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Printspec j-view - 8.5 x 11.0 inches

Medtronic

IN.PACT™ Admiral™

Paclitaxel-coated PTA Balloon Catheter

Instructions for Use

! USA **Caution:** Federal law (USA) restricts this device to sale by or on the order of a physician.

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Symbols

STERILE EO	Sterilized using ethylene oxide
REF	Catalogue number
LOT	Lot number
	Manufacturer
	Manufactured in
	Use by
	Quantity
www.medtronic.com/manuals	Consult instructions for use at this website: www.medtronic.com/manuals
	Consult instructions for use
	Do not reuse
	Do not resterilize
	Keep away from sunlight
	Keep dry
	Do not use if package is damaged
	Outer diameter
	Temperature limit
	Nonpyrogenic
RBP	Do not exceed rated burst pressure
OTW	Over the wire
NP	Nominal pressure
RBP	Rated burst pressure
P	Pressure
BALLOON ∅	Balloon diameter
≥	Minimum sheath inner diameter
	Maximum guidewire diameter
BALLOON	Balloon length
	Usable catheter length

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1. Product Name

IN.PACT™ Admiral™ paclitaxel-coated percutaneous transluminal angioplasty (PTA) balloon catheter

2. Product Description

The IN.PACT Admiral paclitaxel-coated PTA balloon catheter is an over-the-wire [OTW] balloon catheter with a drug-coated balloon at the distal tip. The drug component, referred to as the FreePac™ drug coating, consists of the drug paclitaxel and the excipient urea. The device component physically dilates the vessel lumen by PTA, and the drug is intended to reduce the

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proliferative response that is associated with restenosis. Product Component Description (Table 1) summarizes the characteristics of the device, hereafter referred to as IN.PACT Admiral DCB.

Table 1. Product Component Description

<table>
<tr><td rowspan="6">Available Balloon Diameters (mm) and Lengths (mm)</td><td>Balloon Diameter (mm)</td><td colspan="6">Balloon Length (mm)</td></tr>
<tr><td></td><td>20</td><td>40</td><td>60</td><td>80</td><td>120</td><td>150</td></tr>
<tr><td>4.0</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>5.0</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>6.0</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td><td>x</td></tr>
<tr><td>7.0</td><td>x</td><td>x</td><td>x</td><td>x</td><td>---</td><td>---</td></tr>
<tr><td colspan="7">Note: “---” indicates size not offered; “x” indicates sizes offered</td></tr>
<tr><td>Balloon Coating (Drug Component)</td><td colspan="7">Paclitaxel (Active Pharmaceutical Ingredient) and Urea (excipient)</td></tr>
<tr><td>Catheter Design</td><td colspan="7">Over-the-Wire (OTW)</td></tr>
<tr><td>Usable Catheter Lengths</td><td colspan="7">80 cm and 130 cm</td></tr>
<tr><td>Balloon Inflation Pressure</td><td colspan="7">Nominal Pressure: 8 atm (811 kPa)
Rated Burst Pressure: 14 atm (1419 kPa)</td></tr>
<tr><td rowspan="6">Minimum Introducer Sheath Compatibility</td><td colspan="2">Balloon Diameter</td><td colspan="2">Max Crossing Profile</td><td colspan="2">Introducer Sheath</td></tr>
<tr><td colspan="2">4.0 mm (all lengths)</td><td colspan="2">5.6 Fr (1.88 mm)</td><td colspan="2">5 Fr</td></tr>
<tr><td colspan="2">5.0 mm (all lengths)</td><td colspan="2">6.0 Fr (2.00 mm)</td><td colspan="2" rowspan="2">6 Fr</td></tr>
<tr><td colspan="2">6.0 mm (all lengths except 120 mm)</td><td colspan="2">6.3 Fr (2.10 mm)</td></tr>
<tr><td colspan="2">6.0 mm (120 mm length)</td><td colspan="2">6.3 Fr (2.10 mm) or 7.0 Fr (2.33 mm) (consult device label to verify)</td><td colspan="2">6 Fr or 7 Fr (consult device label to verify)</td></tr>
<tr><td colspan="2">7.0 mm (all lengths)</td><td colspan="2">7.0 Fr (2.33 mm)</td><td colspan="2">7 Fr</td></tr>
<tr><td>Guidewire Compatibility</td><td colspan="7">The catheter is compatible with a guidewire diameter of 0.035 in (0.89 mm).</td></tr>
</table>

2.1. Device Component Description

The OTW balloon catheter consists of a proximal hub, dual-lumen shaft, and a distal dilatation balloon. The central lumen extends to the distal tip and is used to pass the catheter over a guidewire with a diameter of 0.035 in (0.89 mm). The balloon-inflation lumen is used to inflate and deflate the balloon with a mixture of contrast medium and saline solution. Two radiopaque platinum-iridium markers indicate the working length of the balloon to position the balloon across the target lesion during fluoroscopy. See IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter (Figure 1).

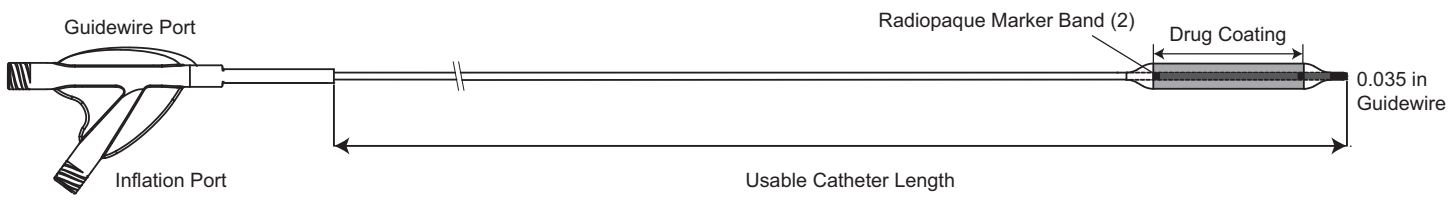

Figure 1. IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter

2.2. Drug Component Description

The FreePac™ drug coating on the balloon of the IN.PACT Admiral DCB consists of the drug paclitaxel and the excipient urea. The balloon surface has a nominal paclitaxel dose density of 3.5 µg/mm^2.

2.2.1. Paclitaxel

The active pharmaceutical ingredient in the IN.PACT Admiral DCB is paclitaxel. 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 of paclitaxel is:

Benzenepropanoic acid, (2aR-(2aα,4ß,4aß,6ß,9α(α R*,ßS*),11α,12α,12bα))-ß-(Benzoylamino)-α- hydroxybenzenepropanoic acid 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9- yl ester.

See Chemical Structure of Paclitaxel (Figure 2) below.

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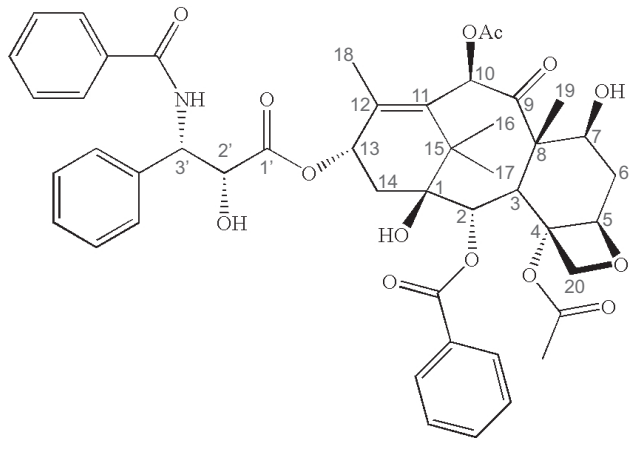

Figure 2. Chemical Structure of Paclitaxel

Paclitaxel is a diterpenoid with a characteristic taxane skeleton of 20 carbon atoms, a molecular weight of 853.91 g/mol, and a molecular formula of $C_{47}H_{51}NO_{14}$. It is a white powder, has extremely low water solubility, is highly lipophilic, and is freely soluble in methanol, ethanol, chloroform, ethyl acetate, and dimethyl sulfoxide.

2.2.2. Urea

The coating utilizes the inactive ingredient urea as an excipient to facilitate the release and transfer of paclitaxel into the arterial wall. See Chemical Structure of Urea (Figure 3) below.

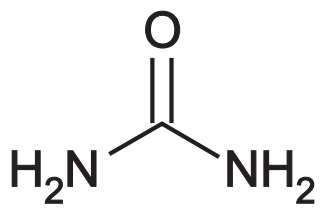

Figure 3. Chemical Structure of Urea

2.2.3. Product Matrix and Paclitaxel Content

Table 2. Product Matrix and Paclitaxel Content

Product Code (80 cm Usable Catheter Length)	Product Code (130 cm Usable Catheter Length)	Nominal Balloon Diameter (mm)	Nominal Balloon Length (mm)	Nominal Paclitaxel Content (µg)
ADM 040 020 08P	ADM 040 020 13P	4.0	20	1089
ADM 040 040 08P	ADM 040 040 13P	4.0	40	1969
ADM 040 060 08P	ADM 040 060 13P	4.0	60	2848
ADM 040 080 08P	ADM 040 080 13P	4.0	80	3728
ADM 040 120 08P	ADM 040 120 13P	4.0	120	5487
ADM 040 150 08P	ADM 040 150 13P	4.0	150	6807
ADM 050 020 08P	ADM 050 020 13P	5.0	20	1454
ADM 050 040 08P	ADM 050 040 13P	5.0	40	2553
ADM 050 060 08P	ADM 050 060 13P	5.0	60	3653
ADM 050 080 08P	ADM 050 080 13P	5.0	80	4752
ADM 050 120 08P	ADM 050 120 13P	5.0	120	6951
ADM 050 150 08P	ADM 050 150 13P	5.0	150	8601
ADM 060 020 08P	ADM 060 020 13P	6.0	20	1850
ADM 060 040 08P	ADM 060 040 13P	6.0	40	3170
ADM 060 060 08P	ADM 060 060 13P	6.0	60	4489
ADM 060 080 08P	ADM 060 080 13P	6.0	80	5809
ADM 060 120 08P	ADM 060 120 13P	6.0	120	8448
ADM 060 150 08P	ADM 060 150 13P	6.0	150	10427
ADM 070 020 08P	ADM 070 020 13P	7.0	20	2279

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Product Code (80 cm Usable Catheter Length)	Product Code (130 cm Usable Catheter Length)	Nominal Balloon Diameter (mm)	Nominal Balloon Length (mm)	Nominal Paclitaxel Content (µg)
ADM 070 040 08P	ADM 070 040 13P	7.0	40	3819
ADM 070 060 08P	ADM 070 060 13P	7.0	60	5358
ADM 070 080 08P	ADM 070 080 13P	7.0	80	6897

3. Indications for Use

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

4. 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.

5. Warnings

- Use the product prior to the Use-by Date specified on the package.
- Contents are supplied sterile. Do not use the product if the inner packaging is damaged or opened.
- Do not use air or any gaseous medium to inflate the balloon. Use only the recommended inflation medium (equal parts contrast medium and saline solution).
- Do not move the guidewire during inflation of the IN.PACT Admiral DCB.
- Do not exceed the rated burst pressure (RBP). The RBP (14 atm [1419 kPa]) is based on the results of in vitro testing. Use of pressures higher than RBP may result in a ruptured balloon with possible intimal damage and dissection.
- The safety and effectiveness of using multiple IN.PACT Admiral DCBs with a total drug dosage exceeding 20,691 µg of paclitaxel in a patient has not been clinically evaluated in the IN.PACT SFA Trial.

6. Precautions

6.1. General Precautions

- This product should only be used by physicians trained in percutaneous transluminal angioplasty (PTA).
- Assess risks and benefits before treating patients with a history of severe reaction to contrast agents.
- Administer appropriate drug therapy to the patient according to standard protocols for PTA before insertion of the dilatation catheter.
- Take precautions to prevent or reduce clotting when any catheter is used. Flush and rinse all products entering the vascular system with heparinized normal saline or a similar solution. For the IN.PACT Admiral DCB catheter, flush the guidewire lumen through the guidewire port with heparinized normal saline until the fluid exits the distal tip. **Do not rinse or wipe the IN.PACT Admiral DCB catheter.**
- Identify allergic reactions to contrast media and antiplatelet therapy before treatment and consider alternatives for appropriate management prior to the procedure.
- Prior to the procedure, inspect the product to verify that the product is intact.
- Handle the product with caution to avoid any damage to the balloon coating or folded balloon.
- This product is not intended for the expansion or delivery of a stent.
- Do not use the IN.PACT Admiral DCB for pre-dilatation or for post-dilatation.
- This product is designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.
- Do not expose the product to organic solvents such as alcohol.
- To reduce the potential for vessel damage, the inflated diameter of the balloon should approximately match the diameter of the vessel just distal to the lesion.

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- The use of this product carries the risks associated with percutaneous transluminal angioplasty, including thrombosis, vascular complications, and/or bleeding events.

6.2. Pre-procedure and Post-procedure Medication Regimen

It is recommended that dual antiplatelet therapy (aspirin with clopidogrel; use ticlopidine as an alternate to clopidogrel in case of allergy) is administered before the procedure and for a minimum of one month after the intervention, and that aspirin is continued for a minimum of six months after the procedure. Prolonged antiplatelet therapy can be given at the discretion of the physician. See Recommended Pre-procedure and Post-procedure Medication Regimen (Table 3).

Table 3. Recommended Pre-procedure and Post-procedure Medication Regimen

Medication		Pre-procedure	During Procedure	Post-procedure[a]
Antiplatelet	Aspirin (ASA)	300-325 mg loading dose within 24 hours prior to procedure[b]	NA	81-325 mg/day (6 months minimum)
Antiplatelet[c, d]	Clopidogrel	75-300 mg within 24 hours prior to procedure or 2 hours post-procedure[e]	NA	75 mg/day (1 month minimum)
	Ticlopidine[f]	500 mg/day for at least 3 consecutive days prior to procedure (last dose within 24 hours of procedure)	NA	500 mg/day (1 month minimum)
Anticoagulation	IV Heparin (or other thrombin inhibitor)	Dosing as per institutional standard[g]		

a For cases of provisional stenting, refer to the published patient management guidelines for dosing instruction.
b ASA loading dose not required for subjects already on a chronic regimen, defined as at least 81 mg daily for at least 5 consecutive days pre-procedure, with the last dose given/taken within 24 hours prior to procedure.
c The safety and efficacy of this dose has not been prospectively studied. Please refer to current package inserts.
d Subjects on a prasugrel or ticagrelor regimen for acute coronary syndrome (ACS) may continue that regimen as antiplatelet therapy. Please refer to the current package insert for information about risks and benefits of these medications, as well as for information on concomitant use of ASA and other medications.
e Clopidogrel loading dose not required for subjects who have been taking 75 mg/day for at least 3 consecutive days before the intervention, with the last dose being taken within 24 hours prior to procedure.
f Recommended in subjects with allergies to clopidogrel.
g It is recommended that a bolus of 3000 to 5000 units of heparin be given prior to the angioplasty procedure, and that anticoagulation is given as needed to maintain an activated clotting time (ACT) of ≥250 seconds, or ≥200 seconds where GP IIb/IIIa inhibitors are concomitantly administered.

6.3. Use of Multiple Balloons

The extent of the patient's exposure to the drug coating is directly related to the number of balloons used. Refer to Using Multiple IN.PACT Admiral DCBs (Section 13.9) and Product Matrix and Paclitaxel Content (Table 2) for details regarding the use of multiple balloons and a product matrix containing the nominal paclitaxel content for each device size, respectively.

6.4. Use in Conjunction with Other Procedures

The safety and effectiveness of the IN.PACT Admiral DCB used in conjunction with other drug-eluting stents or drug-coated balloons in the same procedure has not been evaluated.

6.5. Drug Interaction

Formal drug interaction studies have not been conducted with the IN.PACT Admiral DCB. In the clinical pharmacokinetic (PK) sub-study, systemic levels of paclitaxel following treatment with IN.PACT Admiral DCB(s) were low and cleared rapidly, reducing possible impact of drug-drug interactions due to concomitant medications. Consideration for both systemic and local drug interactions should be given when deciding to use IN.PACT Admiral DCB(s) in a patient who is taking a drug with known interactions to paclitaxel or when deciding to initiate therapy with such a drug in a patient who has recently been treated with IN.PACT Admiral DCB(s). Please refer to Drug Information (Section 8).

6.6. Balloon Handling and Preparation Precautions

- Do not remove the device from the pouch until it is needed for immediate use.
- Handle the device with caution to avoid any damage to the balloon coating or folded balloon.
- Keep the protective sheath in place when purging the balloon catheter of air bubbles.
- Carefully remove and discard the balloon's protective sheath and stylet.
- Do not use the protective sheath or stylet as an introduction aid or a rewrapping tool.
- Do not apply positive pressure to the balloon during preparation.

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6.7. Balloon Placement Precautions

- Manipulate the catheter under fluoroscopic observation when it is exposed to the vascular system. Do not advance or retract the catheter unless the balloon is fully deflated under vacuum.
- Do not move the guidewire during inflation of the balloon.
- Do not manipulate the IN.PACT Admiral DCB while inflated.
- Catheter applications vary. Select the technique on the basis of the patient's condition and the experience of the interventionalist.
- Introducer sheaths used must have lumen sizes that are suitable to accommodate the IN.PACT Admiral DCB. See Product Component Description (Table 1) for the introducer sheath compatibility and crossing profile of each device size.
- If resistance occurs during manipulation, ascertain the cause via fluoroscopy, road mapping, or digital subtraction angiography (DSA) before moving the IN.PACT Admiral DCB backward or forward.
- Do not manipulate the IN.PACT Admiral DCB without sufficient fluoroscopy.
- Use a pressure-monitoring device to prevent overpressurization (nominal pressure: 8 atm [811 kPa], Rated Burst Pressure: 14 atm [1419 kPa]).
- To ensure full coverage of the entire lesion, the balloon diameter must match the reference vessel diameter distal to the lesion and the balloon length must exceed the lesion length by approximately 1 cm on both ends. When using multiple balloons, do so only as described in Using Multiple IN.PACT Admiral DCBs (Section 13.9).
- Never advance the IN.PACT Admiral DCB without the guidewire extending from the tip.
- Maintaining balloon inflation is strongly recommended for 180 seconds. Adequate drug transfer occurs in the first 60 seconds of inflation.
- Appropriate vessel preparation is required prior to use of the IN.PACT Admiral DCB.

  Note: Vessel preparation using only pre-dilatation was studied in the clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with IN.PACT Admiral DCB.

6.8. Balloon Catheter Removal Precautions

- Prior to withdrawing the balloon catheter from the lesion, completely deflate the balloon under vacuum.
- Center the IN.PACT Admiral DCB relative to the introducer sheath when withdrawing, and use caution when removing the IN.PACT Admiral DCB.
- Should unusual resistance be felt at any time when withdrawing the balloon catheter back into the introducer sheath, remove the balloon catheter and the introducer sheath as a single unit to reduce the risk of vascular damage. This must be done under direct visualization with fluoroscopy.
- If removal of the IN.PACT Admiral DCB is required prior to deployment and a repeat attempt is desired, use a new IN.PACT Admiral DCB.

6.9. Post-procedure Precautions

- Administer post-procedure antiplatelet therapy as described in Pre-procedure and Post-procedure Medication Regimen (Section 6.2).

7. Use in Special Populations

7.1. Pregnancy and Lactation

The IN.PACT Admiral DCB is contraindicated in women who are pregnant or breast-feeding. It is unknown whether paclitaxel will be excreted in human milk or whether there is a potential for adverse reaction from paclitaxel exposure in nursing infants. Pregnancy Category C: See Carcinogenicity, Genotoxicity, and Reproductive Toxicity (Section 8.4).

7.2. Gender

Gender was a predefined subgroup that was analyzed in the pivotal clinical study. The outcomes are shown in Primary Safety Composite and Primary Effectiveness by Gender (Table 10). 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.

7.3. Ethnicity

Clinical studies of the IN.PACT Admiral DCB did not include a sufficient number of patients to assess for differences in safety or effectiveness due to ethnicity, regardless of assessment by individual ethnicity categories or assessment by Caucasian or non-Caucasian categories.

7.4. Pediatric Use

The safety and effectiveness of the IN.PACT Admiral DCB in pediatric patients has not been established.

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7.5. Geriatric Use

The pivotal clinical study for the IN.PACT Admiral DCB had an upper age limit of 85 years, and had a predefined study subgroup of subjects 75 years or older (85 subjects). Within this subgroup, the IN.PACT Admiral DCB group showed improvement on the primary safety and effectiveness endpoints.

8. Drug Information

8.1. Mechanism of Action

The mechanism(s) by which the IN.PACT Admiral DCB affects neointimal production has not been fully established. 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. Consequently, the microtubule network may not maintain the dynamic rearrangement required for a normal mitotic process.

8.2. Pharmacokinetics

The pharmacokinetic profile of paclitaxel following treatment with the IN.PACT Admiral DCB was evaluated in 25 patients receiving 2,850 µg to 16,900 µg of paclitaxel. This evaluation was conducted as a sub-study of the randomized clinical trial and is described in Summary of Clinical Studies (Section 11). Paclitaxel systemic exposure in the treated subjects was low and cleared rapidly with a bi-phasic decline. The C_{max} ranged from 1.0 to 35.9 ng/mL and the $AUC_{0-\infty}$ ranged from 11.4 to 128.8 hr*ng/mL. These data indicate that treatment with the IN.PACT Admiral DCB provides low systemic exposure of paclitaxel.

8.3. Metabolism

Metabolic transformation of paclitaxel occurs predominantly in the liver through cytochromes P450 2C8 (CYP2C8) and 3A4 (CYP3A4). Agents which could compete with or inhibit the activity of the CYP2C8 and CYP3A4 isoenzymes may increase paclitaxel plasma levels. For more information on potential drug interactions, see Drug Interaction (Section 6.5).

8.4. Carcinogenicity, Genotoxicity, and Reproductive Toxicity

No long-term studies in animals have been published in peer-reviewed literature to evaluate the carcinogenic potential of paclitaxel. Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay. However, the mechanism by which paclitaxel interferes with cellular proliferation may give rise to loss of chromosomes during cell division as a result of microtubule stabilization during cell division. Paclitaxel is an established aneugenic drug in vitro on human normal cells and will also produce a positive response in the mouse bone marrow micronucleus assay. It has not been established that paclitaxel exerts any direct action on DNA to induce strand fragmentation.

Reproductive toxicity has been previously evaluated in vivo in both rabbits and rats. When administered during rabbit fetal organogenesis, paclitaxel doses of 3.0 mg/kg/day caused embryo- and fetotoxicity; maternal toxicity was also observed. No teratogenic effects were observed at 1.0 mg/kg/day; effects at higher doses could not be assessed due to fetal mortality. In rats, fertility impairment was observed at doses ≥ 1 mg/kg/day. For comparison, the average dose of paclitaxel in the IN.PACT SFA PK Sub-study was 7454 µg, with an average subject weight of 91 kg, for a theoretical normalized dose of 0.082 mg/kg (assuming all the paclitaxel from the coating enters the systemic circulation).

9. Potential Adverse Effects

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

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- 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 the lesion

These complications may result in adverse effects.

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

- 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

Refer to the Physician’s Desk Reference for more information on the potential adverse effects observed with paclitaxel. There may be other potential adverse effects that are unforeseen at this time.

10. Patient Counseling Information

Physicians should consider the following when counseling patients about this product:

- Discuss the risks associated with percutaneous transluminal angioplasty procedures.
- Discuss the risks associated with the IN.PACT Admiral DCB.
- Discuss the risks and benefits of the treatment specific to the patient.
- Discuss short- and long-term post-procedure changes to the patient's lifestyle.
- Discuss the risks of early discontinuation of the antiplatelet therapy.

11. Summary of Clinical Studies

11.1. IN.PACT SFA Trial

11.1.1. Primary Objective

The objective of the IN.PACT SFA Trial was to evaluate the safety and effectiveness of the IN.PACT Admiral DCB as compared with PTA when used to treat atherosclerotic lesions of the superficial femoral artery (SFA) and/or proximal popliteal artery (PPA).

11.1.2. Study Design

The IN.PACT SFA Trial was designed as a two-phase, multicenter, single-blind, randomized trial. Subjects in the IN.PACT SFA I phase were enrolled in Austria, Belgium, Germany, Italy, and Switzerland under ISO 14155:2003, Declaration of Helsinki, and ICH GCP. The second phase, IN.PACT SFA II, was conducted in the United States under an investigational device exemption

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(IDE). Subjects were randomized 2:1 to treatment with the IN.PACT Admiral DCB as compared to PTA. Provisional stenting was used in cases of PTA failure. Follow-up was completed at 30 days, 6 months, and 12 months and will be performed at 2, 3, 4, and 5 years.

The data from the IN.PACT SFA Trial, with greater than 50% subjects coming from the U.S. population (150 subjects Europe and 181 subjects U.S.), have been pooled and comprise the pivotal trial data. This aggregate data provides statistical power for the 12-month primary safety and effectiveness endpoints.

The primary endpoints for the IN.PACT SFA Trial are listed below.

- Primary Safety Composite Endpoint:
  - 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)[1] within 12 months post-index procedure

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

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

H_A: $\pi_T > \pi_C - 0.1$

- Primary Effectiveness Endpoint:
  - Primary patency within 12 months post-index procedure, defined as freedom from clinically-driven target lesion revascularization (TLR)[2] a and freedom from restenosis as determined by duplex ultrasound (DUS)[3] peak systolic velocity ratio (PSVR) ≤ 2.4[4]

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 sample size was estimated using the two-group chi-square test for the primary effectiveness endpoint, and it was driven by the assumptions of a one-sided 0.024995 alpha and at least 80% desired power to show superiority of IN.PACT Admiral DCB to PTA.

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 ≤ 50% (non-stented subjects) or ≤ 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

1 Clinically-driven TVR is defined as any re-intervention within the target vessel due to symptoms or drop of ABI/TBI of ≥ 20% or > 0.15 when compared to post-procedure baseline ABI/TBI
2 Clinically-driven TLR is defined as any re-intervention at the target lesion due to symptoms or drop of ABI/TBI of ≥ 20% or > 0.15 when compared to post-procedure baseline ABI/TBI
3 Post-index procedure DUS (intended to establish a post-treatment baseline) does not contribute to the primary endpoint determination
4 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

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- Days of hospitalization due to the index lesion from procedure through 6, 12, 24, 36 months

As the four primary endpoint tests passed (and in a superiority manner), each at a critical level of 0.024995, several pre-defined secondary endpoints were compared on all ITT non-stented subjects between treatment groups sequentially. These secondary endpoints were analyzed in the following order: (1) CD-TLR at 12 months, (2) primary sustained clinical improvement at 12 months, (3) walking distance at 12 months as assessed by the 6-minute walk test, and (4) duplex-defined binary restenosis (PSVR >2.4) at 24 months or at the time of reintervention. This sequential approach keeps the family-wise error rate at the 0.024995 level across the set of four secondary 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.

11.1.3. Patient Population

Subject demographics, medical history, and risk factors of the 331 subjects are summarized in Baseline Demographics and Medical History (Table 4), which shows similarity between subjects enrolled in both the IN.PACT Admiral DCB and PTA groups.

Table 4. Baseline Demographics and Medical History

	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)	p-value
Age (yr)	67.5 ± 9.5	68.0 ± 9.2	0.612
Male	65.0% (143/220)	67.6% (75/111)	0.713
Race[a]			
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^2)	27.7% (61/220)	25.2% (28/111)	0.694
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[b] (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. Site reported data.			

[a] Race and ethnicity data was not collected in IN.PACT SFA I phase (Europe).
[b] TBI was not measured in IN.PACT SFA I phase.

The baseline lesion characteristics, as reported by the sites and angiographic core laboratories, have been provided in Lesion Characteristics (Table 5), Lesion Characteristics. The total target lesion length treated was similar between treatment 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). Pre-dilatation using a PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 96.4% (212/220) of IN.PACT Admiral DCB subjects.

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Table 5. Lesion Characteristics

	IN.PACT DCB	PTA	p-value
Baseline Lesion Characteristics [a]	**(N=220 Subjects)**	**(N=111 Subjects)**	
Lesion Type			
De novo	95.0% (209/220)	94.6% (105/111)	0.875
Restenotic (non-stented)	5.0% (11/220)	5.4% (6/111)	
Lesion Location [b, c]	**(N=221 Lesions)**	**(N=113 Lesions)**	
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
Angiographic Lesion Characteristics [b]	**(N=221 Lesions)**	**(N=113 Lesions)**	
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 (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
Procedural Characteristics [d]	**(N=220 Subjects)**	**(N=111 Subjects)**	
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.

Note that four subjects in the trial were assessed by site 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.

[a] Site reported data.
[b] Core laboratory reported data. All lesions within artery segment are counted.
[c] All lesions within artery segment are counted
[d] Required for IN.PACT SFA II phase; not required for IN.PACT SFA I phase.

Follow-up compliance through the 12-month follow-up visit is presented in Subject Follow-up Compliance at 12 Months (Table 6). IN.PACT Admiral DCB subject compliance within window at 12 months was 93.1% and PTA subject compliance at 12 months was 90.7%.

Table 6. Subject Follow-up Compliance at 12 Months

	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)
Eligible Subjects[a]	202	108
Death[b]	5	0
Withdrawal[b]	13	3
Follow-up Not Done	5	4

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	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)
Follow-up Visit Within Window[c]	188	98
Follow-up Visit Out of Window[c]	9	6
Follow-up Compliance (%)[d]	93.1%	90.7%
Site reported data.		

[a] 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).
[b] Death and withdrawal are cumulative.
[c] Within window visits are defined as 12-months ± 30 days.
[d] Percentage based on number of subjects who had follow-up visit within window divided by total number of eligible subjects.

11.1.4. Primary Safety and Effectiveness Endpoints

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 predefined 10% non-inferiority margin and showed superiority in safety against the PTA group using a sequential analysis approach. 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.

See Primary Safety and Effectiveness Endpoints (Table 7). Also see Kaplan-Meier Plot - Event-Free from Primary Safety Endpoint through 360 Days (Figure 4) and Kaplan-Meier Plot - Primary Patency through 390 Days (Figure 5).

Table 7. Primary Safety and Effectiveness Endpoints

Outcome	IN.PACT DCB (N=220)	PTA (N=111)	Difference [95% CI]	p-value[a]
Primary Safety Endpoint	95.7% (198/207)	76.6% (82/107)	19.0% [10.5%, 27.5%]	<0.001
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 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[1] and freedom from restenosis as determined by duplex ultrasound[2] (DUS) peak systolic velocity ratio (PSVR) ≤2.4[3] within 12 months. Key primary patency endpoint definition components:
  1. Clinically-driven TLR is defined as any reintervention at the target lesion due to symptoms or drop of ABI/TBI of ≥20% or >0.15 when compared to postprocedure baseline ABI/TBI
  2. Post-index procedure DUS is intended to establish a post-treatment baseline and does not contribute to the primary endpoint determination
  3. 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). CI - Confidence Interval
- Analysis sets: Effectiveness - all randomized subjects with multiple imputation performed on missing data for primary patency are provided in the Difference [95% CI] and p-value columns; 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).
- 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.

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.

[a] all alpha are one-sided with significance of 0.024995 required.

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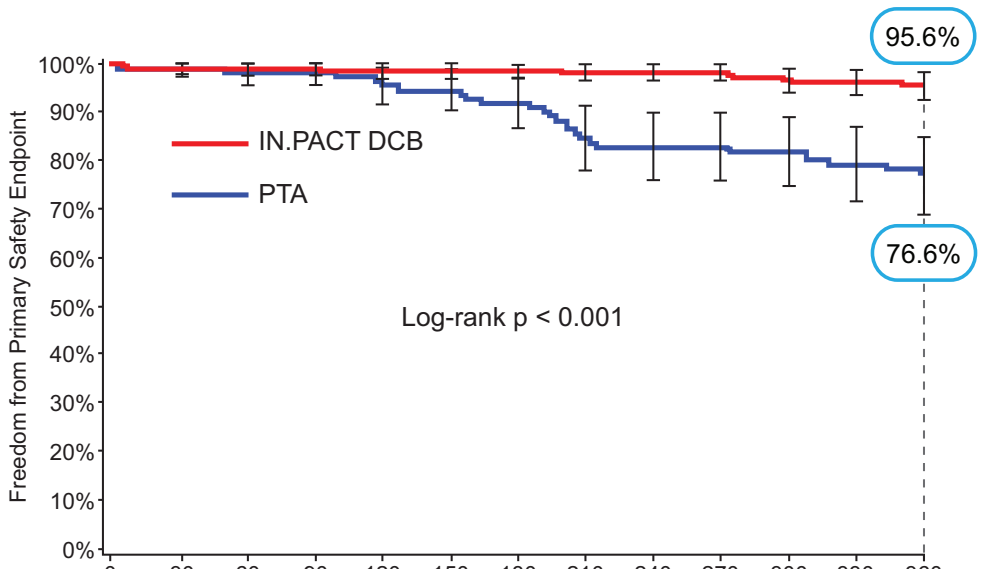

From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210	211 240	241 270	271 300	301 330	331 360
IN.PACT DCB (N=220 Subjects)													
# Entered	220	220	215	214	214	212	210	208	206	205	203	197	195
# Censored	0	3	1	0	1	2	2	1	1	2	3	1	50
# Events	0	2	0	0	1	0	0	1	0	0	3	1	1
Event-free [%]	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%
PTA (N=111 Subjects)													
# 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%

Survival Curves Comparison				
Analysis Method	**Test**	**Chi Square**	**Degr. Freedom**	**p-value**
Kaplan-Meier Analysis	Log-Rank	27.3314	1	<0.001
All events were adjudicated by the independent Clinical Events Committee.				

Figure 4. Kaplan-Meier Plot - Event-Free from Primary Safety Endpoint through 360 Days

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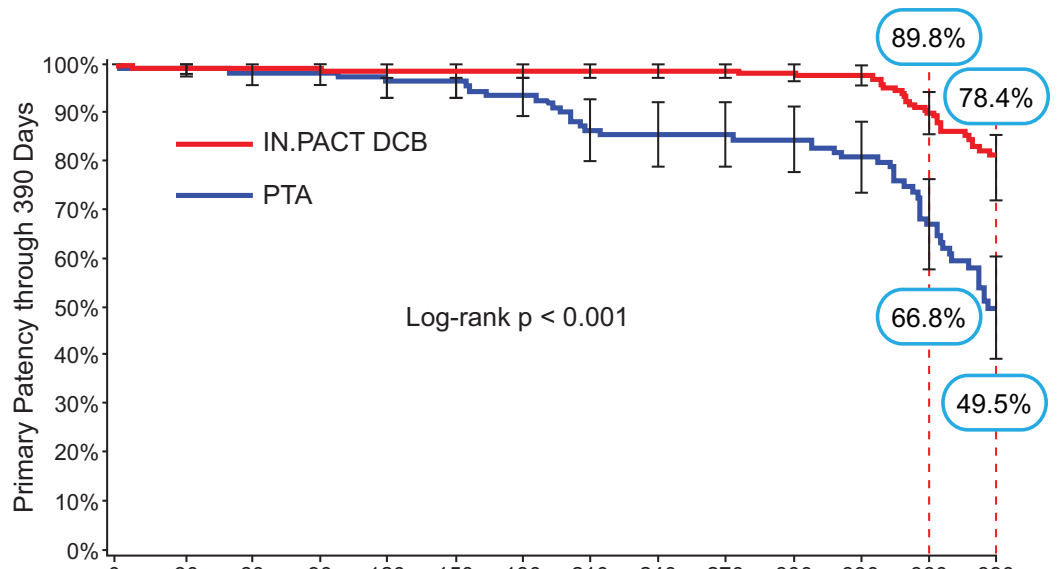

From day X To day Y	0 0	1 30	31 60	61 90	91 120	121 150	151 180	181 210	211 240	241 270	271 300	301 330	331 360	361 390
IN.PACT DCB (N=220 Subjects)														
# Entered	220	220	215	214	214	212	210	208	207	206	204	200	198	141
# Censored	0	3	1	0	1	2	2	1	1	2	3	1	43	39
# Events	0	2	0	0	1	0	0	0	0	0	1	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%
PTA (N=111 Subjects)														
# 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%

Survival Curves Comparison				
Analysis Method	**Test**	**Chi Square**	**Degr. Freedom**	**p-value**
Kaplan-Meier Analysis	Log-Rank	33.2068	1	<0.001

All TLR events were adjudicated by the independent Clinical Events Committee.
All DUSs were analyzed by an independent core laboratory.

Figure 5. Kaplan-Meier Plot - Primary Patency through 390 Days

The primary safety and effectiveness outcomes of all non-stented patients and intent to treat (ITT) population are shown in Outcomes of All ITT and All Non-stented Populations (Table 8).

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Table 8. Outcomes of All ITT and All Non-stented Populations

	All ITT		All Non-Stented	
	IN.PACT DCB	**PTA**	**IN.PACT DCB**	**PTA**
Primary Safety Endpoint	95.7% (198/207)	76.6% (82/107)	95.8% (183/191)	77.7% (73/94)
Primary Effectiveness Endpoint – Primary Patency at 12 Months	82.2% (157/191)	52.4% (54/103)	82.9% (145/175)	52.2% (47/90)

- 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[1] and freedom from restenosis as determined by duplex ultrasound[2] (DUS) peak systolic velocity ratio (PSVR) ≤2.4[3] within 12 months. Key primary patency endpoint definition components:
  1. Clinically-driven TLR is defined as any reintervention at the target lesion due to symptoms or drop of ABI/TBI of ≥20% or >0.15 when compared to postprocedure baseline ABI/TBI
  2. Post-index procedure DUS is intended to establish a post-treatment baseline and does not contribute to the primary endpoint determination
  3. 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 as-observed results for primary patency; Safety - all randomized subjects experiencing at least one component for the safety endpoint or with follow-up of at least 330 days post-procedure (ie, 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.

11.1.5. Principal Safety and Effectiveness Results

A summary of the principal safety and effectiveness results, including major secondary endpoints, have been shown below in Principal Safety and Effectiveness Results (Table 9). 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 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 9. Principal Safety and Effectiveness Results

	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)	Difference [95% CI]	p-value[a]
Safety Parameters				
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
Effectiveness Parameters				

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	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)	Difference [95% CI]	p-value[a]
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
Cumulative complications within 360 days				
MAE Composite (Death, Major Target Limb Amputation, Clinically-driven TVR, Thrombosis)	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
Clinically-driven TLR	2.4% (5/207)	20.6% (22/107)	-18.1% [-26.1%, -10.2%]	<0.001
Any TVR	4.8% (10/207)	23.4% (25/107)	-18.5% [-27.1%, -10.0%]	<0.001

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	IN.PACT DCB (N=220 Subjects)	PTA (N=111 Subjects)	Difference [95% CI]	p-value[a]
Any TLR	2.9% (6/207)	20.6% (22/107)	-17.7% [-25.7%, -9.7%]	<0.001

- Primary sustained clinical improvement was defined as freedom from target limb amputation, TVR, and increase in Rutherford class at 12 months post-procedure.
- Device success defined as successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP.
- Procedure success defined as residual stenosis of ≤50% (non-stented subjects) or ≤30% (stented subjects) by visual estimate.
- Clinical success defined as procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.
- Clinically-driven TLR/TVR is defined as any reintervention within the target vessel due to symptoms or drop of ABI/TBI of ≥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.
- Binary restenosis is defined as duplex restenosis (PSVR >2.4/3.4) or angiographic restenosis of the target lesion at 12 months postprocedure, or at the time of reintervention prior to any prespecified timepoint.

Statistical references:

- Numbers are % (counts/sample size). CI - Confidence Interval
- Analysis sets: Effectiveness - all randomized subjects with multiple imputation performed on missing data for primary patency are provided in the Difference [95% CI] and p-value columns; 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, all duplex ultrasound and angiographic measures were made by the independent core laboratories.

[a] 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.

11.1.6. Subgroup Analysis

Medtronic has analyzed trial results by different pre-defined subgroups to investigate the consistency of results. Primary Safety Endpoint Event at 12 Months (Figure 6), Primary Patency at 12 Months (Figure 7), and Clinically-driven Target Lesion Revascularization at 12 Months (Figure 8) 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.

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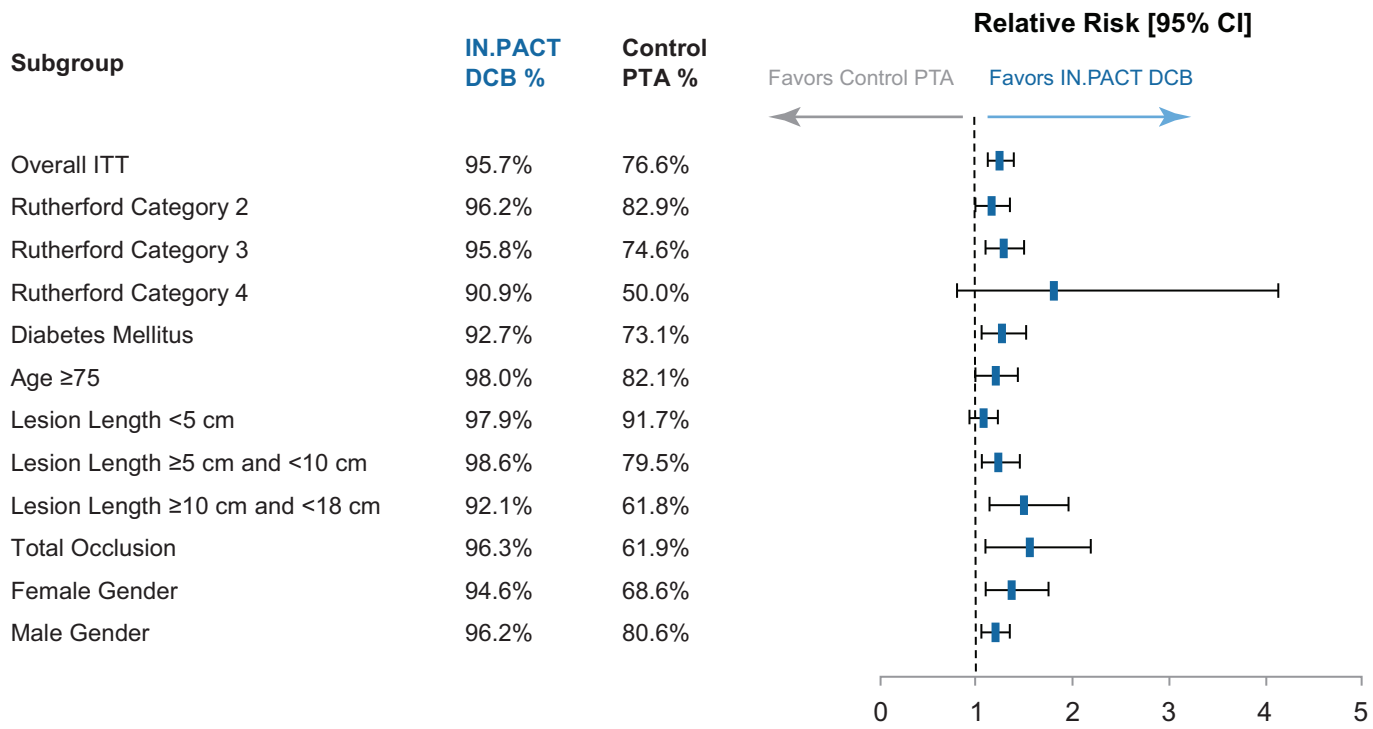

Figure 6. Primary Safety Endpoint Event at 12 Months

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

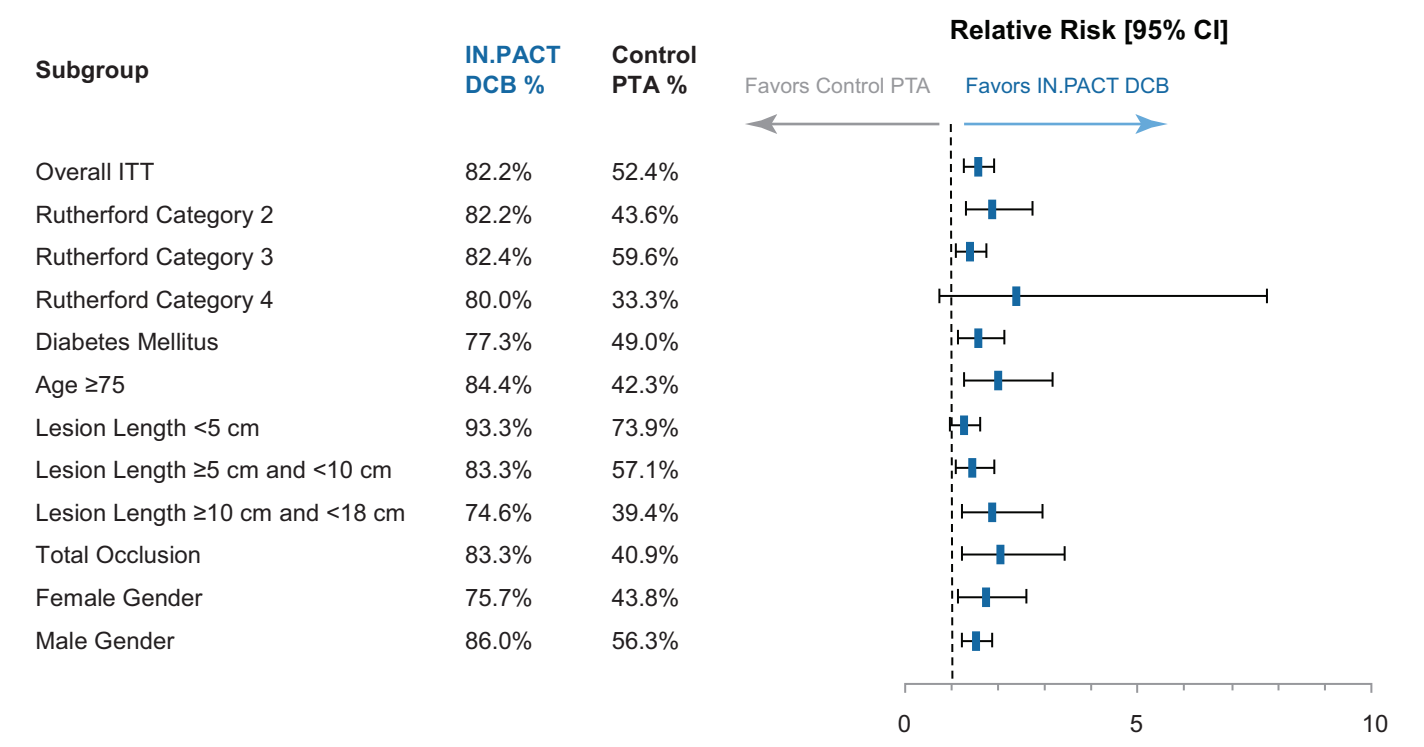

Figure 7. Primary Patency at 12 Months

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

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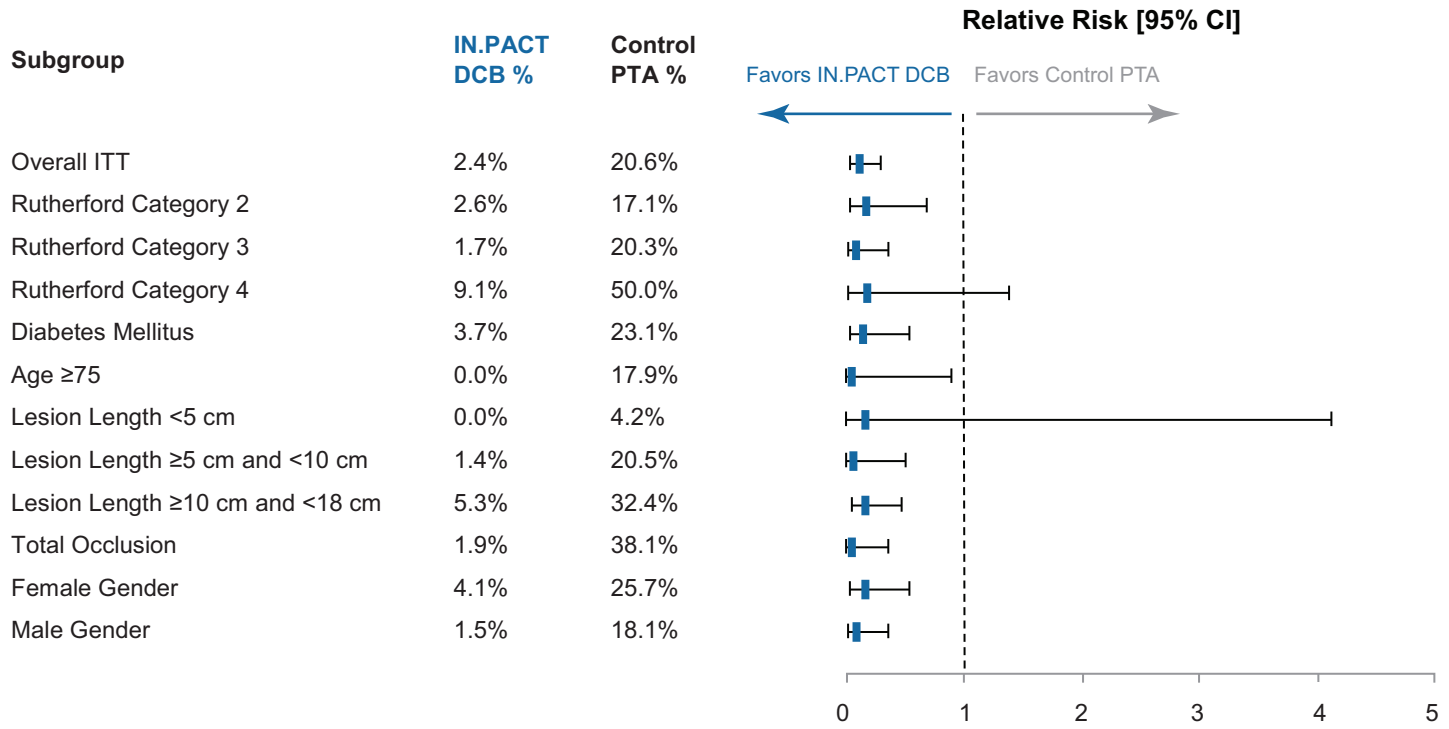

Figure 8. Clinically-driven Target Lesion Revascularization at 12 Months

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.

11.1.7. 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.

Table 10. 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%
Males			
Outcome	**IN.PACT DCB (N=143 Subjects)**	**Standard PTA (N=75 Subjects)**	**Difference**
Primary Safety Endpoint	96.2% (128/133)	80.6% (58/72)	15.7%

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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[1] and freedom from restenosis as determined by duplex ultrasound[2] (DUS) peak systolic velocity ratio (PSVR) ≤2.4[3] within 12 months. Key primary patency endpoint definition components:
  1. Clinically-driven TLR is defined as any reintervention at the target lesion due to symptoms or drop of ABI/TBI of ≥20% or >0.15 when compared to postprocedure baseline ABI/TBI
  2. Post-index procedure DUS is intended to establish a post-treatment baseline and does not contribute to the primary endpoint determination
  3. 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 (ie, 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.

11.1.8. Summary of Adverse Events

Serious Adverse Event Rates by SOC and Preferred Term through 360 Days (Table 11) 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) was defined as an adverse event that:

- led to a death,
- led to a serious deterioration in the health of the subject that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient hospitalization or prolongation of an existing hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Table 11. 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
Subjects with One or More Serious Adverse Events	46.4% (102/220)	55.9% (62/111)	0.105
Blood and Lymphatic System Disorders [a]	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)	
Cardiac Disorders [a]	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)	

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Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
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)	
Ear and Labyrinth Disorders [a]	0.5% (1/220)	0.0% (0/111)	1.000
Vertigo	0.5% (1/220)	0.0% (0/111)	
Eye Disorders [a]	0.5% (1/220)	0.0% (0/111)	1.000
Diabetic Retinopathy	0.5% (1/220)	0.0% (0/111)	
Gastrointestinal Disorders [a]	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)	
General Disorders and Administration Site Conditions [a]	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)	
Hepatobiliary Disorders [a]	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)	
Infections and Infestations [a]	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)	

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Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
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)	
Injury, Poisoning and Procedural Complications [a]	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)	
Investigations [a]	0.0% (0/220)	0.9% (1/111)	0.335
Prostatic Specific Antigen Increased	0.0% (0/220)	0.9% (1/111)	
Metabolism and Nutrition Disorders [a]	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)	
Musculoskeletal and Connective Tissue Disorders [a]	4.5% (10/220)	4.5% (5/111)	1.000
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)	
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) [a]	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)	
Nervous System Disorders [a]	5.0% (11/220)	6.3% (7/111)	0.615
Amnesia	0.5% (1/220)	0.0% (0/111)	

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Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
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)	
Renal and Urinary Disorders [a]	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)	
Renal Failure	0.0% (0/220)	0.9% (1/111)	
Renal Failure Acute	0.5% (1/220)	0.0% (0/111)	
Reproductive System and Breast Disorders [a]	0.5% (1/220)	0.0% (0/111)	1.000
Postmenopausal Haemorrhage	0.5% (1/220)	0.0% (0/111)	
Respiratory, Thoracic and Mediastinal Disorders [a]	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)	
Skin and Subcutaneous Tissue Disorders[a]	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)	
Surgical and Medical Procedures [a]	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)	
Vascular Disorders [a]	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)	
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)	

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Serious Adverse Events	IN.PACT DCB (N=220 Subjects)	Standard PTA (N=111 Subjects)	p-value
Subclavian Artery Stenosis	0.0% (0/220)	0.9% (1/111)	
Total Serious Adverse Events	**195**	**118**	

a 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.

11.2. Pharmacokinetic Sub-study

Human pharmacokinetics was investigated as a sub-study of the IN.PACT SFA Trial. This sub-study was a prospective, multi-center, non-randomized study arm (IN.PACT Admiral DCB) conducted at multiple prespecified investigational sites, designed to evaluate the levels of paclitaxel in the systemic circulation of subjects at multiple time points. Pharmacokinetic parameters were determined for a total of 24 subjects (16 male and 8 female). A summary of the pharmacokinetic parameters is presented in Summary of Pharmacokinetic Parameters (Table 12). The pharmacokinetic sub-study demonstrated low systemic exposure with rapid clearance of paclitaxel.

Table 12. Summary of Pharmacokinetic Parameters

Parameter	Mean (N=24)	Standard Deviation	%CV	Range
T_{max} (hr)	0.17	0.067	38.8	0.07 – 0.32
C_{max} (ng/mL)	7.9	7.70	97.9	1.0 - 35.9
$AUC_{0\text{-}last}$ (hr*ng/mL)	29.4	22.06	75.0	3.2 – 91.6
$AUC_{0\text{-}inf}$ (hr*ng/mL)	47.8	28.98	60.6	11.4 – 128.8
$T_{1/2}$ (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_{max} (hr)	The timepoint where Cmax is reached			
C_{max} (ng/mL)	Maximum plasma concentration			
$AUC_{0\text{-}last}$ (hr*ng/mL)	Area under plasma concentration-time curve from time zero to time of last measurable concentration			
$AUC_{0\text{-}inf}$ (hr*ng/mL)	Area under the plasma concentration-time curve from time zero extrapolated to infinity			
$T_{1/2}$ (hr)	Terminal half-life			
CL/F (L/hr)	Apparent clearance			

11.3. IN.PACT Global Study

11.3.1. Study Overview

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 were provided to FDA for consideration as part of the PMA submission.

11.4. Summary of Rare Adverse Events

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.

11.5. IN.PACT Admiral DCB ISR Clinical Evaluation

11.5.1. Primary Objective

The objective of this clinical evaluation was to assess the safety and effectiveness of the IN.PACT Admiral DCB as compared with PTA when used to treat in-stent restenotic (ISR) lesions of the superficial femoral artery (SFA) or popliteal artery.

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11.5.2. Design

This clinical evaluation was designed as an observational, propensity score-adjusted, comparative analysis of IN.PACT Admiral DCB subjects selected from the real-world IN.PACT Global Study ("DCB ISR Cohort") and PTA subjects provided from the Society of Vascular Surgery (SVS) Vascular Quality Initiative (VQI) Registry database ("PTA ISR Comparator").

A total of 164 DCB subjects from the IN.PACT Global Study comprised the DCB ISR Cohort, and a total of 153 PTA subjects from the SVS VQI Registry comprised the PTA ISR Comparator. Patients in the DCB ISR Cohort were treated at 31 sites in Austria, Belgium, Canada, Egypt, Germany, Hungary, Italy, The Netherlands, Poland, Singapore, Slovakia, South Korea, and Switzerland between June 6, 2012 and December 16, 2013, and patients in the PTA ISR Comparator were treated at 23 sites in the United States between 2011 and 2014.

The objective of this analysis was to demonstrate that the primary endpoint of 12-month target lesion revascularization (TLR) was significantly lower in the DCB ISR Cohort when compared to the PTA ISR Comparator group for the treatment of ISR.

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

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

$$H_0: p_T \geq p_C$$

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

$$H_A: p_T < p_C$$

Due to the nature of this non-randomized retrospective comparison, it was necessary to adjust for expected baseline differences between the subjects in the two groups to ensure objectivity of the clinical evaluation design and the validity of the results. As pre-specified in the statistical analysis plan, propensity score analysis was performed using clinically relevant baseline characteristics. The propensity score calculation was carried out by an independent statistician without access to the outcomes of either group. The calculation results were submitted to the FDA for review and approval prior to performing the primary endpoint analyses.

The primary endpoint of the powered statistical analysis comparing ISR outcomes in the DCB ISR Cohort and the PTA ISR Comparator was the incidence of TLR through 12 months.

The clinically relevant secondary endpoints assessed included:

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

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

11.5.3. Patient Population

Table 13 below presents the baseline demographics and clinical characteristics for the 164 DCB ISR Cohort subjects and the 153 PTA ISR Comparator subjects. These 20 baseline variables were pre-specified as the covariates in the propensity score analysis, and all of the variables were included in the propensity score calculation except for the TASC lesion type due to a missing data rate in the DCB ISR Cohort that exceeded the pre-specified cutoff of 20%.

Table 13. Baseline Demographics and Clinical Characteristics

Baseline Characteristics	DCB ISR Cohort (N=164)	PTA ISR Comparator (N=153)	Propensity Score Adjusted p-value[a]
Baseline Demographics			
Age (yrs)			
Mean±SD (N)	66.95±9.84 (163)	66.79±11.23 (153)	0.795
Median (Q1, Q3)	67.00 (60.00,74.00)	66.00 (58.00,75.00)	
Range (Min, Max)	(39.00,86.00)	(44.00,89.00)	
Male	72.6% (119/164)	51.6% (79/153)	0.536
BMI (kg/m^2)			
Mean±SD (N)	26.34±4.39 (164)	28.21±6.06 (153)	0.835
Median (Q1, Q3)	25.94 (23.63,28.57)	28.00 (24.00,30.00)	
Range (Min, Max)	(16.46,43.26)	(13.00,50.00)	

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Baseline Characteristics	DCB ISR Cohort (N=164)	PTA ISR Comparator (N=153)	Propensity Score Adjusted p-value[a]
Ankle-Brachial Index (ABI) (mmHg ratio)			
Mean±SD (N)	0.64±0.22 (147)	0.70±0.41 (140)	0.786
Median (Q1, Q3)	0.65 (0.51,0.77)	0.64 (0.48,0.81)	
Range (Min, Max)	(0.00,1.43)	(0.00,2.00)	
Baseline Clinical Characteristics			
Hypertension	83.4% (136/163)	87.6% (134/153)	0.972
Diabetes	36.6% (60/164)	49.0% (75/153)	0.920
Insulin-dependent Diabetes	16.5% (27/164)	22.9% (35/153)	0.946
On Dialysis	3.0% (5/164)	1.3% (2/153)	0.579
Coronary artery disease	20.5% (30/146)	24.2% (37/153)	0.964
Current smoker	36.0% (59/164)	32.7% (50/153)	0.915
Previous limb amputation (major or minor)	5.5% (9/164)	4.6% (7/153)	0.980
Renal insufficiency (per serum creatinine ≥1.5 mg/dl)	9.5% (14/147)	9.9% (15/151)	0.931
Baseline Lesion and Procedural Characteristics			
TASC lesion type			0.906
A	20.2% (21/104)	30.7% (47/153)	
B	30.8% (32/104)	27.5% (42/153)	
C	36.5% (38/104)	30.1% (46/153)	
D	12.5% (13/104)	11.8% (18/153)	
Lesion length (cm)			
Mean±SD (N)	17.59±10.49 (164)	13.16±9.61 (151)	0.735
Median (Q1, Q3)	16.00 (10.00,27.00)	10.00 (6.00,20.00)	
Range (Min, Max)	(1.00,47.00)	(2.00,47.00)	
Total occlusion	40.9% (67/164)	68.7% (103/150)	0.990
Occluded lesion length (cm)			
Mean±SD (N)	7.47±11.65 (164)	7.87±9.40 (150)	0.709
Median (Q1, Q3)	0.00 (0.00,10.50)	4.00 (0.00,14.00)	
Range (Min, Max)	(0.00,42.00)	(0.00,45.00)	
Pre-op aspirin	95.7% (157/164)	83.0% (127/153)	0.422
Indication of Claudication - Rutherford Classification or equivalent	87.8% (144/164)	74.5% (114/153)	0.633
Lesion Location: SFA	71.3% (117/164)	86.9% (133/153)	0.706
Provisional stent	15.9% (26/164)	33.3% (51/153)	0.814

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

Categorical variables between groups were compared using the chi-squared test or Fisher's exact test as appropriate, and continuous variables were compared using Student's t-test.

Site reported data.

All of the variables in this table were included in the propensity score calculation except TASC lesion type due to a missing data rate that exceeded the pre-specified cutoff of 20%.

p-values are not adjusted for multiplicity

[a] The propensity score adjusted p-value was based on all subjects for each baseline variable. For each variable with missing values (<20%), a gender-specific imputation was performed by replacing the missing values of the variable with the gender-specific median observed value within each group.

Follow-up compliance for the 12-month follow-up visits is presented in Table 14 for the DCB ISR Cohort subjects. The rate of in-window follow-up visit completion at 12 months was 92.3%.

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Table 14. Subject Follow-up Compliance – IN.PACT Global DCB ISR Cohort Subjects

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

[a] 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)
[b] Death and withdrawal are cumulative
[c] Within window visits are defined as: 12-month ± 60 days.
[d] Percentage based on number of subjects who had follow-up visit within window divided by total number of eligible subjects
Site reported data

11.5.4. Safety and Effectiveness Results

Primary Endpoint Analysis

The results of the powered statistical analysis comparing the 12-month primary endpoint between the DCB ISR Cohort and the PTA ISR Comparator are shown in Table 15.

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

Table 15. Primary Effectiveness Endpoint Results

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

Statistical references:

- Numbers are cumulative incidence % (number of failures) based on Kaplan-Meier method. CI – Confidence Interval
- Analysis sets: The primary analysis set was based on the intent-to-treat (ITT) principle. All subjects enrolled through the selection process specified in SAP Section 3.1 were included as ITT subjects.
- [a] To analyze the treatment differences between the DCB ISR Cohort and PTA ISR Comparator groups in the clinical/safety endpoints such as TLR, a propensity-quintile-stratified Cox proportional hazards model was employed, with time to event as the dependent variable and treatment group as the independent variable.

The Kaplan-Meier analysis of this primary effectiveness endpoint, presented as freedom from target lesion revascularization, is shown in Figure 9.

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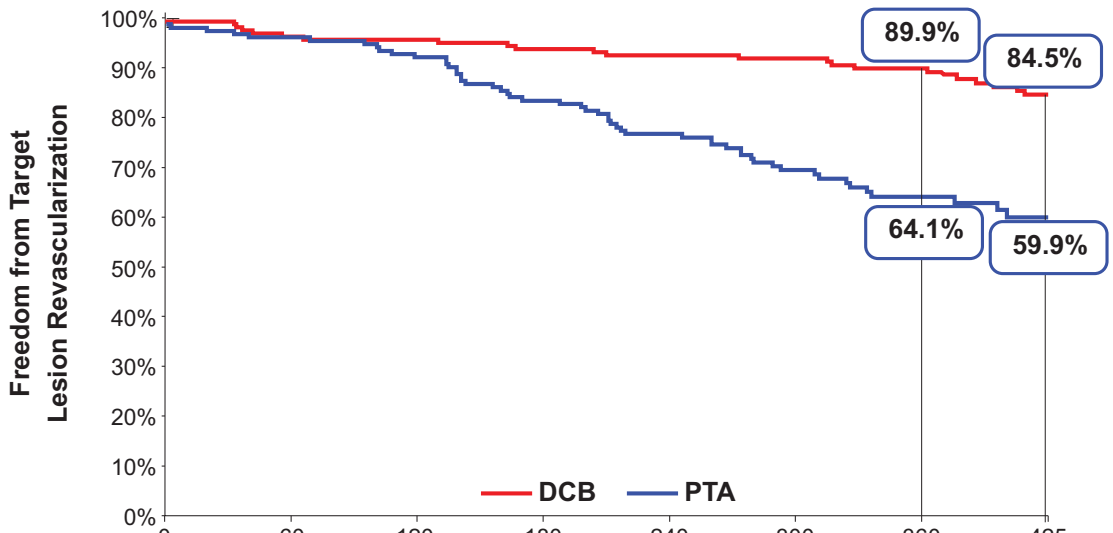

Target Lesion Revascularization	0	1-60	61-120	121-180	181-240	241-300	301-360	361-425
DCB								
# Entered	164	163	154	152	148	143	141	126
# Censored	0	4	1	1	3	0	12	15
# Events	1	5	1	3	2	1	3	7
Survived [%]	99.39%	96.27%	95.65%	93.75%	92.47%	91.82%	89.87%	84.53%
PTA								
# Entered	153	151	144	138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

Figure 9. Kaplan-Meier Plot - Event-free from Target Lesion Revascularization through 360 and 425 Days

Secondary Safety and Effectiveness Endpoints

The results of the secondary endpoints for the IN.PACT Admiral DCB ISR Clinical Evaluation are shown in Table 16.

In both the DCB ISR Cohort and the PTA ISR Comparator, there were high rates of acute success. Since the acute success definitions differed, these were not able to be directly compared, but the DCB ISR Cohort had high rates of device success (99.5%), procedural success (99.4%), and clinical success (98.8%), while the PTA ISR Comparator had a high rate of technical success (97.4%). The definitions of each of these endpoints are provided in the footnotes of Table 16.

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

There were no major target limb amputations in the DCB ISR Cohort and three major target limb amputations in the PTA ISR Comparator within 12 months. Lastly, there was one death in the DCB ISR Cohort and no deaths in the PTA ISR Comparator within 12 months. One subject in the DCB ISR Cohort experienced a non-cardiac death at day 276 post-index procedure. The independent clinical events committee determined that the event was not device-related and not procedure-related.

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Table 16. Secondary Safety and Effectiveness Endpoint Results

	DCB ISR Cohort (N=164)	PTA ISR Comparator (N=153)
Effectiveness Parameters		
Device Success[a]	99.5% (364/366)	NA
Procedural Success[a]	99.4% (163/164)	NA
Clinical Success[a]	98.8% (162/164)	NA
Technical Success[a]	NA	97.4% (149/153)
Safety Parameters		
Cumulative complications within 30 days		
Death (all-cause)	0.00% (0)	0.00% (0)
Target Vessel Revascularization	0.61% (1)	2.61% (4)
Major Target Limb Amputation	0.00% (0)	0.00% (0)
Target Lesion Revascularization	0.61% (1)	2.61% (4)
Cumulative complications within 180 days		
Death (all-cause)	0.00% (0)	0.00% (0)
Target Vessel Revascularization	6.88% (11)	17.28% (26)
Major Target Limb Amputation	0.00% (0)	1.33% (2)
Target Lesion Revascularization	6.25% (10)	16.61% (25)
Cumulative complications within 360 days		
Death (all-cause)	0.65% (1)	0.00% (0)
Target Vessel Revascularization	11.41% (18)	38.07% (54)
Major Target Limb Amputation	0.00% (0)	2.08% (3)

Other Major Secondary Endpoints at 12 Months	**DCB ISR Cohort (N=164)**	**PTA ISR Comparator (N=153)**
Time to all-cause mortality (days)		
Mean±SD (N)	276.00 (1)	--
Median	276.00	--
(Min, Max)	(276.00,276.00)	--
Time to first TLR (days)		
Mean±SD (N)	148.44±115.25 (16)	182.33±93.53 (51)
Median	146.50	187.00
(Min, Max)	(0.00,328.00)	(0.00,335.00)

Endpoint definitions:

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

Statistical references:

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

Subgroup Analyses

Medtronic has analyzed the clinical evaluation results by the male and female gender subgroups. Both the male and female gender subgroups showed favorable trends on the primary effectiveness endpoint of 12-month TLR (male subgroup: 8.72% DCB vs. 32.94% PTA, and female subgroup: 14.08% DCB vs. 39.11% PTA). Favorable clinical trends were also noted for the

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secondary endpoint of 12-month TVR (male subgroup: 10.48% DCB vs. 34.67% PTA, and female subgroup: 14.08% DCB vs. 41.76% PTA).

Summary of Adverse Events

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

Table 17 provides a summary of serious adverse event rates by system-organ class (SOC) through 360 days occurring in the DCB ISR Cohort.

Table 17. Serious Adverse Event Rates by SOC and Preferred Term through 360 Days – IN.PACT Global DCB ISR Cohort Subjects

Serious Adverse Event	DCB ISR Cohort (N=164 Subjects)
Subjects with One or More Serious Adverse Events	**41.5% (68/164)**
CARDIAC DISORDERS[a]	**2.4% (4/164)**
ACUTE MYOCARDIAL INFARCTION	0.6% (1/164)
ATRIAL FIBRILLATION	0.6% (1/164)
CONGESTIVE CARDIOMYOPATHY	0.6% (1/164)
CORONARY ARTERY DISEASE	0.6% (1/164)
MYOCARDIAL INFARCTION	0.6% (1/164)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS[a]	**0.6% (1/164)**
CONGENITAL CYSTIC KIDNEY DISEASE	0.6% (1/164)
EYE DISORDERS[a]	**1.2% (2/164)**
CATARACT	0.6% (1/164)
RETINAL ARTERY OCCLUSION	0.6% (1/164)
GASTROINTESTINAL DISORDERS[a]	**1.2% (2/164)**
GASTRITIS	0.6% (1/164)
OESOPHAGEAL HAEMORRHAGE	0.6% (1/164)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS[a]	**1.2% (2/164)**
DEATH	0.6% (1/164)
DEVICE BREAKAGE	0.6% (1/164)
HEPATOBILIARY DISORDERS[a]	**1.2% (2/164)**
ACUTE HEPATIC FAILURE	0.6% (1/164)
CHOLECYSTITIS	0.6% (1/164)
CHOLELITHIASIS	0.6% (1/164)
INFECTIONS AND INFESTATIONS[a]	**3.0% (5/164)**
CLOSTRIDIUM DIFFICILE COLITIS	0.6% (1/164)
GANGRENE	0.6% (1/164)
GROIN INFECTION	0.6% (1/164)
PILONIDAL CYST	0.6% (1/164)
PNEUMONIA	0.6% (1/164)
PSEUDOMEMBRANOUS COLITIS	0.6% (1/164)
URINARY TRACT INFECTION	0.6% (1/164)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS[a]	**7.3% (12/164)**
ARTERIAL RESTENOSIS	2.4% (4/164)
IN-STENT ARTERIAL RESTENOSIS	4.3% (7/164)
IN-STENT CORONARY ARTERY RESTENOSIS	0.6% (1/164)
PERIPHERAL ARTERIAL REOCCLUSION	0.6% (1/164)
VASCULAR PSEUDOANEURYSM	1.2% (2/164)
INVESTIGATIONS[a]	**0.6% (1/164)**
INTERNATIONAL NORMALISED RATIO INCREASED	0.6% (1/164)
METABOLISM AND NUTRITION DISORDERS[a]	**1.2% (2/164)**

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Serious Adverse Event	DCB ISR Cohort (N=164 Subjects)
DIABETES MELLITUS	0.6% (1/164)
DIABETIC FOOT	0.6% (1/164)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS[a]	**3.7% (6/164)**
BACK PAIN	0.6% (1/164)
INTERVERTEBRAL DISC PROTRUSION	0.6% (1/164)
MUSCULOSKELETAL DISORDER	0.6% (1/164)
MYOFASCIAL PAIN SYNDROME	0.6% (1/164)
PAIN IN EXTREMITY	0.6% (1/164)
SPINAL COLUMN STENOSIS	0.6% (1/164)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)[a]	**3.7% (6/164)**
LUNG NEOPLASM	0.6% (1/164)
LUNG NEOPLASM MALIGNANT	0.6% (1/164)
MALIGNANT NEOPLASM PROGRESSION	0.6% (1/164)
NEOPLASM SKIN	0.6% (1/164)
OESOPHAGEAL CARCINOMA	0.6% (1/164)
PROSTATE CANCER RECURRENT	0.6% (1/164)
NERVOUS SYSTEM DISORDERS[a]	**2.4% (4/164)**
CAROTID ARTERY STENOSIS	0.6% (1/164)
CEREBROVASCULAR ACCIDENT	0.6% (1/164)
FACIAL PALSY	0.6% (1/164)
PARAESTHESIA	0.6% (1/164)
RENAL AND URINARY DISORDERS[a]	**1.2% (2/164)**
BLADDER TAMPONADE	0.6% (1/164)
NEPHROLITHIASIS	0.6% (1/164)
RENAL COLIC	0.6% (1/164)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS[a]	**0.6% (1/164)**
UTERINE POLYP	0.6% (1/164)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS[a]	**1.2% (2/164)**
DYSPNOEA	1.2% (2/164)
SURGICAL AND MEDICAL PROCEDURES[a]	**0.6% (1/164)**
LEG AMPUTATION	0.6% (1/164)
VASCULAR DISORDERS[a]	**25.0% (41/164)**
ARTERIAL OCCLUSIVE DISEASE	0.6% (1/164)
ARTERIAL STENOSIS LIMB	0.6% (1/164)
ARTERIAL THROMBOSIS	0.6% (1/164)
ARTERIAL THROMBOSIS LIMB	3.0% (5/164)
ARTERIOSCLEROSIS OBLITERANS	0.6% (1/164)
EMBOLISM	0.6% (1/164)
FEMORAL ARTERIAL STENOSIS	6.7% (11/164)
FEMORAL ARTERY OCCLUSION	4.3% (7/164)
HAEMORRHAGE	0.6% (1/164)
HYPERTENSION	0.6% (1/164)
HYPERTENSIVE CRISIS	0.6% (1/164)
INTERMITTENT CLAUDICATION	3.7% (6/164)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	4.3% (7/164)
PERIPHERAL EMBOLISM	0.6% (1/164)
PERIPHERAL ISCHAEMIA	3.0% (5/164)
VESSEL PERFORATION	0.6% (1/164)

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Serious Adverse Event	DCB ISR Cohort (N=164 Subjects)
Total Serious Adverse Events	**123**

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

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

Site reported data.

12. How Supplied

STERILE: The IN.PACT Admiral DCB is sterilized by ethylene oxide (EtO) and is nonpyrogenic. It is intended for single use only. Do not resterilize. Do not use if package is opened or damaged.

CONTENTS: The package contains 1 IN.PACT Admiral DCB.

STORAGE: Store the device in the original container. Store between 15°C and 30°C (59°F and 86°F). Use product by the Use-by Date noted on the package. Do not store near radiation or ultraviolet light sources.

DISPOSAL INSTRUCTIONS: After use, this product may be a biohazard. Handle and dispose of all such devices in accordance with accepted medical practice and applicable hospital, administrative, and government regulations.

DEVICE RETURN INSTRUCTIONS: In the case of a product failure or malfunction related to the product, contact a Medtronic Vascular representative for return or replacement. Any ancillary devices involved in the incident should also be returned to Medtronic, if possible.

13. Instructions for Use

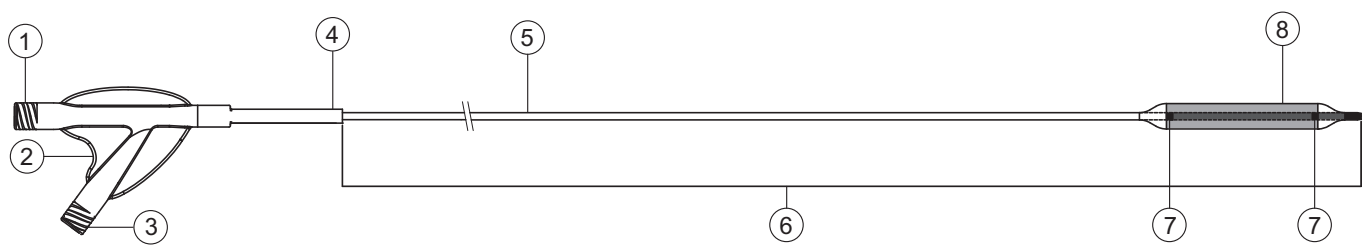

Figure 10. Schematic of the IN.PACT Admiral Paclitaxel-coated PTA Balloon Catheter

1. Guidewire Port
2. Hub
3. Inflation Port
4. Strain Relief
5. Shaft
6. Usable Catheter Length
7. Radiopaque Marker
8. Balloon

13.1. Equipment

- 0.035 in Guidewire
- Introducer sheath
- Vessel preparation device
- Contrast medium
- Sterile saline
- Inflation device with manometer
- Luer lock syringe for purging

13.2. Balloon Catheter Size Selection

- The nominal balloon diameter must match the diameter of the vessel distal to the lesion. The balloon length must exceed the lesion length by about 1 cm on the proximal and distal ends.
- If the lesion is longer than the longest available IN.PACT Admiral DCB, use multiple IN.PACT Admiral DCBs to treat the lesion, using the recommended overlap, as described in Using Multiple IN.PACT Admiral DCBs (Section 13.9), Recommended Overlap When Using Multiple IN.PACT Admiral DCBs (Figure 12), and Treatment of a Tandem Lesion with Multiple IN.PACT Admiral DCBs (Figure 14).

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13.3. Recommendations for Optimal PTA

- Appropriate vessel preparation is required prior to the use of the IN.PACT Admiral DCB.

  Note: Vessel preparation using only pre-dilatation was studied in the clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with IN.PACT Admiral DCB.
- When using a PTA balloon for vessel preparation, use a PTA balloon with a diameter 1 mm smaller than the reference vessel diameter to facilitate the passage of the appropriately sized IN.PACT Admiral DCB.

  Note: Following vessel preparation, if the lesion cannot be crossed with the first inserted IN.PACT Admiral DCB, the second attempt must be made with a new IN.PACT Admiral DCB in order to ensure effective drug delivery.
- As noted in Delivery and Dilatation Procedure (Section 13.7), for optimal mechanical dilatation of the vessel, an inflation time of 180 seconds is strongly recommended for the IN.PACT Admiral DCB. Adequate drug transfer occurs in the first 60 seconds of inflation.
- When using a device other than a PTA balloon for vessel preparation, use the device per its Instructions for Use.
- Post-dilatation should be completed according to the physician's discretion. If adequate PTA results are not obtained after the IN.PACT Admiral DCB(s) balloon inflation, post-dilatation using a non–drug-coated PTA balloon of shorter length than the previously used IN.PACT Admiral DCB is recommended.

  Note: In the randomized trial, provisional stenting with bare-metal stents was completed in cases where adequate results could not be obtained after using post-dilatation balloons, such as in the case of remaining residual stenosis [≥ 50%] or major [≥ Grade D] flow-limiting dissection after post-dilatation.
- It is important to provide drug delivery to the entire length of the treated artery prior to post-dilatation or provisional stenting.

13.4. PTA Preparation

1. Prepare the inflation device, introducer sheath, and guidewire according to the manufacturer's instructions. See Minimum Introducer Sheath Compatibility (Table 18) for help selecting the appropriately sized introducer sheath.

Table 18. Minimum Introducer Sheath Compatibility

Balloon Diameter	Max Crossing Profile	Introducer Sheath
4.0 mm (all lengths)	5.6 Fr (1.82 mm)	5 Fr
5.0 mm (all lengths)	6.0 Fr (2.00 mm)	6 Fr
6.0 mm (all lengths except 120 mm)	6.3 Fr (2.10 mm)	
6.0 mm (120 mm length)	6.3 Fr (2.10 mm) or 7.0 Fr (2.33 mm) (consult device label to verify)	6 Fr or 7 Fr (consult device label to verify)
7.0 mm (all lengths)	7.0 Fr (2.33 mm)	7 Fr

Note: Use of a long introducer sheath extending beyond the iliac bifurcation is recommended if a contralateral approach is used.

2. Administer the appropriate medication to the patient prior to treatment as described in Pre-procedure and Post-procedure Medication Regimen (Section 6.2).
3. Prepare the vascular access site according to standard practice.
4. Insert a guidewire through the hemostatic valve following the manufacturer's instructions or standard practice. Advance the guidewire carefully into the introducer sheath.
5. Attach a torque device to the wire, if desired. Under fluoroscopy, advance the guidewire to the desired vessel, then across the stenosis. Remove the torque device once the guidewire is positioned.

   Note: If treating an in-stent restenosis, ensure the guidewire has traversed the lesion intraluminally.

13.5. IN.PACT Admiral DCB Preparation

1. The catheter is packaged in a protective blister. Verify that the catheter and sterile packaging have not been damaged in shipment. After all preparation has been completed, carefully remove the catheter from the package. Do not remove the IN.PACT Admiral DCB from the packaging until it is ready for insertion.

   Note: Avoid exposing the balloon drug coating to excessive handling or contact with liquids prior to preparation and delivery as the coating may be susceptible to damage or premature drug release.
2. The folded balloon catheter may contain air that should be purged prior to use. Connect a stopcock to the balloon port of the catheter hub. Connect a luer-lock syringe partially filled with saline solution to the stopcock. Open the stopcock. Keeping the syringe in a downward vertical position, draw back the plunger of the syringe and create a vacuum for 30 seconds in the balloon inflation line until air is completely evacuated.

   Caution: If the air bubbles cannot be completely evacuated, there may be a leak in the catheter. Discard the device and select a new IN.PACT Admiral DCB.

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Note: It is important to maintain the vacuum seal in order to keep the balloon profile tight before insertion into the introducer sheath.

Note: Keep the protective sheath in place during the purging procedure.

3. After air is completely evacuated, close the stopcock and remove the syringe.
4. Remove the stylet and the protective sheath from the balloon and discard. Do not use the protective sheath as an introduction aid or rewrapping tool.
5. Connect the filled syringe to the guidewire port. Flush the guidewire lumen through the guidewire port with heparinized normal saline until the fluid exits the distal tip.

   Note: Drops of saline must emerge from the device tip.

   Note: To minimize the introduction of air, aspirate and flush the system and keep a tight catheter connection throughout the procedure.

13.6. Inflation Device Connection to the IN.PACT Admiral DCB

1. Fill the inflation device with 10 mL of saline-contrast mixture. Do not use air or any gaseous medium to inflate the balloon. Use only the recommended inflation medium (equal parts contrast medium and saline solution). Do not apply positive pressure to the balloon during preparation.
2. Evacuate all air present in the inflation device.

   Note: The inflation device should have no air bubbles present, either in the tube or in the cylinder; to remove any air lodged, keeping the tip upward, purge approximately 1cc of saline-contrast mixture.
3. With the stopcock connected to the balloon port in the closed position, securely couple the inflation device to the stopcock. Verify that no air is evident in both the stopcock and the inflation device's connection.

13.7. Delivery and Dilatation Procedure

1. Load the distal tip of the balloon catheter over the prepositioned guidewire, which has been placed through the lesion.
2. Advance the catheter under direct fluoroscopic visualization. To avoid kinking, advance the catheter through the hemostatic valve slowly and in small increments while the stopcock is closed. Open the hemostatic valve to allow for easy passage of the balloon and to prevent damage to the balloon coating. Once the balloon has passed through, the hemostatic valve should be closed as much as is needed to prevent blood return while still permitting easy movements of the catheter.

   Note: If significant resistance is encountered, do not advance the catheter through the introducer sheath.
3. Under fluoroscopy, use the balloon radiopaque markers to position the balloon within the lesion to be dilated. If the inflation device has not already been connected, connect the inflation device according to instructions in Inflation Device Connection to the IN.PACT Admiral DCB (Section 13.6).
4. Open the stopcock and inflate the balloon to the appropriate pressure as described in the Compliance Chart included in the device packaging, then close the stopcock to maintain pressure. For optimal mechanical dilatation of the vessel, balloon inflation time of 180 seconds is strongly recommended. Adequate drug transfer occurs in the first 60 seconds of inflation. If the IN.PACT Admiral DCB was inflated for at least 60 seconds but the vessel requires additional dilatation due to suboptimal PTA results, a plain PTA balloon of the operator's choice can be used (PTA balloon should be of shorter length compared to the IN.PACT Admiral DCB).

   Warning: Do not exceed rated burst pressure as indicated on the device label. Use of pressures higher than those specified on the device label may result in a ruptured balloon with possible intimal damage and dissection.

   Note: The IN.PACT Admiral DCB is intended for single inflation only.

13.8. Removal Procedure

1. Open the stopcock and deflate the balloon by applying negative pressure to the inflation device. Allow approximately 60 seconds for full balloon deflation. Larger balloons may require more time for deflation. Deflation of the balloon should be confirmed by absence of contrast medium within the balloon.

   Note: The balloon must be completely deflated before removal.
2. Upon confirmation of full deflation, disconnect the inflation device, then open the hemostatic valve and withdraw the deflated balloon catheter from the introducer sheath, through the hemostatic valve. Tighten the knurled knob on the hemostatic valve.
3. If necessary, the balloon catheter can be exchanged for different balloon types or sizes using the guidewire/ introducer that remains in the vessel.

   Note: If further dilatation is required, post-dilatation should be performed with a non–drug-coated PTA balloon of shorter length than the IN.PACT Admiral DCB.
4. When complete, withdraw the guidewire/introducer, and close the hemostatic valve.

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Note: After use, this device may be a biohazard. Handle and dispose of all such devices in accordance with accepted medical practice and applicable hospital, administrative, and government regulations.

13.9. Using Multiple IN.PACT Admiral DCBs

Warning: The safety and effectiveness of using multiple IN.PACT Admiral DCBs with a total drug dosage exceeding 20,691 µg paclitaxel in a patient has not been clinically evaluated in the IN.PACT SFA Trial.

Additional IN.PACT Admiral DCBs should be used to treat a lesion only under either of the following circumstances:

- The first IN.PACT Admiral DCB bursts prior to 60 seconds of inflation time.
- The lesion length requires more than 1 IN.PACT Admiral DCB to fully cover the lesion and extend about 1 cm at both the proximal and distal edges.

If multiple IN.PACT Admiral DCBs are required due to a lesion length greater than the longest available DCB, the balloons must overlap by at least 1 cm. The size of additional DCBs should not be longer than required to allow for this overlap and complete the lesion coverage with about 1 cm extended beyond the lesion both proximally and distally. Proper size selection is important to avoid excessive overlap. Refer to Figure 11 through Figure 14 for further guidance.

Note: In order to reduce procedure-related complications, use only the minimum number of devices needed to cover the lesion(s).

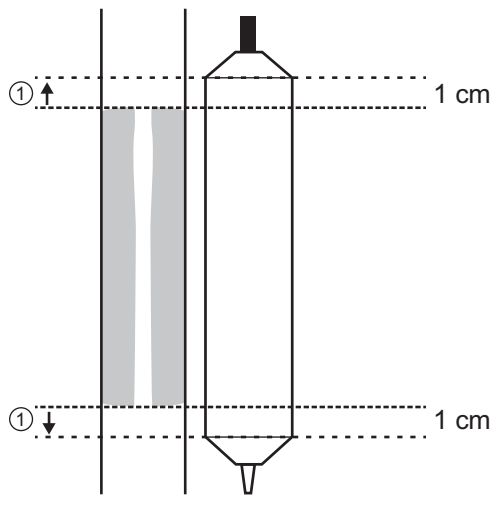

Figure 11. Treatment of a Single Lesion

1. approximately 1 cm

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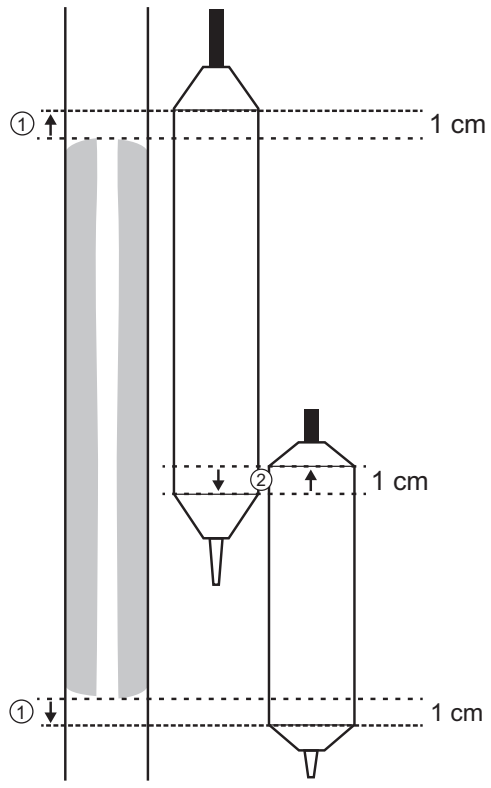

Figure 12. Recommended Overlap When Using Multiple IN.PACT Admiral DCBs

1. approximately 1 cm
2. at least 1 cm balloon overlap

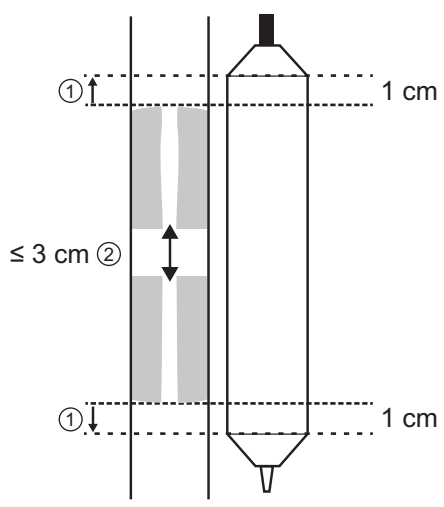

Figure 13. Treatment of a Tandem Lesion with a Single IN.PACT Admiral DCB

1. approximately 1 cm
2. lesion gap ≤ 3 cm

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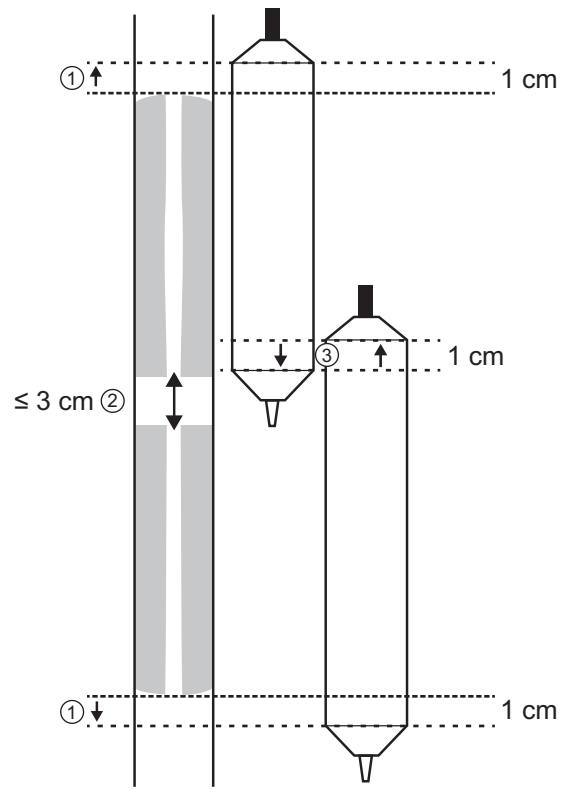

Figure 14. Treatment of a Tandem Lesion with Multiple IN.PACT Admiral DCBs

1. approximately 1 cm
2. lesion gap ≤ 3 cm
3. at least 1 cm balloon overlap

14. DISCLAIMER OF WARRANTY

ALTHOUGH THE IN.PACT ADMIRAL DRUG-COATED BALLOON CATHETER, HEREAFTER REFERRED TO AS “PRODUCT”, HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, MEDTRONIC, INC., AND AFFILIATES (COLLECTIVELY, “MEDTRONIC”) HAVE NO CONTROL OVER CONDITIONS UNDER WHICH THIS PRODUCT IS USED. THE WARNINGS CONTAINED IN THE PRODUCT LABELING PROVIDE MORE DETAILED INFORMATION AND ARE CONSIDERED AN INTEGRAL PART OF THIS DISCLAIMER OF WARRANTY. MEDTRONIC THEREFORE DISCLAIMS ALL WARRANTIES, BOTH EXPRESSED AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. MEDTRONIC SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL, OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE, OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT, OR OTHERWISE. NO PERSON HAS ANY AUTHORITY TO BIND MEDTRONIC TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.

The exclusions and limitations set out above are not intended to and should not be construed so as to contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable, or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected.

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