within 360 Days	0.0% (0/207)	0.0% (0/107)	NA	> 0.999
Clinically-driven TVR within 360 Days	4.3% (9/207)	23.4% (25/107)	-19.0% [-27.5%, -10.5%]	< 0.001
Death (all-cause) within 30 days	0.0% (0/218)	0.0% (0/111)	NA	> 0.999
MAE Composite (Death, Major Target Limb Amputation, Clinically-driven TVR, Thrombosis) within 360 days	6.3% (13/207)	24.3% (26/107)	-18.0% [-26.8%, -9.2%]	< 0.001
Death (all-cause)	1.9% (4/207)	0.0% (0/107)	1.9% [0.1%, 3.8%]	0.926
Clinically-driven TVR	4.3% (9/207)	23.4% (25/107)	-19.0% [-27.5%, -10.5%]	< 0.001
Major Target Limb Amputation	0.0% (0/207)	0.0% (0/107)	NA	> 0.999
Thrombosis	1.4% (3/207)	3.7% (4/107)	-2.3% [-6.2%, 1.7%]	0.096
Any TVR within 360 days	4.8% (10/207)	23.4% (25/107)	-18.5% [-27.1%, -10.0%]	< 0.001

**Endpoint definitions:**

- Clinically-driven TLR/TVR is defined as any re-intervention within the target vessel due to symptoms or drop of ABI/TBI of  $\geq 20\%$  or  $> 0.15$  when compared to post-procedure baseline ABI/TBI.
- Major Adverse Events (MAE) defined as all-cause death, clinically-driven TLR/TVR, major target limb amputation, thrombosis at the target lesion site at 360 days.

**Statistical references:**

- Numbers are % (counts/sample size) unless otherwise stated. CI – Confidence Interval
- Analysis set: All randomized subjects experiencing at least one component for the safety endpoint or with follow-up of at least 330 days post-procedure (i.e. the denominator was adjusted for missing data).
- <sup>a</sup> all alpha are one-sided with significance of 0.024995 required. All tests were for superiority using the chi-square test for binary variables and t-test for continuous variables.

**Data sources:**

All events were adjudicated by the independent Clinical Events Committee, all duplex ultrasound and angiographic measures were made by the independent core laboratories, and all other data were site reported.

**Serious Adverse Event (SAE) that occurred in the PMA clinical study:**

Serious Adverse Event Rates by SOC and Preferred Term through 360 Days (Table 14) shows serious adverse event rates by subject and stratified by System-Organ Class (SOC) and preferred term. Serious adverse events were site-reported, and SOC was assigned via MedDRA version 13.0 coding.

A Serious Adverse Event (SAE) is defined as an Adverse Event that:

- a) led to a death,

- b) led to a serious deterioration in the health of the subject that either resulted in:
- 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, or
  - 3) in-patient hospitalization or prolongation of an existing hospitalization, or
  - 4) 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.

**Table 14** provides a summary of serious adverse event rates by SOC through 360 days occurring in the control and treatment groups.

**Table 14: Serious Adverse Event Rates by SOC and Preferred Term through 360 Days**

Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
<b>SUBJECTS WITH ONE OR MORE SERIOUS ADVERSE EVENTS</b>	46.4% (102/220)	55.9% (62/111)	0.105
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS<sup>a</sup></b>	2.3% (5/220)	1.8% (2/111)	1.000
ANAEMIA	1.8% (4/220)	0.9% (1/111)	
HAEMORRHAGIC ANAEMIA	0.5% (1/220)	0.0% (0/111)	
PANCYTOPENIA	0.0% (0/220)	0.9% (1/111)	
<b>CARDIAC DISORDERS<sup>a</sup></b>	9.5% (21/220)	6.3% (7/111)	0.405
ACUTE CORONARY SYNDROME	0.5% (1/220)	0.0% (0/111)	
ACUTE MYOCARDIAL INFARCTION	1.4% (3/220)	0.0% (0/111)	
ANGINA PECTORIS	0.9% (2/220)	0.9% (1/111)	
ANGINA UNSTABLE	0.0% (0/220)	0.9% (1/111)	
ARRHYTHMIA	0.5% (1/220)	0.0% (0/111)	
ATRIAL FIBRILLATION	0.9% (2/220)	1.8% (2/111)	
CARDIAC ARREST	0.5% (1/220)	0.0% (0/111)	
CARDIAC FAILURE CONGESTIVE	2.7% (6/220)	0.9% (1/111)	
CORONARY ARTERY DISEASE	3.2% (7/220)	0.9% (1/111)	
CORONARY ARTERY THROMBOSIS	0.0% (0/220)	0.9% (1/111)	
MYOCARDIAL INFARCTION	0.9% (2/220)	0.9% (1/111)	
MYOCARDIAL ISCHAEMIA	0.5% (1/220)	0.0% (0/111)	
SINUS TACHYCARDIA	0.5% (1/220)	0.0% (0/111)	
SUPRAVENTRICULAR TACHYCARDIA	0.0% (0/220)	0.9% (1/111)	
VENTRICULAR TACHYCARDIA	0.5% (1/220)	0.0% (0/111)	
<b>EAR AND LABYRINTH DISORDERS<sup>a</sup></b>	0.5% (1/220)	0.0% (0/111)	1.000

Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
VERTIGO	0.5% (1/220)	0.0% (0/111)	
<b>EYE DISORDERS<sup>a</sup></b>	0.5% (1/220)	0.0% (0/111)	1.000
DIABETIC RETINOPATHY	0.5% (1/220)	0.0% (0/111)	
<b>GASTROINTESTINAL DISORDERS<sup>a</sup></b>	4.1% (9/220)	0.9% (1/111)	0.174
ABDOMINAL PAIN	0.5% (1/220)	0.0% (0/111)	
ANAL FISTULA	0.5% (1/220)	0.0% (0/111)	
GASTROINTESTINAL HAEMORRHAGE	0.9% (2/220)	0.9% (1/111)	
GASTROOESOPHAGEAL REFLUX DISEASE	0.5% (1/220)	0.0% (0/111)	
IMPAIRED GASTRIC EMPTYING	0.5% (1/220)	0.0% (0/111)	
INTESTINAL OBSTRUCTION	0.5% (1/220)	0.0% (0/111)	
LARGE INTESTINE PERFORATION	0.5% (1/220)	0.0% (0/111)	
MELAENA	0.0% (0/220)	0.9% (1/111)	
PANCREATITIS	0.5% (1/220)	0.0% (0/111)	
PERITONITIS	0.5% (1/220)	0.0% (0/111)	
SMALL INTESTINAL OBSTRUCTION	0.5% (1/220)	0.0% (0/111)	
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS<sup>a</sup></b>	5.5% (12/220)	4.5% (5/111)	0.798
ADVERSE DRUG REACTION	0.5% (1/220)	0.0% (0/111)	
CHEST PAIN	0.9% (2/220)	0.9% (1/111)	
DEVICE OCCLUSION	0.5% (1/220)	0.9% (1/111)	
IMPAIRED HEALING	0.5% (1/220)	0.9% (1/111)	
IMPLANT SITE THROMBOSIS	0.5% (1/220)	0.0% (0/111)	
MASS	0.0% (0/220)	0.9% (1/111)	
MULTI-ORGAN FAILURE	0.5% (1/220)	0.0% (0/111)	
NECROSIS	0.0% (0/220)	0.9% (1/111)	
OEDEMA PERIPHERAL	0.5% (1/220)	0.0% (0/111)	
POLYP	0.5% (1/220)	0.0% (0/111)	
SUDDEN DEATH	0.5% (1/220)	0.0% (0/111)	
VESSEL PUNCTURE SITE HAEMATOMA	0.9% (2/220)	0.0% (0/111)	
<b>HEPATOBIILIARY DISORDERS<sup>a</sup></b>	0.9% (2/220)	0.9% (1/111)	1.000
BILE DUCT OBSTRUCTION	0.5% (1/220)	0.0% (0/111)	
CHOLECYSTITIS	0.5% (1/220)	0.0% (0/111)	
HEPATIC CIRRHOSIS	0.0% (0/220)	0.9% (1/111)	
LIVER DISORDER	0.5% (1/220)	0.0% (0/111)	

<b>Serious Adverse Events</b>	<b>IN.PACT DCB (N=220 Subjects)</b>	<b>Standard PTA (N=111 Subjects)</b>	<b>p-value</b>
<b>INFECTIONS AND INFESTATIONS<sup>a</sup></b>	3.6% (8/220)	1.8% (2/111)	0.505
ARTHRITIS BACTERIAL	0.5% (1/220)	0.0% (0/111)	
BILIARY SEPSIS	0.5% (1/220)	0.0% (0/111)	
BRONCHIECTASIS	0.0% (0/220)	0.9% (1/111)	
GANGRENE	0.9% (2/220)	0.0% (0/111)	
GASTROENTERITIS	0.5% (1/220)	0.0% (0/111)	
INFECTED LYMPHOCELE	0.5% (1/220)	0.0% (0/111)	
LOCALISED INFECTION	0.5% (1/220)	0.0% (0/111)	
OSTEOMYELITIS	0.0% (0/220)	0.9% (1/111)	
PNEUMONIA	0.5% (1/220)	0.0% (0/111)	
SEPSIS	0.5% (1/220)	0.0% (0/111)	
URINARY TRACT INFECTION	0.5% (1/220)	0.0% (0/111)	
WEST NILE VIRAL INFECTION	0.5% (1/220)	0.0% (0/111)	
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS<sup>a</sup></b>	5.9% (13/220)	12.6% (14/111)	0.053
ARTERIAL RESTENOSIS	0.5% (1/220)	3.6% (4/111)	
FACIAL BONES FRACTURE	0.5% (1/220)	0.0% (0/111)	
FALL	0.0% (0/220)	0.9% (1/111)	
FEMORAL NECK FRACTURE	0.5% (1/220)	0.9% (1/111)	
FIBULA FRACTURE	0.5% (1/220)	0.0% (0/111)	
FRACTURED COCCYX	0.5% (1/220)	0.0% (0/111)	
IN-STENT ARTERIAL RESTENOSIS	1.4% (3/220)	0.9% (1/111)	
IN-STENT CORONARY ARTERY RESTENOSIS	0.5% (1/220)	0.0% (0/111)	
LUMBAR VERTEBRAL FRACTURE	0.5% (1/220)	0.0% (0/111)	
PERIPHERAL ARTERIAL REOCCLUSION	0.0% (0/220)	3.6% (4/111)	
VASCULAR GRAFT OCCLUSION	0.5% (1/220)	0.0% (0/111)	
VASCULAR PSEUDOANEURYSM	1.4% (3/220)	2.7% (3/111)	
<b>INVESTIGATIONS<sup>a</sup></b>	0.0% (0/220)	0.9% (1/111)	0.335
PROSTATIC SPECIFIC ANTIGEN INCREASED	0.0% (0/220)	0.9% (1/111)	
<b>METABOLISM AND NUTRITION DISORDERS<sup>a</sup></b>	1.4% (3/220)	0.0% (0/111)	0.554
HYPERGLYCAEMIA	0.5% (1/220)	0.0% (0/111)	
HYPERKALAEMIA	0.5% (1/220)	0.0% (0/111)	
OBESITY	0.5% (1/220)	0.0% (0/111)	
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS<sup>a</sup></b>	4.5% (10/220)	4.5% (5/111)	1.000

<b>Serious Adverse Events</b>	<b>IN.PACT DCB (N=220 Subjects)</b>	<b>Standard PTA (N=111 Subjects)</b>	<b>p-value</b>
BACK PAIN	0.5% (1/220)	0.9% (1/111)	
EXOSTOSIS	0.5% (1/220)	0.0% (0/111)	
INTERVERTEBRAL DISC PROTRUSION	0.0% (0/220)	0.9% (1/111)	
LUMBAR SPINAL STENOSIS	0.9% (2/220)	0.9% (1/111)	
MUSCULOSKELETAL PAIN	0.5% (1/220)	0.0% (0/111)	
OSTEOARTHRITIS	0.9% (2/220)	0.0% (0/111)	
PAIN IN EXTREMITY	0.9% (2/220)	0.9% (1/111)	
SPINAL COLUMN STENOSIS	0.0% (0/220)	0.9% (1/111)	
SPINAL OSTEOARTHRITIS	0.5% (1/220)	0.0% (0/111)	
SPONDYLOLISTHESIS	0.5% (1/220)	0.0% (0/111)	
SYNOVIAL CYST	0.5% (1/220)	0.0% (0/111)	
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)<sup>a</sup></b>	0.9% (2/220)	4.5% (5/111)	0.045
BASAL CELL CARCINOMA	0.0% (0/220)	0.9% (1/111)	
BLADDER CANCER	0.0% (0/220)	0.9% (1/111)	
COLON CANCER METASTATIC	0.0% (0/220)	0.9% (1/111)	
LIPOMA	0.0% (0/220)	0.9% (1/111)	
PROSTATE CANCER	0.5% (1/220)	0.0% (0/111)	
RENAL CANCER	0.0% (0/220)	0.9% (1/111)	
TONSIL CANCER	0.5% (1/220)	0.0% (0/111)	
<b>NERVOUS SYSTEM DISORDERS<sup>a</sup></b>	5.0% (11/220)	6.3% (7/111)	0.615
AMNESIA	0.5% (1/220)	0.0% (0/111)	
CAROTID ARTERY DISEASE	0.0% (0/220)	0.9% (1/111)	
CAROTID ARTERY STENOSIS	0.5% (1/220)	1.8% (2/111)	
CEREBRAL INFARCTION	0.5% (1/220)	0.9% (1/111)	
CEREBROVASCULAR ACCIDENT	0.5% (1/220)	0.0% (0/111)	
EMBOLIC CEREBRAL INFARCTION	0.5% (1/220)	0.0% (0/111)	
HAEMORRHAGE INTRACRANIAL	0.5% (1/220)	0.0% (0/111)	
HYPOAESTHESIA	0.5% (1/220)	0.0% (0/111)	
LUMBAR RADICULOPATHY	0.5% (1/220)	0.0% (0/111)	
PARAESTHESIA	0.0% (0/220)	0.9% (1/111)	
SYNCOPE	0.5% (1/220)	1.8% (2/111)	
TRANSIENT ISCHAEMIC ATTACK	1.4% (3/220)	0.0% (0/111)	
<b>RENAL AND URINARY DISORDERS<sup>a</sup></b>	0.5% (1/220)	2.7% (3/111)	0.112
HAEMATURIA	0.0% (0/220)	0.9% (1/111)	
RENAL COLIC	0.0% (0/220)	0.9% (1/111)	

Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
RENAL FAILURE	0.0% (0/220)	0.9% (1/111)	
RENAL FAILURE ACUTE	0.5% (1/220)	0.0% (0/111)	
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS<sup>a</sup></b>	0.5% (1/220)	0.0% (0/111)	1.000
POSTMENOPAUSAL HAEMORRHAGE	0.5% (1/220)	0.0% (0/111)	
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS<sup>a</sup></b>	1.4% (3/220)	0.9% (1/111)	1.000
ACUTE PULMONARY OEDEMA	0.5% (1/220)	0.0% (0/111)	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0.5% (1/220)	0.0% (0/111)	
DYSPNOEA EXERTIONAL	0.5% (1/220)	0.0% (0/111)	
RESPIRATORY FAILURE	0.5% (1/220)	0.9% (1/111)	
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS<sup>a</sup></b>	0.0% (0/220)	1.8% (2/111)	0.112
DRY GANGRENE	0.0% (0/220)	0.9% (1/111)	
NEUROPATHIC ULCER	0.0% (0/220)	0.9% (1/111)	
<b>SURGICAL AND MEDICAL PROCEDURES<sup>a</sup></b>	0.9% (2/220)	0.9% (1/111)	1.000
JOINT SURGERY	0.5% (1/220)	0.0% (0/111)	
PERIPHERAL REVASCULARISATION	0.0% (0/220)	0.9% (1/111)	
THERAPEUTIC EMBOLISATION	0.5% (1/220)	0.0% (0/111)	
<b>VASCULAR DISORDERS<sup>a</sup></b>	22.7% (50/220)	35.1% (39/111)	0.018
ARTERIAL OCCLUSIVE DISEASE	0.5% (1/220)	0.0% (0/111)	
ARTERIAL STENOSIS LIMB	0.5% (1/220)	2.7% (3/111)	
ARTERIOVENOUS FISTULA	0.0% (0/220)	1.8% (2/111)	
ARTERY DISSECTION	3.2% (7/220)	1.8% (2/111)	
FEMORAL ARTERIAL STENOSIS	6.8% (15/220)	9.0% (10/111)	
FEMORAL ARTERY DISSECTION	1.8% (4/220)	4.5% (5/111)	
FEMORAL ARTERY OCCLUSION	1.4% (3/220)	4.5% (5/111)	
HAEMATOMA	0.0% (0/220)	0.9% (1/111)	
HAEMORRHAGE	0.5% (1/220)	0.0% (0/111)	
HYPOTENSION	0.5% (1/220)	0.0% (0/111)	
ILIAC ARTERY STENOSIS	0.9% (2/220)	0.9% (1/111)	
INTERMITTENT CLAUDICATION	3.2% (7/220)	9.9% (11/111)	
ORTHOSTATIC HYPOTENSION	0.5% (1/220)	0.9% (1/111)	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	3.6% (8/220)	4.5% (5/111)	

Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
PERIPHERAL ARTERY DISSECTION	1.4% (3/220)	3.6% (4/111)	
PERIPHERAL EMBOLISM	0.5% (1/220)	0.9% (1/111)	
PERIPHERAL ISCHAEMIA	0.9% (2/220)	1.8% (2/111)	
PERIPHERAL VASCULAR DISORDER	0.9% (2/220)	0.0% (0/111)	
SHOCK HAEMORRHAGIC	0.5% (1/220)	0.0% (0/111)	
SUBCLAVIAN ARTERY STENOSIS	0.0% (0/220)	0.9% (1/111)	
<b>TOTAL SERIOUS ADVERSE EVENTS</b>	<b>195</b>	<b>118</b>	

<sup>a</sup>Event verbatim terms are reported by sites, coded using MedDRA version 13.0, and stratified by SOC and preferred term.  
Numbers are % (counts/sample size). Patients may be counted in this table more than once by preferred term, but are only counted once in the SOC summary line. Site reported data.

## 2. Effectiveness Results

The analysis of effectiveness was based on the 331 evaluable patients at the 12 month time point. The primary effectiveness endpoint, primary patency at 12 months, was 82.2% in the IN.PACT Admiral DCB group and 52.4% for the PTA group (p<0.001). The IN.PACT Admiral DCB group showed statistical superiority against the PTA group, as seen in **Table 15**. The Kaplan-Meier Plot primary patency is shown in **Figure 6**.

**Table 15: Primary Effectiveness Endpoint**

Outcome	IN.PACT DCB (N=220)	PTA (N=111)	Difference [95% CI]	p-value <sup>a</sup>
Primary Effectiveness Endpoint – Primary Patency at 12 Months	82.2% (157/191)	52.4% (54/103)	26.2% [15.1%, 37.3%]	< 0.001

- Primary patency is defined as freedom from clinically-driven TLR<sup>1</sup> and freedom from restenosis as determined by duplex ultrasound<sup>2</sup> (DUS) Peak Systolic Velocity Ratio (PSVR)  $\leq 2.4$ <sup>3</sup> within 12 months. Key Primary Patency endpoint definition components:
  - Clinically-driven TLR is defined as any re-intervention at the target lesion due to symptoms or drop of ABI/TBI of  $\geq 20\%$  or  $>0.15$  when compared to post-procedure baseline ABI/TBI
  - Post-index procedure DUS is intended to establish a post-treatment baseline and does not contribute to the Primary Endpoint determination
  - Restenosis determined by either PSVR  $>2.4$  as assessed by an independent DUS core laboratory or  $>50\%$  stenosis as assessed by an independent angiographic core laboratory.
- Post-index procedure DUS did not contribute to the Primary Effectiveness Endpoint Determination. Therefore, effectiveness results do not reflect four DCB patients who had post-procedure binary restenosis which was later not observed at 12 months.

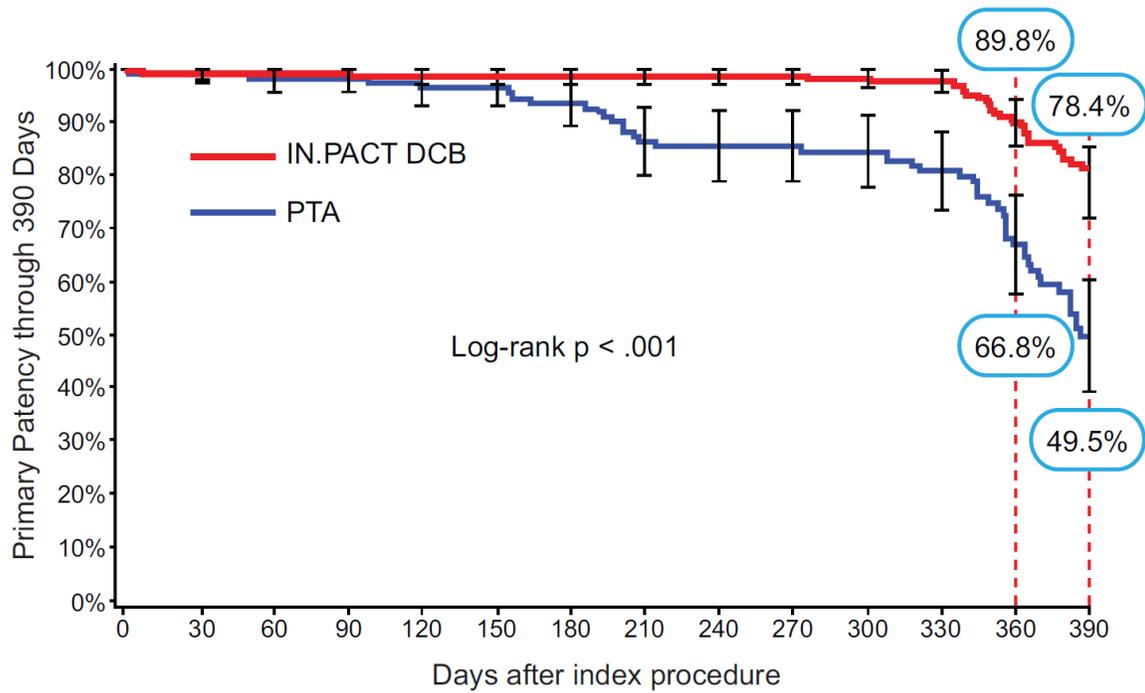
**Statistical references:**

- CI – Confidence Interval
- Analysis set: All randomized subjects with multiple imputation performed on missing data for primary patency are provided in the Difference [95% CI] and p-value columns.

<sup>a</sup> all alpha are one-sided with significance of 0.024995 required.

**Data sources:**

All events were adjudicated by the independent Clinical Events Committee and all duplex ultrasound and angiographic measures were made by the independent core laboratories.



From day X To day Y	0	1	31	61	91	121	151	181	211	241	271	301	331	361	390
<b>IN.PACT DCB (N=220 Subjects)</b>															
# Entered	220	220	215	214	214	212	210	208	207	206	204	200	198	141	
# Censored	0	3	1	0	1	2	2	1	1	2	3	1	43	39	
# Events	0	2	0	0	1	0	0	0	0	0	1	1	14	15	
Event-free [%]	100.0%	99.1%	99.1%	99.1%	98.6%	98.6%	98.6%	98.6%	98.6%	98.6%	98.1%	97.6%	89.8%	78.4%	
Greenwood SE [%]	0.0%	0.6%	0.6%	0.6%	0.8%	0.8%	0.8%	0.8%	0.8%	0.8%	0.9%	1.0%	2.2%	3.4%	
<b>PTA (N=111 Subjects)</b>															
# Entered	111	111	109	108	108	106	106	103	93	92	92	91	86	55	
# Censored	0	1	0	0	0	0	0	2	0	0	0	1	18	9	
# Events	0	1	1	0	2	0	3	8	1	0	1	4	13	13	
Event-free [%]	100.0%	99.1%	98.2%	98.2%	96.4%	96.4%	93.6%	86.3%	85.3%	85.3%	84.4%	80.7%	66.8%	49.5%	
Greenwood SE [%]	0.0%	0.9%	1.3%	1.3%	1.8%	1.8%	2.3%	3.3%	3.4%	3.4%	3.5%	3.8%	4.7%	5.4%	
<b>Survival Curves Comparison</b>															
<b>Analysis Method</b>	<b>Test</b>		<b>Chi Square</b>		<b>Degr. Freedom</b>		<b>p-value</b>								
Kaplan-Meier Analysis	Log-Rank		33.2068		1		<math>p < .001</math>								
All TLR events were adjudicated by the independent Clinical Events Committee.															
All DUSs were analyzed by an independent core laboratory.															

**Figure 6: Kaplan-Meier Plot – Primary Patency (390 Days)**

## Principal Effectiveness Results

A summary of the principal effectiveness results, including major secondary endpoints, are shown below in **Table 16**. Secondary safety endpoints were more favorable in the IN.PACT Admiral DCB group. The 12-month major adverse event rate was 6.3% in the IN.PACT Admiral DCB group versus 24.3% in the PTA group ( $p < 0.001$ ). This statistical significance was primarily driven by a dramatic reduction in the clinically-driven target vessel revascularization (CD-TVR) rate. The IN.PACT Admiral DCB group also showed highly statistically significant results of secondary effectiveness, such as clinically-driven TLR (CD-TLR) and primary sustained clinical improvement, both of which passed hierarchical testing.

**Table 16: Principal Effectiveness Results**

	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)	Difference [95% CI]	p-value <sup>a</sup>
Primary Effectiveness Endpoint – Primary Patency at 12 Months	82.2% (157/191)	52.4% (54/103)	26.2% [15.1%, 37.3%]	< 0.001
Primary Sustained Clinical Improvement at 12 Months	85.2% (167/196)	68.9% (73/106)	16.3% [6.2%, 26.5%]	< 0.001
Device Success	99.0% (308/311)	98.5% (128/130)	0.6% [-1.8%, 3.0%]	0.302
Procedural Success	99.5% (219/220)	98.2% (109/111)	1.3% [-1.3%, 4.0%]	0.111
Clinical Success	99.1% (218/220)	97.3% (108/111)	1.8% [-1.5%, 5.1%]	0.103
Binary Restenosis (PSVR >2.4) at 12 months	16.5% (31/188)	33.7% (29/86)	-17.2% [-28.5%, -5.9%]	0.001
Binary Restenosis (PSVR >3.4) at 12 months	7.3% (13/178)	21.4% (18/84)	-14.1% [-23.7%, -4.6%]	< 0.001
Clinically-driven TLR within 360 days	2.4% (5/207)	20.6% (22/107)	-18.1% [-26.1%, -10.2%]	< 0.001
Any TLR within 360 days	2.9% (6/207)	20.6% (22/107)	-17.7% [-25.7%, -9.7%]	< 0.001
<b>Endpoint definitions:</b>				
<ul style="list-style-type: none"> <li>• Primary sustained clinical improvement was defined as freedom from target limb amputation, TVR, and an increase in Rutherford class at 12-months post-procedure.</li> <li>• Device success defined as successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP.</li> <li>• Procedure success defined as residual stenosis of <math>\leq 50\%</math> (non-stented subjects) or <math>\leq 30\%</math> (stented subjects) by visual estimate.</li> <li>• Clinical success defined as procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.</li> <li>• Clinically-driven TLR is defined as any re-intervention within the target lesion due to symptoms or drop of ABI/TBI of <math>\geq 20\%</math> or <math>&gt; 0.15</math> when compared to post-procedure baseline ABI/TBI.</li> <li>• Binary restenosis is defined as duplex restenosis (PSVR &gt; 2.4/3.4) or angiographic restenosis of the target lesion at 12 months post-procedure, or at the time of reintervention prior to any pre-specified timepoint.</li> </ul>				
<b>Statistical references:</b>				
<ul style="list-style-type: none"> <li>• Numbers are % (counts/sample size) unless otherwise stated. <span style="float: right;">CI – Confidence Interval</span></li> <li>• Analysis set: All randomized subjects with multiple imputation performed on missing data for primary patency are provided in the Difference [95% CI] and p-value columns.</li> <li>• <sup>a</sup> all alpha are one-sided with significance of 0.024995 required. All tests were for superiority using the chi-square test for binary variables and t-test for continuous variables.</li> </ul>				

	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)	Difference [95% CI]	p-value <sup>a</sup>
<b>Data sources:</b> All events were adjudicated by the independent Clinical Events Committee, all duplex ultrasound and angiographic measures were made by the independent core laboratories, and all other data were site reported.				

### Pharmacokinetic Sub-Study

Human pharmacokinetics was investigated as a sub-study of the IN.PACT SFA Trial. This sub-study was a prospective, multicenter, non-randomized study arm (IN.PACT Admiral DCB) conducted at multiple pre-specified investigational sites, designed to evaluate the levels of paclitaxel in the systemic circulation of subjects at multiple time points up to seven days. Pharmacokinetic parameters were determined for a total of 24 subjects (16 male and 8 female) with an age range of 42 to 79 years and paclitaxel doses ranging from approximately 2.8 mg to 16.8 mg. A summary of the pharmacokinetic parameters is presented in **Table 7**.

**Table 17: Pharmacokinetic Parameters**

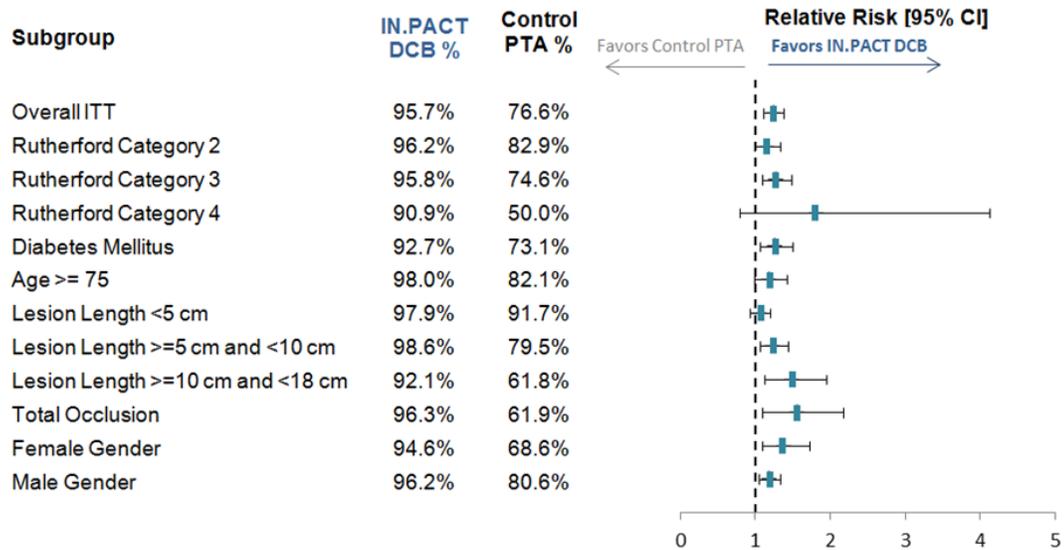
Parameter	Mean (N=24)	Standard Deviation	%CV	Range
T <sub>max</sub> (hr)	0.17	0.067	38.8	0.07 – 0.32
C <sub>max</sub> (ng/mL)	7.9	7.70	97.9	1.0 - 35.9
AUC <sub>0-last</sub> (hr*ng/mL)	29.4	22.06	75.0	3.2 – 91.6
AUC <sub>0-inf</sub> (hr*ng/mL)	47.8	28.98	60.6	11.4 – 128.8
T <sub>1/2</sub> (hr)	72.5	39.70	54.7	8.2 – 153.5
CL/F (L/hr)	192.2	103.44	53.8	54.7 – 472.7

T<sub>max</sub> (hr) The timepoint where C<sub>max</sub> is reached  
C<sub>max</sub> (ng/mL) Maximum plasma concentration  
AUC<sub>0-last</sub> (hr\*ng/mL) Area under plasma concentration-time curve from time zero to time of last measurable concentration  
AUC<sub>0-inf</sub> (hr\*ng/mL) Area under the plasma concentration-time curve from time zero extrapolated to infinity  
T<sub>1/2</sub> (hr) Terminal half-life  
CL/F (L/hr) Apparent clearance

Paclitaxel systemic exposures in the IN.PACT SFA PK Sub-study in subjects treated with IN.PACT Admiral DCB were low and cleared rapidly with a biphasic decline. The mean peak concentration was 7.9 ng/mL, declined in an hour by over 87% to 1.0 ng/mL, and was followed by a continued decline to very low concentration levels at day 7. The data show that treatment with the IN.PACT Admiral DCB provided low systemic exposure of paclitaxel.

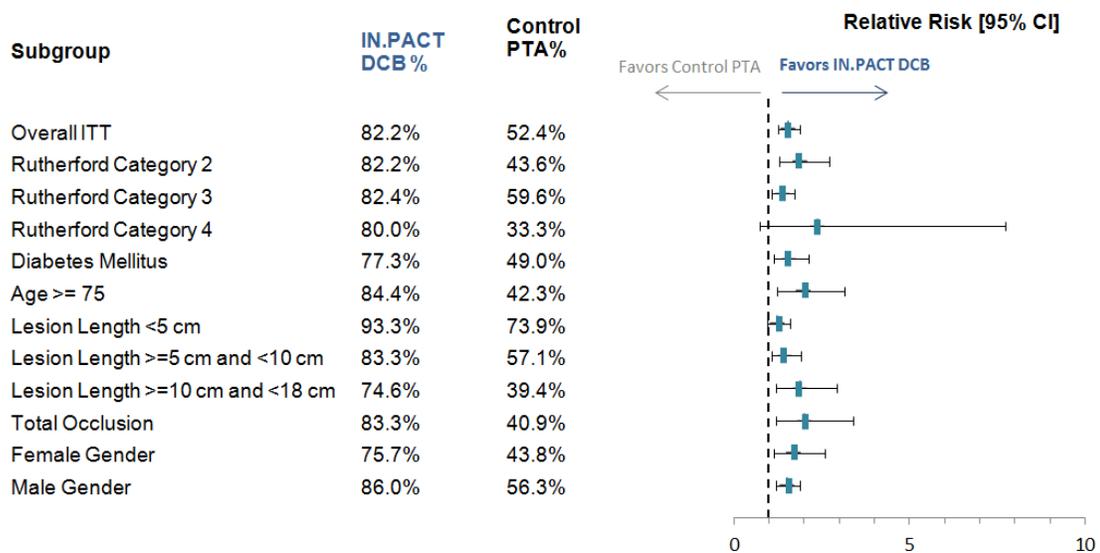
### 3. Subgroup Analyses

Medtronic has analyzed trial results by different pre-defined subgroups, such as Rutherford Category, lesion length, and gender, to investigate the consistency of results. Results for the primary safety endpoint at 12 Months (**Figure 7**), primary patency at 12 Months (**Figure 8**), and clinically-driven target lesion revascularization at 12 Months (**Figure 9**) have been illustrated for each subgroup in the forest plots below. All data for the subgroup analyses trended in favor of IN.PACT Admiral DCB over PTA.



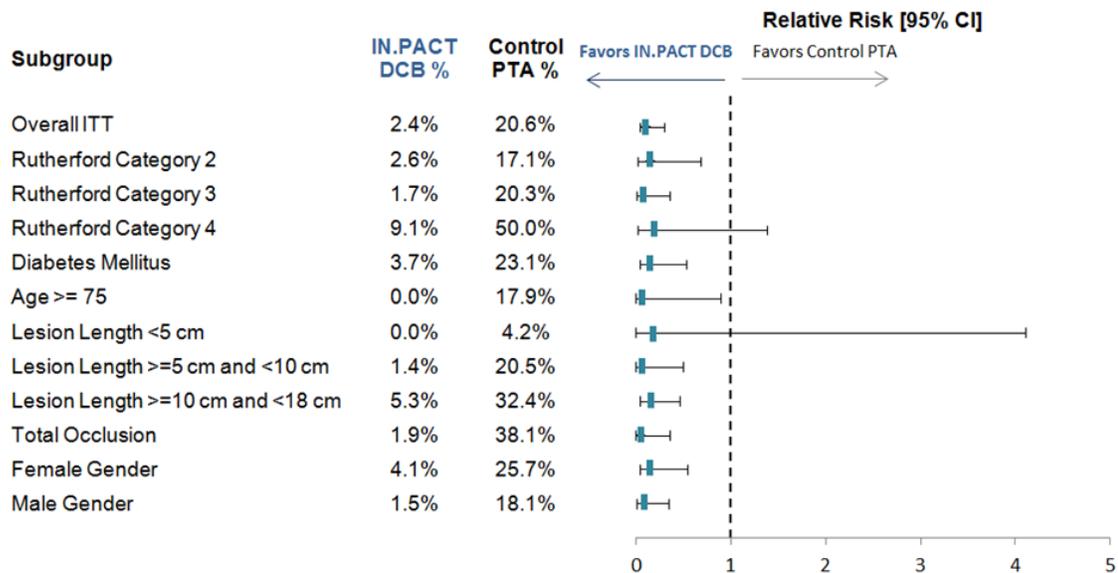
**Note:** There were no significant treatment-by-subgroup interactions ( $p>0.15$ ). The 95% confidence intervals were unadjusted for multiplicity.

**Figure 7: Primary Safety Endpoint Event at 12 Months**



**Note:** There were no significant treatment-by-subgroup interactions ( $p>0.15$ ). The 95% confidence intervals were unadjusted for multiplicity.

**Figure 8: Primary Patency at 12 Months**



**Note:** There were no significant treatment by subgroup interactions ( $p > 0.15$ ) except in diabetes mellitus ( $p = 0.027$ ). The 95% confidence intervals were unadjusted for multiplicity.

**Figure 9: Clinically-driven Target Lesion Revascularization at 12 Months**

### Gender Analysis

There were 218 males and 113 females enrolled in the pivotal study. Based on gender subgroup analyses, both female and male subgroups showed improvement on the primary safety and effectiveness endpoints. The results of an interaction analysis indicate that the treatment differences between IN.PACT Admiral DCB and PTA groups are consistent between male and female subjects (see **Table 18**).

**Table 18: Primary Safety Composite and Primary Effectiveness by Gender**

Females			
Outcome	IN.PACT DCB (N=77 Subjects)	Standard PTA (N=36 Subjects)	Difference
Primary Safety Endpoint	94.6% (70/74)	68.6% (24/35)	26.0%
Primary Effectiveness Endpoint – Primary Patency at 12 Months	75.7% (53/70)	43.8% (14/32)	29.3%

<b>Males</b>			
<b>Outcome</b>	<b>IN.PACT DCB (N=143 Subjects)</b>	<b>Standard PTA (N=75 Subjects)</b>	<b>Difference</b>
Primary Safety Endpoint	96.2% (128/133)	80.6% (58/72)	15.7%
Primary Effectiveness Endpoint – Primary Patency at 12 Months	86.0% (104/121)	56.3% (40/71)	25.0%

Primary safety endpoint is defined as freedom from device- and procedure-related death through 30 days, target limb major amputation within 360 days, and clinically-driven TVR within 360 days.

Primary patency is defined as freedom from clinically-driven TLR<sup>1</sup> and freedom from restenosis as determined by duplex ultrasound<sup>2</sup> (DUS) peak systolic velocity ratio (PSVR)  $\leq 2.4$ <sup>3</sup> within 12 months. Key primary patency endpoint definition components:

<sup>1</sup> Clinically-driven TLR is defined as any re-intervention at the target lesion due to symptoms or drop of ABI/TBI of  $\geq 20\%$  or  $>0.15$  when compared to post-procedure baseline ABI/TBI

<sup>2</sup> Post-index procedure DUS is intended to establish a post-treatment baseline and does not contribute to the primary endpoint determination

<sup>3</sup> Restenosis determined by either PSVR  $>2.4$  as assessed by an independent DUS core laboratory or  $>50\%$  stenosis as assessed by an independent angiographic core laboratory.

Post-index procedure DUS did not contribute to the primary effectiveness endpoint determination. Therefore, effectiveness results do not reflect four DCB patients who had post-procedure binary restenosis which was later not observed at 12 months.

**Statistical references:**

Numbers are % (counts/sample size).

Analysis sets: Effectiveness - all randomized subjects with multiple imputation performed on missing data for primary patency are provided in the Difference column; Safety - all randomized subjects experiencing at least one component for the safety endpoint or with follow-up of at least 330 days post-procedure (i.e. the denominator was adjusted for missing data).

**Data sources:**

All events were adjudicated by the independent Clinical Events Committee and all duplex ultrasound and angiographic measures were made by the independent core laboratories.

**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 274 investigators of which 14 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Significant payment of other sorts: 14

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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

### **A. IN.PACT Global Study**

The IN.PACT Global Study is a prospective, multi-center, single-arm study designed to collect and assess global safety and effectiveness data on the IN.PACT Admiral DCB in treatment of atherosclerotic disease of the superficial femoral and/or popliteal arteries in a real-world population. The study is estimated to continue follow-up through 2019. The study will enroll approximately 1500 subjects at more than 60 sites in Europe, Australia, Asia, Northern Africa, Canada, the Middle East, and South America. Follow-up will be completed at 30 days, 6 months, and 12 months and 2, 3, 4, and 5 years. The interim data from the IN.PACT Global Study that were available at the time of PMA review were incorporated in FDA's assessment of product safety and effectiveness, as described below.

### **B. Summary of Rare Adverse Events (RAE)**

Medtronic has provided an evaluation of rare adverse events (RAE) in more than 800 subjects from the IN.PACT SFA Trial, the IN.PACT SFA PK Sub-study, and the IN.PACT Global Study.

The following RAEs were adjudicated by the independent Clinical Events Committees (CEC): paclitaxel-related vessel thrombosis within 30 days, paclitaxel-related distal embolic events within 360 days, paclitaxel-related neutropenia within 360 days, and paclitaxel-related drug hypersensitivity/reaction within 360 days. The rate of paclitaxel-related thrombosis within 30 days was 0.2% (2/890). There were no paclitaxel-related distal embolic events within 360 days (0/806), paclitaxel-related neutropenia within 360 days (0/806), or paclitaxel-related drug hypersensitivity/reaction within 360 days (0/806).

The current RAE outcomes demonstrate no increased risk of adverse events due to the paclitaxel coating.

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

In accordance with the provisions of section 515(c)(2) 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.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

The IN.PACT SFA trial met its primary effectiveness endpoint for primary patency, demonstrating superiority in the IN.PACT Admiral DCB group compared to the PTA group. The 12-month primary patency rate was 82.2% in the IN.PACT Admiral DCB group vs. 52.4% in the PTA group ( $p < 0.001$ ). Secondary effectiveness endpoints showed significant results in favor of the IN.PACT Admiral DCB group on primary sustained clinical improvement, binary restenosis, and clinically-driven TLR. In conclusion, the primary effectiveness hypothesis of the study was met, indicating that the Medtronic

DCB provides a significantly higher rate of primary patency compared to standard PTA. These results support the effectiveness of the Medtronic DCB for the treatment of symptomatic vascular disease of the superficial femoral and popliteal arteries.

## **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 studies conducted to support PMA approval, as described above. The IN.PACT SFA trial met its primary safety endpoint: the IN.PACT Admiral DCB group met the pre-defined 10% non-inferiority margin and showed superiority against the PTA group using a sequential analysis approach. The 12-month freedom from primary safety composite was 95.7% in the IN.PACT Admiral DCB group and 76.6% in the PTA group ( $p < 0.001$ ). Secondary safety endpoints favored the IN.PACT Admiral DCB group. The 12-month major adverse event rate was 6.3% in the IN.PACT Admiral DCB group vs. 24.3% in the PTA group ( $p < 0.001$ ). The statistical significance was driven by a reduction in clinically-driven TVR (IN.PACT Admiral DCB 4.3% vs. PTA 23.4%;  $p < 0.001$ ). There were no procedure- or device-related deaths and no major amputations through 12 months in either treatment group. In conclusion, the primary safety hypothesis of the study was met, indicating that the IN.PACT Admiral DCB provides superior safety than treatment with standard PTA. Additional data from the IN.PACT SFA PK Sub-Study and IN.PACT Global Study did not detect a significant safety signal with respect to rare or long-term adverse device or drug effects. These results support the safety of the IN.PACT Admiral DCB for the treatment of symptomatic vascular disease of the superficial femoral and popliteal arteries.

## **C. Benefit-Risk Conclusions**

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 probable benefit of the IN.PACT Admiral DCB improving patients' symptoms and quality of life outweigh the probable risks associated with use of the device. Additional factors to be considered in determining probable risks and benefits for the IN.PACT Admiral DCB include:

1. The clinical study was well designed and conducted.
  - a. Adequate follow-up (12 months) was obtained to evaluate safety and effectiveness.
  - b. Separate analyses were conducted to assess the impact of missing data.
  - c. Pivotal clinical data were collected in two phases, involving international (SFAI) and domestic (SFAII) clinical sites. The study methodology was sufficiently similar between these two phases to allow pooling of the data, and no significant differences as a function of geography were observed.
2. The device is intended for use in patients with peripheral vascular disease of the superficial-femoral artery. The results adequately support general use in the identified population.
3. There are alternative treatments available for this disease, such as percutaneous transluminal angioplasty (PTA) alone, but this treatment has been shown to be more effective than PTA alone with regard to safety and effectiveness.

4. Patient risk is minimized by limiting the use to operators who have the necessary training to use the device safely and effectively. Adherence to the recommended periprocedural medication regimens is also stressed.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for percutaneous transluminal angioplasty, after predilatation, of de novo or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-7 mm.

### **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 safety and effectiveness of the IN.PACT Admiral DCB was superior to the safety and effectiveness of the control PTA.

## **XIV. CDRH DECISION**

CDRH issued an approval order on December 30, 2014. The final conditions of approval cited in the approval order are described below.

### Non-Clinical

1. Within 12 months of PMA approval, the sponsor should submit a non-clinical post-approval report discussing the results of particulate testing conducted on manufactured lots. If this information indicates that tightening of the particulate specification is appropriate, the sponsor has agreed to submit a PMA supplement requesting such a change.
2. The sponsor should provide stability data supporting the 12-month shelf-life of the commercial product.

### Clinical

1. *IN.PACT SFA Extended Follow-Up Study*: The sponsor has agreed to a study outline on November 7, 2014 (email). This study will evaluate the long-term safety and effectiveness of the IN.PACT Admiral DCB in 331 subjects from the premarket study (IN.PACT SFA trial). The IN.PACT SFA trial was designed as a two-phase, global, multicenter, single-blind, randomized (2:1 IN.PACT Admiral DCB to PTA) trial. Subjects will be followed annually through 5 years post-procedure with no more than 20% attrition.

The primary effectiveness endpoint is primary patency of the target lesion at 24 months. A minimum of 241 subjects evaluable at 24 months are required to show superiority of the IN.PACT Admiral DCB to PTA. This sample size assumes a two-sided 0.05 alpha and at least 80% power.

The primary safety endpoint is a composite of freedom from device- and procedure-related death at 30 days and freedom from target limb major amputation and clinically-driven target vessel revascularization (CD-TVR) at 24 months. A minimum of 224 subjects evaluable at 24 months are required to show non-inferiority of the IN.PACT Admiral DCB to PTA. This sample size assumes a one-sided 0.025 alpha, at least 80% power and 10% margin.

The endpoints to be assessed through 5 years post-procedure are: (1) major adverse event (MAE) composite and its individual components (all-cause mortality, CD-TVR, major target limb amputation, and thrombosis at the target lesion site), (2) clinically-driven target lesion revascularization (CD-TLR), (3) all TVR, (4) all TLR, and (5) serious adverse events. The endpoints to be assessed at 2 and 3 years post-procedure are: (1) primary sustained clinical improvement, (2) secondary sustained clinical improvement, (3) duplex-defined binary restenosis (peak systolic velocity ratio (PSVR) > 2.4) of the target lesion, (4) duplex-defined binary restenosis (PSVR > 3.4) of the target lesion, (5) quality of life assessment by EQ-5D questionnaire, and (6) walking capacity assessment by walking impairment questionnaire (WIQ).

2. *Continued Follow-up of Subjects in the IN.PACT SFA Global Clinical Program:* The sponsor has agreed to a study outline on November 7, 2014 (email). This study will continue the follow-up of subjects enrolled in the IN.PACT SFA Global Clinical Program. The objective of the study is to descriptively characterize the long-term safety and effectiveness of the IN.PACT Admiral DCB in patients enrolled in the IN.PACT SFA Global Clinical Program. Subjects will be followed annually through 5 years post-procedure with no more than 20% attrition.

The study population includes at least 1,600 IN.PACT Admiral DCB subjects from the IN.PACT SFA Trial (n=220), the IN.PACT SFA PK Sub-study (n=25), and the IN.PACT Global Study (n=1,400). The endpoints to be assessed through 5 years post-procedure are: (1) MAE composite and its individual components (all-cause mortality, CD-TVR, major target limb amputation, and thrombosis at the target lesion site), (2) CD-TLR, (3) all TVR, (4) all TLR, and (5) serious adverse events. The endpoints to be assessed at 2 and 3 years post-procedure are: (1) primary sustained clinical improvement, (2) secondary sustained clinical improvement, (3) quality of life assessment by EQ-5D questionnaire, and (4) walking capacity assessment by WIQ.

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

## **XV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

**XVI. REFERENCES**

None