SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Coated Balloon (DCB) Percutaneous Transluminal Angioplasty Catheter
Device Trade Name:	SurVeil™ Drug Coated Balloon
Device Procode:	ONU
Applicant's Name and Address:	Surmodics, Inc. 9924 West 74th Street Eden Prairie, MN 55344 USA
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P210025
Date of FDA Notice of Approval:	6/16/2023

II. INDICATIONS FOR USE

The SurVeil™ DCB is indicated for use for percutaneous transluminal angioplasty, after appropriate vessel preparation, of *de novo* or restenotic lesions (≤ 180 mm in length) in femoral and popliteal arteries having reference vessel diameters of 4 mm to 7 mm.

III. CONTRAINDICATIONS

The SurVeil DCB is contraindicated for use in:

- Patients with known hypersensitivity to paclitaxel or structurally related compounds.
- 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.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children.
- Coronary, renal and supra-aortic/cerebrovascular arteries.

IV. WARNINGS AND PRECAUTIONS

A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial

disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients.

Adhere to the following use parameters for the index procedure:
- **Do not use more balloons than necessary. No more than 200 mm of total balloon length should be used, for a total maximum treatable length of 180 mm.**
- **This product should not be used bilaterally or in multiple lesions that cannot be treated with up to 200 mm total balloon length.**
- **The safety of exposure to higher doses of the paclitaxel/polyethyleneimine (PEI) drug coating has not been established.**

Additional warnings and precautions can be found in the SurVeil™ Drug Coated Balloon Catheter labeling.

V. DEVICE DESCRIPTION

The SurVeil™ Drug Coated Balloon Catheter (SurVeil DCB) (Figure 1) is a sterile, single-use, over-the-wire (OTW) device/drug combination product comprised of two regulated components:

- Base percutaneous transluminal angioplasty (PTA) Balloon Catheter: PTA balloon catheter uses mechanical force of balloon expansion across a lesion to establish patency
- Balloon Drug Coating: A formulation of the active pharmaceutical ingredient paclitaxel with an excipient, to serve as an adjunct to the mechanical action of balloon angioplasty by reducing restenosis and repeat revascularization rates at the treatment site

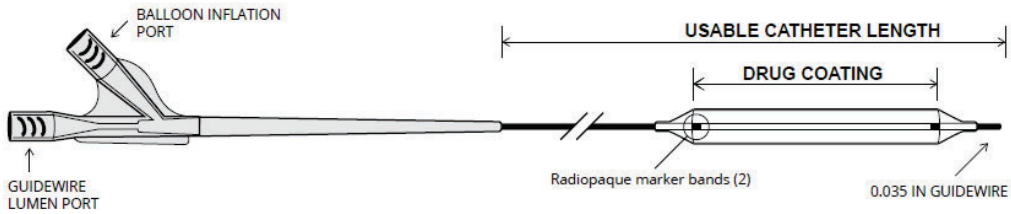


Figure 1: SurVeil™ DCB Catheter

The SurVeil DCB is available in multiple balloon sizes as listed in Table 1.

Table 1: SurVeil™ DCB Product Matrix

Balloon diameter (mm)	Balloon length (mm)					
	40	60	80	100	120	150
4	X	X	X	X	X	X

5	X	X	X	X	X	X
6	X	X	X	X	X	X
7	X	X	X	X	--	--

Device Component

The SurVeil DCB uses a standard 0.035" over-the-wire (OTW) PTA catheter, with a 135 cm usable catheter length and a semi-compliant balloon at the distal tip. A portion of the distal catheter shaft is coated with Surmodics™ PhotoLink™ lubricious coating. The SurVeil DCB is compatible with 5-7 Fr sheaths (depending on balloon size). The nominal inflation pressure is 6 atm and the rated burst pressure is 10-14 atm (depending on balloon size).

Drug Component

The drug coating of the SurVeil DCB comprises the active pharmaceutical ingredient paclitaxel and a polyethyleneimine polymer excipient. The drug coating is uniformly distributed across the balloon surface at a nominal paclitaxel dose density of 2.0 µg/mm². The key functional characteristic of the excipient in the drug coating is to facilitate efficient transfer of paclitaxel to the arterial wall.

Based on the nominal drug dose density of 2.0 µg/mm², the total amount of paclitaxel for each balloon size is provided in Table 2.

Table 2: Nominal Paclitaxel Dose per Balloon size

Balloon diameter (mm)	**Balloon length (mm)**					
	40	**60**	**80**	**100**	**120**	**150**
4.0	1005 µg	1508 µg	2011 µg	2513 µg	3016 µg	3770 µg
5.0	1257 µg	1885 µg	2513 µg	3142 µg	3770 µg	4712 µg
6.0	1508 µg	2262 µg	3016 µg	3770 µg	4524 µg	5655 µg
7.0	1759 µg	2639 µg	3519 µg	4398 µg	--	--

Active Pharmaceutical Ingredient (API) – Paclitaxel

The API of the SurVeil 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 and the chemical formula is $C_{47}H_{51}NO_{14}$. The chemical structure of paclitaxel is illustrated in Figure 2.

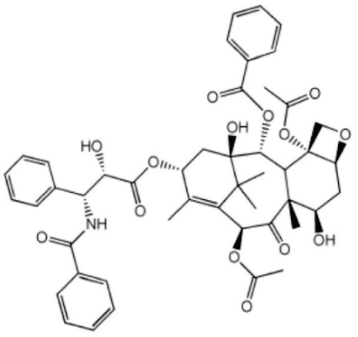


Figure 2: Paclitaxel Chemical Structure

Excipient – Polyethyleneimine

The polycationic polymer polyethyleneimine is used as an excipient to facilitate delivery and efficient transfer of the active pharmaceutical ingredient (paclitaxel) from the balloon to the vessel wall upon balloon expansion. The CAS Registry number of polyethyleneimine is 9002-98-6 and the chemical formula is $(C_2H_5N)_n$. The number average molecular weight is labeled as 70 kDa. The chemical structure of PEI is shown in Figure 3.

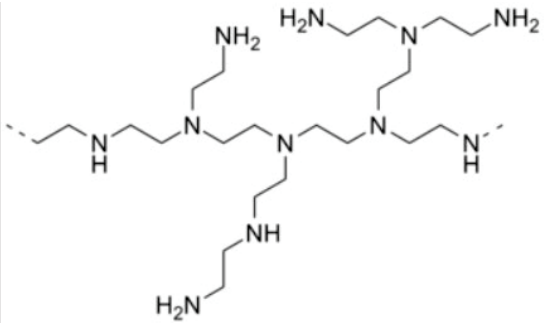


Figure 3: Representative structure of branched PEI

Mechanism of Action

The primary mode of action for SurVeil DCB is mechanical dilatation of de novo or restenotic lesions by means of percutaneous transluminal angioplasty, with a secondary action of reducing neointimal proliferation from vessel injury due to PTA, and thereby reducing the rate of restenosis, through the application of paclitaxel to the vessel wall.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

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

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

VII. MARKETING HISTORY

The SurVeil DCB has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Acute re-occlusion necessitating surgical intervention
- Allergic reaction to contrast solution, anti-platelet therapy, or catheter system components
- Amputation
- Aneurysm
- Arrhythmias
- Arterio-venous fistula
- Bleeding
- Death
- Endocarditis
- Femoral nerve compression with associated neuropathy
- Groin area bruising and discomfort
- Ischemia or infarction of tissue/organ
- Renal insufficiency or failure
- Local hematoma
- Local hemorrhage
- Local infections
- Local or distal thromboembolic episodes
- Low blood pressure
- Pain and tenderness
- Pseudoaneurysm
- Pyrogenic reaction
- Respiratory failure
- Restenosis of the dilated artery
- Sepsis/infection
- Short-term hemodynamic deterioration
- Stroke
- Systemic embolization
- Total occlusion or thrombosis
- Vessel damage, dissection, perforation, rupture, or spasm

Potential adverse events that may be unique to the paclitaxel drug coating may include, but are not limited to:

- Allergic/immunologic reaction
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/arthralgia
- Myelosuppression
- Peripheral neuropathy

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

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies were performed on the SurVeil DCB. These studies included biocompatibility, preclinical animal studies, in vitro bench testing, packaging, shelf life, and sterilization. A summary for each is provided below.

A. Biocompatibility

Biocompatibility testing was completed on the SurVeil DCB in accordance with ISO 10993-1. Biocompatibility testing was conducted separately on 1) the balloon with drug coating, 2) the balloon with excipient only, 3) the balloon catheter with excipient only, and 4) balloon catheter with no drug coating. Thrombogenicity was evaluated in the large animal safety study of the entire drug coated balloon catheter. In addition, chemical characterization and toxicological risk assessment was conducted to support various biocompatibility endpoints for the SurVeil DCB.

The balloon with the drug coating was categorized as an implant device with permanent blood contact (> 30 days), and the base balloon catheter was categorized as an externally communicating device with limited contact duration (≤ 24 hours) with circulating blood. A summary of the biocompatibility testing and results can be found in **Table 3**.

Table 3: Summary of Biocompatibility Testing

Test Name	Test Description	Balloon with drug coating	Balloon with excipient, no drug	Balloon catheter with excipient, no drug	Balloon catheter, no excipient, no drug	Results
Cytotoxicity	Minimum Essential Medium (MEM) Extraction Cytotoxicity Assay Using L-929 Cells	X	--	X	X	Non-toxic response for catheter body; acceptable response for the coated balloon and balloon catheter with excipient only after extract dilutions*
Sensitization	ISO Guinea Pig Maximization	X	--	X	X	Non-sensitizing
Irritation	ISO Intracutaneous Reactivity	X	--	X	X	Non-irritating for catheter body with excipient only and without excipient/ drug; extract dilution of coated balloon non-irritating.
Acute Systemic Toxicity	ISO Systemic Toxicity	X	--	X	X	Non-toxic response for catheter body; acceptable response for coated balloon through determination of no observed adverse effect level (NOAEL) and tolerable intake
Pyrogenicity	Material Mediated Pyrogenicity	X	--	X	X	Non-pyrogenic response for catheter body; Acceptable response for the coated balloon and balloon catheter with excipient only after extract dilutions **
Hemocompatibility	American Society of Testing and Materials (ASTM) Hemolysis	X	X	X	X	Non-hemolytic for catheter body without drug/excipient coating (direct and indirect); non-hemolytic for the coated balloon (indirect) and acceptable hemolytic response for excipient and drug coated balloon (direct)***.

	Clinically-relevant *in vitro* hemolysis (direct contact)	X	--	--	--	Non-hemolytic ***
	Complement Activation Assay (SC5b-9)	X	--	X	X	Not a complement activator
	Partial Thromboplastin Time (PTT)	X	--	X	X	Non-activator of intrinsic coagulation pathway
	Platelet and leukocyte count	X	--	--	X	Acceptable response for coated balloon****
	In vivo thrombogenicity	Finished device (catheter and coated balloon)				The test article showed similar thrombogenic potential in comparison to a currently marketed device.
Genotoxicity	Ames Bacterial Reverse Mutation Assay	X	--	X	--	Non-mutagenic and non-clastogenic
	Mouse Lymphoma Assay	--	X	X	--	
	In Vivo Mouse Micronucleus Assay	--	--	X	--	
Chemical Characterization	Gas Chromatography – Mass Spectroscopy (GC/MS) for volatile and semi-volatile, organic compounds	X	X	--	X*****	Compounds consistent with manufacturing materials and amounts do not raise toxicity concerns for the endpoints of carcinogenicity, genotoxicity, and sub-chronic/chronic systemic toxicity
	Inductively Coupled Plasma (ICP) Spectroscopy for metallic compounds	X	X	--	X*****	Compounds consistent with manufacturing materials and amounts do not raise toxicity concerns for the endpoints of carcinogenicity, genotoxicity, and sub-chronic/chronic systemic toxicity
	Liquid Chromatography – Mass Spectroscopy (LC/MS) for semi-volatile and non-volatile organic compounds	X	X	--	X*****	Compounds consistent with manufacturing materials and amounts do not raise toxicity concerns for the endpoints of carcinogenicity, genotoxicity, and sub-chronic/chronic systemic toxicity

**Although a cytotoxic response was noted for the neat extract of the balloon, the results are considered acceptable following extract dilutions and based on acceptable implantation response from in vivo safety study*
***Animal deaths were noted for neat extracts. Acceptable results were observed using more clinically relevant dosages*
****Direct contact hemolysis testing demonstrated elevated hemolytic indices for the coated balloon. This may be due to background interference of the drug coated balloon. Clinically relevant hemolysis testing was conducted and the results were comparable to negative control. Thus, the hemolysis testing was considered acceptable*
*****Although the platelet counts showed significant change, the results were considered acceptable based on more clinically relevant hemocompatibility testing and in vivo testing*
******Balloon-only portion extracted*

The endpoints of implantation, subchronic toxicity, and chronic toxicity were evaluated as part of other *in vivo* studies conducted to evaluate the safety of the SurVeil DCB in a porcine iliofemoral model, as described in the summary of Animals Studies in Section IX.H below. These studies demonstrated acceptable local tissue response and no indication of toxicity when the device was used in a clinically relevant vascular location.

Chemical characterization and toxicological risk assessments were also conducted to support sub-acute (sub-chronic) toxicity, chronic toxicity, genotoxicity, and carcinogenicity endpoints.

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

B. In Vitro Bench Testing

Table 4 provides an overview of the functional engineering testing performed with the SurVeil DCB. The table includes the tests performed, the objective of the tests, the acceptance criteria, and the result of the test.

Table 4: Summary of Bench Testing Performed

Test	Test Description and/or Objective	Acceptance Criteria	Pass/Fail
Delivery system dimensions (balloon diameter and length)	Confirm balloon meets labeled dimensions	Diameter: ± 5% of nominal Length: ± 5% of nominal	Pass
Delivery system dimensions (inner marker band distance, tip length, shaft OD, usable catheter length, proximal bond OD)	Confirm dimensions and to confirm compatibility with accessory devices	Tip length: 5.0 ± 0.5 mm Shaft OD: 1.70 +0.06/-0.03 mm Usable catheter length: 1350 ± 20 mm	Pass
		Marker band distance: **Balloon** | **Distance**	Pass

<table>
<tr><th>Test</th><th>Test Description and/or Objective</th><th>Acceptance Criteria</th><th>Pass/Fail</th></tr>
<tr><td></td><td></td><td><table><tr><th>Length</th><th></th></tr><tr><td>40 mm</td><td>36 +0 / -2 mm</td></tr><tr><td>60 mm</td><td>55 +1 / -3 mm</td></tr><tr><td>80 mm</td><td>75 +1 / -3 mm</td></tr><tr><td>100 mm</td><td>94 +1 / -3 mm</td></tr><tr><td>120 mm</td><td>113 +1 / -3 mm</td></tr><tr><td>150 mm</td><td>141 +1 / -3 mm</td></tr></table></td><td></td></tr>
<tr><td></td><td></td><td>Proximal bond OD:
4 mm diameter: ≤ 1.90 mm (5.7 Fr)
5 mm diameter: ≤ 2.00 mm (6 Fr)
6 mm diameter: ≤ 2.08 mm (6.24 Fr)
7 mm diameter: ≤ 2.15 mm (6.45 Fr)</td><td>Pass</td></tr>
<tr><td>Trackability</td><td>Catheter is tracked through a simulated use track model over guidewire</td><td>Able to track through model on 0.035” guidewire</td><td>Pass</td></tr>
<tr><td>Burst pressure
(balloon, catheter shaft)</td><td>Balloon catheter is steadily inflated until burst and balloon rated burst pressure is calculated</td><td>Balloon burst pressure ≥ RBP
RBP for 4-5 mm diameter: 14 atm/bar
RBP for 6 mm diameter: 12 atm/bar
RBP for 7 mm diameter: 10 atm/bar
Shaft burst pressure ≥ 24 bar</td><td>Pass</td></tr>
<tr><td>Balloon Fatigue (Repeat Balloon Inflations)</td><td>Balloon is inflated to RBP and deflated a minimum of 20 times</td><td>Balloons withstand 20x inflations up to RBP with no failure</td><td>Pass</td></tr>
<tr><td>Balloon compliance</td><td>Balloon is incrementally inflated and diameter measured to determine compliance curve</td><td>Diameter within 5%</td><td>Pass</td></tr>
<tr><td>Catheter Bond Tensile Strength:
a) Stem-to-balloon
b) Balloon-to-shaft
c) Shaft-to-stem
d) Hub-to-shaft</td><td>Confirm the tensile strength of the catheter</td><td>a) ≥ 10 N
b) ≥ 20 N
c) ≥ 10 N
d) ≥ 20 N</td><td>Pass</td></tr>
<tr><td>Balloon crossing profile</td><td>Determine the maximum diameter between the proximal end of the balloon and the distal tip of the catheter</td><td>4 mm diameter: ≤ 1.80 mm (5.4 Fr)
5 mm diameter: ≤ 2.08 mm (6.24 Fr)
6-7 mm diameter: ≤ 2.15 mm (6.45 Fr)</td><td>Pass</td></tr>
<tr><td>Balloon deflation time</td><td>Time to deflate the balloon from RBP using contrast media</td><td>≤ 87 seconds</td><td>Pass</td></tr>
<tr><td>Sheath passage, Insertion, and Retraction</td><td>Measure the axial force required to move the device through the recommended introducer sheath in the IFU pre-inflation (insertion) and post-inflation (retraction)</td><td>Insertion: ≤ 3 N
Retraction: ≤ 20 N</td><td>Pass</td></tr>
<tr><td>Kink evaluation</td><td>Catheter is tracked through a fixture of decreasing radius until 0.5” radius is reached</td><td>Traverse 0.5” radius without kinking</td><td>Pass</td></tr>
</table>

Test	Test Description and/or Objective	Acceptance Criteria	Pass/Fail
Torque Strength	Demonstrate catheter is able to withstand torque forces without damage	Minimum of 10 rotations without failure	Pass
Hub Durability	Demonstrate ability to meet performance standard	ISO 80369-7	Pass
Radiopacity	Confirm the marker bands are acceptably visible under fluoroscopic imaging	Visible under fluoroscopy	Pass

C. Coating Characterization

Testing was conducted to characterize the drug coating on the SurVeil DCB following ASTM F3320-18. See summary in **Table 5** below.

Table 5: Coating Characterization Summary

Test	Test Description and/or Objective	Results
Coating Integrity and Appearance	Characterization of the drug coating morphology on the balloon surface using optical and SEM techniques	N/A (characterization only)
Drug Coating Thickness	Characterization of the drug coating thickness on the balloon surface	N/A (characterization only)
Drug Coating Uniformity – Circumferential	Measure the relative uniformity of the drug content around the balloon circumference with a specification of ±15% of nominal	Pass
Drug Coating Uniformity – Longitudinal	Measure the relative uniformity of the drug content along the balloon length with a specification of ±15% of nominal	Pass
Particulates (Simulated use)	Particulate sizes and counts measured	Pass
Particulate Identification	Chemical identification of the particulate generated	N/A (characterization only)
Crystallinity Characterization	Characterize degree of crystallinity of the coating	N/A (characterization only)

D. Chemistry, Manufacturing and Controls (CMC) Testing

Analytical testing was conducted to determine the identity, safety, purity, and quality of the SurVeil DCB, including coating containing drug substance (paclitaxel) and excipient (PEI). See summary in **Table 6** below.

Table 6: Summary of Analytical Testing

Test	Description	Acceptance Criteria
Finished Goods Appearance	Visual inspection was conducted to verify the SurVeil DCB drug coating meets the appearance criteria	Must meet visual standards
Paclitaxel Content (Assay)	Quantitative assay to determine the total amount of paclitaxel on the SurVeil DCB	Drug content must be within 90-110% of nominal values for each balloon size
Paclitaxel Content Uniformity	Verification of the content uniformity of the paclitaxel coating from balloon to balloon	Units shall meet uniformity of dosage requirements in USP <905>
Paclitaxel Impurities	Quantitative determination of the type and amount of impurities and degradation products on the SurVeil DCB	ICH Q3B
Paclitaxel Identification	Test for identity and ensure conformity to specifications (matches reference spectrum)	Identity must be confirmed by two different tests
PEI Identity	Test for identity and ensure conformity to specifications	Identity confirmed by UV-vis
PEI Molecular Weight (MW)	Test PEI MW by gel permeation chromatography (GPC).	For information only
Dissolution	Dissolution tests are performed to verify the drug release profile of the SurVeil DCB	USP <711>
Particulates	Particulate sizes and counts are measured for the SurVeil DCB following simulated use	Particulate sizes and counts must be within specified limits
Residual Solvent	Quantitative assay to determine the amount of residual solvents on the SurVeil DCB	ICH Q3C
Endotoxin	Conduct LAL test to confirm lack of endotoxin.	≤20 EU/device
Sterility	Confirm product sterility	Pass dosimetric release per ISO 11137

E. Packaging

Packaging verification tests were performed on SurVeil DCB packaging subjected to the worst-case shipping simulation and then aged to ensure that the packaging would remain acceptable and maintain sterile barrier throughout the shelf life of the SurVeil DCB. Package integrity testing included a visual assessment, bubble leak testing, and seal strength testing. Testing was conducted on both packaging at the baseline condition and packaging aged to the product shelf life. Testing indicated that packaging will ensure product sterility throughout its shelf life.

F. Shelf Life

Finished product shelf life for the SurVeil DCB was established based on drug coating stability, functional/mechanical performance, and packaging testing. Appropriate mechanical tests were performed on aged product and compared to baseline to ensure that the SurVeil DCB performed acceptably. A stability study was conducted according to International Conference on Harmonization (ICH) guidelines on SurVeil DCB finished product to establish shelf life. The data generated from the stability and shelf life studies supports the 24-month labeled shelf life.

G. Sterilization

The SurVeil DCB is sterilized using E-beam sterilization. The sterilization process is validated per ISO 11137-1 *Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*, ISO 11137-2 *Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose*, and ANSI/AAMI/ISO TIR13004 *Sterilization of health care products — Radiation — Substantiation of a selected sterilization dose: Method* VD_{max}^{SD}. Results show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the amounts of bacterial endotoxin are verified on every lot to be within the specification limit.

H. Animal studies

Surmodics conducted four (4) studies compliant with 21 CRF 58 (Good Laboratory Practices) to evaluate the safety and biological effect of the SurVeil DCB (**Table 7**).

Table 7: Summary of GLP Preclinical Animal Studies Demonstrating Safety and Biological Effect of the SurVeil DCB

Study ID (Primary Focus)	Animal Count and Type	Study Arms (local exposure)	Balloon Sizes	Major Endpoints & Study Term	Endpoint Met
UTE018 (Local Safety)	n=38 (n=20 Domestic	DCB 1X DCB 3X Excipient-only	4x40 mm 5x40 mm 6x40 mm	Artery Histopathology: 28, 90, 180, 365 days	Yes

	Yorkshire; n=18 Yucatan	Uncoated *SurVeil DCB Only*			
UTE019 (Downstream and Systemic Safety)	n=25 (n=16 Domestic Yorkshire; n=9 Yucatan)	DCB 1X DCB 3X *SurVeil DCB Only*	5x80 mm	Downstream histopathology and PK: 28, 90, 180 days Plasma PK: 0, 5, 15, 60 minutes, 1 day, term Artery Histopathology (secondary): 28, 90, 180 days	Yes
UTE107 (Downstream and Systemic Safety)	n=7 (All Domestic Yorkshire)	DCB 4X *SurVeil DCB & IN.PACT Admiral DCB*	5x80 mm	Downstream histopathology and PK: 30 days Plasma PK: 0, 15, 60 minutes, 1 day, term	Yes
UTE020 (Pharmacokinetics)	n=25 (n=20 Domestic Yorkshire; n=5 Yucatan)	DCB 1X *SurVeil DCB Only*	4x40 mm 5x40 mm 6x40 mm	PK of local artery, downstream muscles, & non-target organs: 1, 6, 12, 24 hours, 3, 7, 14, 21, 28, 90, 180, 365 days Plasma PK: 0, 5, 15, 60 minutes, 1 day, term	Yes

Collectively, the results of these preclinical studies confirm the safety and biological effect of the SurVeil DCB as demonstrated by the following:

- Successful deployment of the SurVeil DCB with no sign of device-related adverse effects.
- Animals were generally healthy through the duration of their terms following treatment.
- Local analyses showed the desired biological effects of paclitaxel with substantial resolution within one year and no evidence of unacceptable vessel toxicity or aneurysmal dilatation at up to 3X dosing.
- Downstream embolic evaluations with up to 4X local treatment demonstrated acceptable outcomes.

- Evidence of the expected pharmacokinetic profile with clearance from all tissues within one year.
  - Paclitaxel plasma concentrations peaked immediately after treatment and were below limits of quantification beyond 24 hours in all studies.
  - The treated artery showed the highest tissue paclitaxel concentration, which peaked at 1-hour and was undetectable at 365 days with an estimated half-life of 19 days.
  - Downstream muscle and non-target organ concentrations peaked within 72 hours and paclitaxel was not detected in any tissue beyond 180 days. The half-life values ranged from 8.0 to 73 days.
  - The observed concentrations of paclitaxel in non-target organs was not associated with adverse effects.

X. SUMMARY OF PRIMARY CLINICAL STUDY

TRANSCEND TRIAL

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous transluminal angioplasty with the SurVeil™ Drug-Coated Balloon, after appropriate vessel preparation, for treatment of *de novo* or restenotic lesions in femoral and popliteal arteries having reference vessel diameters (RVD) of 4 mm to 7 mm at US and OUS sites under IDE # G150121. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between October 20, 2017 and August 17, 2019. The database for this PMA reflected data collected through November 13, 2020 and included 446 patients. There were 65 investigational sites, located in the United States, Australia, New Zealand, and Europe.

The TRANSCEND Study is a global, prospective, multi-center, single-blind, randomized, controlled trial (RCT) to evaluate the noninferiority of the SurVeil DCB compared to the Medtronic IN.PACT Admiral DCB. Subjects with a stenosed femoral and/or popliteal artery were randomized in a 1:1 ratio to either the SurVeil or the IN.PACT Admiral DCB.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the TRANSCEND study was limited to patients who met the following inclusion criteria:

- Subject was ≥18 years of age.
- Subject had target limb Rutherford classification 2, 3, or 4.

- Subject provided written informed consent and was willing to comply with the study follow-up requirements.
- De novo lesion(s) or non-stented restenotic lesion(s) occurring >90 days after prior POBA or >180 days after prior DCB treatment.
- Target lesion started ≥10 mm below the common femoral bifurcation and terminated distally at or above the end of the P1 segment of the popliteal artery.
- Target vessel diameter ≥4 mm and ≤7 mm.
- Target lesion with angiographic evidence of ≥70% stenosis by operator visual estimate.
- Chronic total occlusions were allowed only after successful, uncomplicated wire crossing of the target lesion via an anterograde approach. Successful crossing of the target lesion occurred when the tip of the guide wire was distal to the target lesion without the occurrence of flow-limiting dissection or perforation and was judged by visual inspection to be within the true lumen. Subintimal dissection techniques were allowed if re-entry occurred above the knee and without the use of re-entry devices.
- Target lesion was ≤180 mm in length (one long lesion or multiple serial lesions) by operator visual estimate.
- Target lesion was located at least 30 mm from any stent if target vessel was previously stented.
- Successful, uncomplicated (without use of a crossing device) wire crossing of target lesion. Successful crossing of the target lesion occurred when the tip of the guide wire was distal to the target lesion without the occurrence of flow-limiting dissection or perforation and was judged by visual inspection to be within the true lumen.
- After pre-dilatation, the target lesion had ≤70% residual stenosis, absence of a flow limiting dissection and treatable with available device matrix.
- A patent inflow artery free from significant stenosis (≥50% stenosis) as confirmed by angiography.
- At least one patent native outflow artery to the ankle or foot, free from significant stenosis (≥50% stenosis) as confirmed by angiography.

Patients were <u>not</u> permitted to enroll in the TRANSCEND study if they met any of the following exclusion criteria:

- Subject had acute limb ischemia.
- Subject underwent intervention involving the target vessel within 90 days of enrollment.
- Subject underwent any lower extremity percutaneous treatment in the ipsilateral limb using a paclitaxel-eluting stent or a DCB within 90 days of enrollment.
- Subject underwent PTA of the target lesion using a DCB within 180 days of enrollment.
- Subject had prior vascular intervention in the contralateral limb within 14 days before the planned index procedure or subject had planned vascular intervention in the contralateral limb within 30 days after the index

procedure.

- Women who were pregnant, breast-feeding or intended to become pregnant or men who intended to father children during the time of the study.
- Subject had life expectancy of less than 2 years.
- Subject had a known allergy to contrast medium that could not be adequately premedicated.
- Subject was allergic to ALL antiplatelet treatments.
- Subject had impaired renal function (i.e., serum creatinine level ≥2.5 mg/dL).
- Subject was dialysis dependent.
- Subject was receiving immunosuppressant therapy.
- Subject had known or suspected active infection at the time of the index procedure.
- Subject had platelet count <100,000/mm^3 or >700,000/mm^3.
- Subject had history of gastrointestinal hemorrhage requiring a transfusion within 90 days prior to the index procedure.
- Subject was diagnosed with coagulopathy that precluded treatment with systemic anticoagulation and/or DAPT.
- Subject had history of stroke within 90 days of enrollment.
- Subject had history of MI within 30 days of enrollment.
- Subject was unable to tolerate blood transfusions because of religious beliefs or other reasons.
- Subject was incarcerated, mentally incompetent, or abusing drugs or alcohol.
- Subject was participating in another investigational drug or medical device study that had not completed primary endpoint(s) evaluation or that clinically interfered with the endpoints from this study, or subject was planning to participate in such studies prior to the completion of this study.
- Subject had any major (e.g., cardiac, peripheral, abdominal) surgical procedure or intervention unrelated to this study within 30 days prior to the index procedure or had planned major surgical procedure or intervention within 30 days after the index procedure.
- Subject had previous bypass surgery of the target lesion.
- Subject had previous treatment of the target vessel with thrombolysis or surgery.
- Subject was unwilling or unable to comply with procedures specified in the protocol or had difficulty or inability to return for follow-up visits as specified by the protocol.
- Target lesion had severe calcification (as defined by the Peripheral Academic Research Consortium [PARC] classification of calcification).
- Target lesion involved an aneurysm or was adjacent to an aneurysm (within 5 mm).
- Target lesion required treatment with alternative therapy such as stenting, laser, atherectomy, cryoplasty, brachytherapy, or re-entry devices.
- Significant target vessel tortuosity or other parameters prohibiting access to the target lesion.

- Presence of thrombus in the target vessel.
- Iliac inflow disease requiring treatment unless the iliac artery disease was successfully treated first during the index procedure. Success was defined as ≤30% residual diameter stenosis without death or major complications.
- Presence of an aortic, iliac or femoral artificial graft.

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at 1 month, 6 months, 12 months, 2 years, 3 years, 4 years and 5 years postoperatively.

Preoperatively, screening and baseline procedures and assessments were completed within 14 days of the index procedure. Table 8 below presents the study procedures and assessments performed at the respective time intervals in the study.

Table 8: Schedule of Treatments and Assessments

Study Requirement (Visit Window)	**Screening/ Baseline** (Within 14 Days Prior to Procedure)	**Index Procedure to Discharge** (Day 1)	**1 Month** (30 -2 to +15 Days)	**6 Months** 180 ±30 Days)	**12 Months** (365 ±30 Days)	**24 Months** (730 ±60 Days)	**36 Months**[1] (1095 ±60 Days)	**48 Months**[1] (1460 ±60 Days)	**60 Months**[1] (1825 ±60 Days)	**Unscheduled Visit(s)**[6]
Contact Type	Office Visit		Office Visit	Office Visit	Office or Telephone Visit	Office or Telephone Visit	Telephone or Office Visit	Telephone or Office Visit	Telephone or Office Visit	Office Visit
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Physical Exam[2]	X		X	X	X	X				X
Medications	X	X	X	X	X X[10]	[10]	X	X	X	X
Target Limb Resting ABI (TBI if ABI can't be assessed)	X[3]			X	X	X				X
Rutherford Classification	X		X	X	XX[10, 12]	[10, 12]				X
PARC Classification	X		X	X	X X[10]	[10]				X
Pregnancy Test[4]	X									
CBC	X		X							
Comprehensive Metabolic Panel[5]	X		X							
PAQ	X		X		X X[10]	[10]				X
WIQ	X		X		X X[10]	[10]				X
6-MWT	X				X	X				X
Angiogram		X								X[7]
Randomization		X								

Study Requirement (Visit Window)	**Screening/ Baseline** (Within 14 Days Prior to Procedure)	**Index Procedure to Discharge** (Day 1)	**1 Month** (30 -2 to +15 Days)	**6 Months** 180 ±30 Days)	**12 Months** (365 ±30 Days)	**24 Months** (730 ±60 Days)	**36 Months**[1] (1095 ±60 Days)	**48 Months**[1] (1460 ±60 Days)	**60 Months**[1] (1825 ±60 Days)	**Unscheduled Visit(s)**[6]
DUS			X[8]	X	X[9]	[9]				X
AE/SAE Collection[11]	X	X	X	X	X[10]	[10]	X	X	X	X

Abbreviations: 6-MWT, 6-minute walk test; ABI, ankle brachial index; AE, adverse event; CBC, complete blood count; DUS, duplex ultrasound; PAQ: peripheral artery questionnaire; PARC, Peripheral Academic Research Consortium; SAE, serious adverse event; TBI, toe brachial index; WIQ, walking impairment questionnaire.

[1] The 36-, 48-, and 60-month visits may be conducted via a telephone call or at the clinic.

[2] Physical exam (PE) included weight, height, blood pressure, target limb examination at Baseline/Screening. PE included exam of access site and target limb at the 1-month visit. PE includes clinical assessment of target limb at the 6-, 12-, and 24-month and unscheduled visits.

[3] Target limb resting ABI or TBI could have been collected up to 90 days prior to the index procedure, provided that the subject had signed the informed consent form and that there was no change in the subject's clinical symptoms between the ABI/TBI assessment and the baseline visit. If there was a change in the subject's clinical symptoms, the target limb ABI/TBI should have been reassessed.

[4] For women of childbearing potential only, per standard of care.

[5] Comprehensive metabolic panel included kidney and liver function tests.

[6] An unscheduled visit is defined as any visit for an ischemic event of the target limb.

[7] Angiogram to be performed only if re-intervention is deemed necessary from clinical symptoms.

[8] 30-Day DUS was intended to establish a post-treatment baseline and help to inform the primary endpoint assessment.

[9] A mobile DUS may be performed.

[10] When conducting a telephone visit, these assessments will be performed.

[11] All AEs (serious and non-serious) will be recorded for the entire study period to the extent required by national and/or local requirements. For US sites only: After the 12-month visit, ongoing AEs will be followed through to resolution or until the event becomes stable, and only SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.

[12] When conducting a telephone visit, target limb Rutherford classification without the use of treadmill may only be performed. If a treadmill had been previously used in the assessment, it must consistently be used throughout the study and therefore would require an office visit.

3. Clinical Endpoints

Primary Safety Endpoint:
The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days post-index procedure and freedom from major target limb amputation (above the ankle) and clinically-driven target vessel revascularization (TVR) through 12 months post-index procedure. This effectiveness endpoint was designed to demonstrate that the 12 month safety for the SurVeil™ Drug-Coated Balloon is non-inferior to the Medtronic IN.PACT® Admiral® Drug-Coated Balloon.

Primary Effectiveness Endpoint:
The primary effectiveness endpoint was primary patency, defined as a composite of freedom from clinically-driven TLR and binary restenosis (restenosis defined as DUS peak systolic velocity ratio [PSVR] ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs) through 12 months post-index procedure. This effectiveness endpoint was designed to demonstrate that the 12 month primary patency for the SurVeil™ Drug-Coated Balloon is non-inferior to the Medtronic IN.PACT® Admiral® Drug-Coated Balloon.

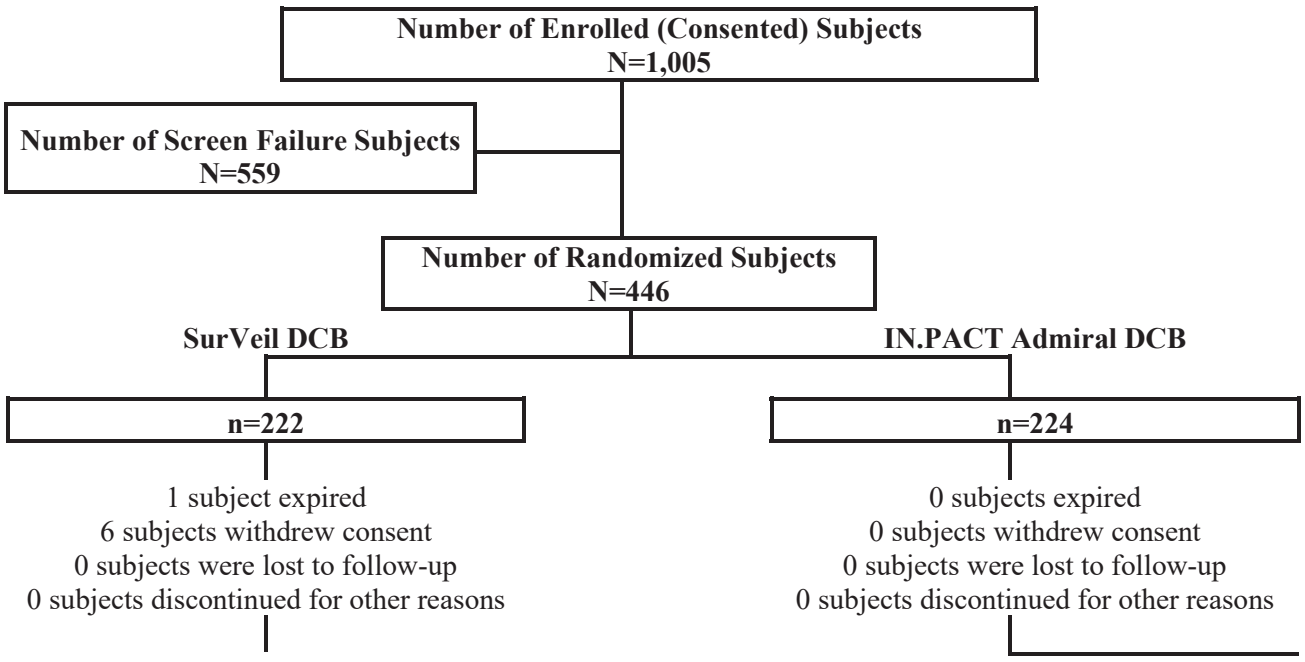
Secondary Endpoints:
- Device Success: defined as successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below rated burst pressure, and achievement of <50% residual stenosis of the target lesion (by core lab-assessed quantitative angiography [QA]) without flow-limiting arterial dissection using only the study device
- Technical Success: defined as achievement of a final residual diameter stenosis of <50% (by core lab-assessed QA) without flow-limiting arterial dissection at the end of the procedure
- Procedure Success: defined as evidence of both acute technical success and absence of Peripheral Academic Research Consortium major adverse events (PARC MAEs; e.g., death, stroke, myocardial infarction, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and or need for urgent/emergent vascular surgery) within 72 hours of the index procedure
- Freedom from all-cause death, major target limb amputation and TVR through 30 days
- Primary patency through 24 months
- Target vessel patency, defined as freedom from clinically-driven TVR and binary restenosis (restenosis defined as DUS PSVR ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs), within 12 and 24 months
- Sustained clinical improvement, defined as freedom from major target limb amputation, TVR and worsening target limb Rutherford class, within 6, 12, and 24 months

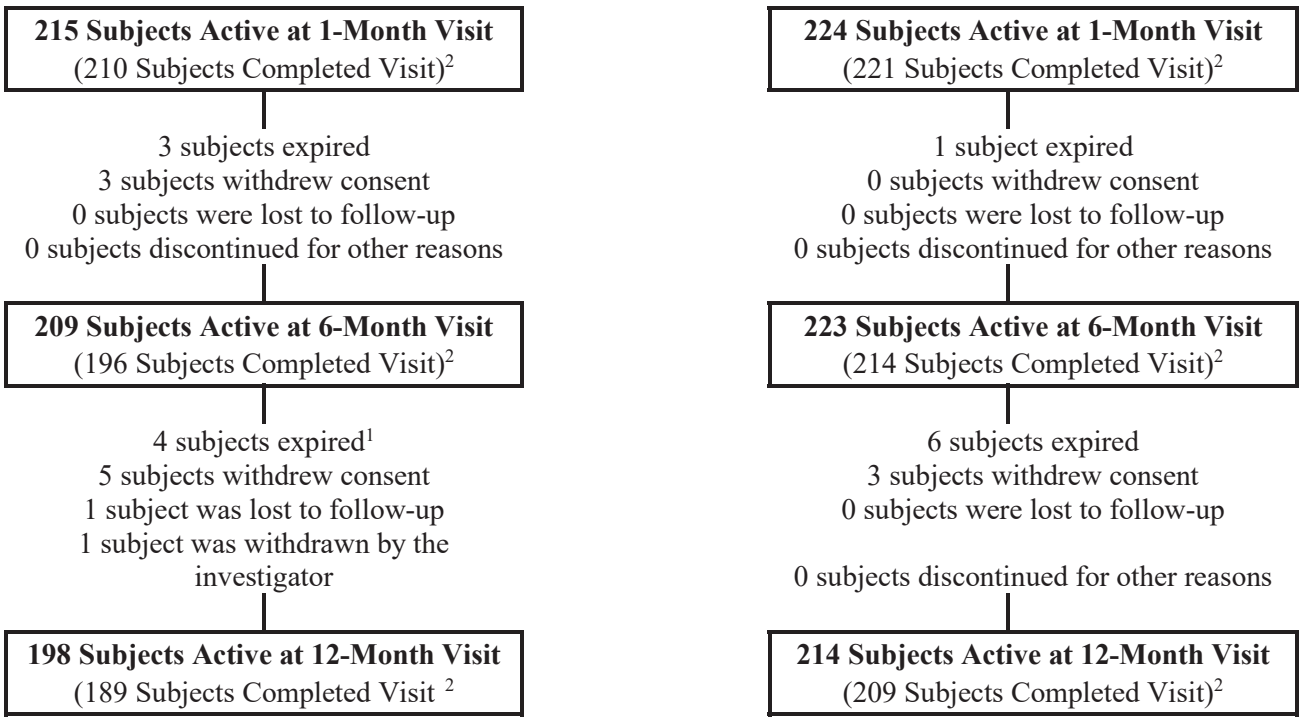
- Clinically-driven TLR within 6, 12, 24, 36, 48, and 60 months
- Historical major adverse events (Historical MAEs), defined as composite of all-cause death, clinically-driven TLR, major target limb amputation, or thrombosis at the target lesion within 6, 12, 24, 36, 48, and 60 months
- Major target-limb amputation within 6, 12, 24, 36, 48, and 60 months
- Thrombosis at the target lesion within 6, 12, 24, 36, 48, and 60 months
- Change in target limb Rutherford class from baseline to 1, 6, 12, and 24 months
- Change in target limb PARC clinical symptom classification from baseline to 1, 6, 12, and 24 months
- Decrease in target limb resting ankle brachial index (ABI) or toe brachial index (TBI) ≥0.15 from baseline to 6, 12, and 24 months
- Change in Walking Impairment Questionnaire (WIQ) score from baseline to 1, 12, and 24 months
- Change in 6-minute walk test (6-MWT) from baseline to 12 and 24 months
- Change in Peripheral Artery Questionnaire (PAQ) score from baseline to 1, 12, and 24 months

With regard to success/failure criteria, the study was considered successful if both primary safety and effectiveness endpoints were met.

B. Accountability of PMA Cohort

At the time of database snapshot on November 13, 2020, of 446 patients randomized in the PMA study, 89% (n=398) patients were available for the primary endpoint analysis, the 12-month postoperative visit. **Figure 4** displays the subject disposition at each follow-up visit for the RCT.





[1] Includes one subject who died on day 366 post-procedure before completing the 12-month follow-up visit.
[2] Difference between Subjects Active at Visit and Subjects Completed Visit is Follow-up Visit Not Done (see Table 9)

Figure 4: Subject Flow Chart through 12 Months

Follow-up compliance through the 12-month follow-up visit is presented in **Table 9** below. At the 12 month primary endpoint assessment visit, 87.9% (174/198) of subjects in the SurVeil DCB group and 88.8% (190/214) in the IN.PACT Admiral DCB group completed their visit within window. In the SurVeil DCB group, 7.6% (15/198 of subjects completed their visits outside the visit window on average 24 days outside of the window (3 subjects completed the visit before the window opened and 12 completed the visit after the window closed). In the IN.PACT Admiral group, 8.9% (19/214) of subjects completed their visit on average 50 days outside of the window (5 came in before the window opened and 14 completed their visit after the window had closed).

A total of 398 of 412 eligible subjects (96.6%) completed their 12-month follow-up visit. Of them, 182 (45.7%) had their 12-month follow-up visit occur between 1 March 2020 and 30 August 2020; concurrent with the COVID-19 pandemic, which created challenges for completing timely in-person follow-up with study subjects. Of the 182 subjects that completed their 12-month follow-up visit during that 6-month time frame, 169 were within window and 13 were out of window (12 months ±30 days).

Overall, visit compliance was complicated by a global pandemic; however, visit completion for the 12-month primary endpoint visit (both in- and out-of-window visits) was satisfactory for both groups.

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

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
1 Month		
Eligible Subjects[1]	215	224
Death[2]	1	0
Withdrawal[2]	6	0
Lost to follow-up[2]	0	0
Physician decision[2]	0	0
Follow-up Visit Within Window[3]	187	204
Follow-up Visit Out of Window[3]	23	17
Follow-up visit Not Done	5	3
Follow-up Compliance (%)[4]	87.0%	91.1%
6 Months		
Eligible Subjects[1]	209	223
Death[2]	4	1
Withdrawal[2]	9	0
Lost to follow-up[2]	0	0
Physician decision[2]	0	0
Follow-up Visit Within Window[3]	186	195
Follow-up Visit Out of Window[3]	10	19
Follow-up Visit Not Done	13	9
Follow-up Compliance (%)[4]	89.0%	87.4%
12 Months		
Eligible Subjects[1]	198	214
Death[2]	8	7
Withdrawal[2]	14	3
Lost to follow-up[2]	1	0
Physician decision[2]	1	0
Follow-up Visit Within Window[3]	174	190
Follow-up Visit Out of Window[3]	15	19
Follow-up Visit Not Done	9	5
Follow-up Compliance (%)[4]	87.9%	88.8%

[1] Eligible subjects are all subjects who either have a follow-up visit form or are past due for their follow-up (beyond the upper limit of window and did not exit the study before the upper limit of the window).

[2] Death, withdrawal, lost to follow-up and physician decision are cumulative through the follow-up period.

[3] Within window visits are defined as visits within Day 30 (-2 days/+15 days) for the 1-month visit, Day 180 (±30 days) for the 6-month visit and Day 365(±30 days) for the 12-month visit and include those subjects with a protocol deviation for a delayed in-office visit due to COVID-19.

[4] Percentage is based on the number of subjects who had a follow-up visit within window divided by the total number of eligible subjects.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PAD study performed in the US. **Table 10** provides a review of baseline demographics and medical history of the 446 subjects enrolled into the TRANSCEND study.

Table 10: Baseline Demographics and Medical History – TRANSCEND RCT (N=446)

Patient Characteristics	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Demographics		
Age (years)		
Mean ± SD (N)	68.7±9.4 (222)	67.4±9.3 (224)
Median (Q1,Q3)	69.0 (62.0,76.0)	67.0 (60.0,74.0)
Range (Min,Max)	(44.0,93.0)	(38.0,99.0)
Male	62.6% (139/222)	63.4% (142/224)
Race		
White	86.0% 191/222	88.8% 199/224
Black or African American	10.4% (23/222)	9.4% (21/224)
Asian	0.5% (1/222)	0.4% (1/224)
Native Hawaiian or Other Pacific Islander	0.0% (0/222)	0.0% (0/224)
American Indian or Alaska Native	0.5% (1/222)	0.0% (0/224)
Other	0.5% (1/222)	0.9% (2/224)
Not Answered	2.3% (5/222)	0.4% (1/224)
Ethnicity		
Hispanic or Latino	2.7% (6/222)	3.1% (7/224)
Not Hispanic or Latino	95.5% (212/222)	96.4% (216/224)
Not Answered	1.8% 4/222)	0.4% (1/224)
Medical History		
Smoking Status		
Current Smoker	41.9% (93/222)	37.9% 85/224
Former Smoker	42.8% 95/222	46.0% (103/224)
Never Smoked	15.3% (34/222)	16.1% (36/224)
Diabetes Mellitus	41.4% (92/222)	40.2% (90/224)
Diabetes Control Method		
No Treatment	1.1% (1/92)	1.1% (1/90)
Diet and/or Exercise Only	7.6% (7/92)	2.2% (2/90)
Oral or Other Non-Insulin Therapies	51.1% (47/92)	58.9% 53/90)
Requiring Insulin	40.2% (37/92)	37.8% 34/90)
Rutherford Classification at Baseline		
2 - Moderate claudication	21.6% 48/222	34.4% (77/224)
3 - Severe claudication	75.7% 168/222	61.2% (137/224)
4 - Ischemic rest pain	2.7% (6/222)	4.5% (10/224)
Hypertension	91.4% (203/222)	87.9% 197/224
Hypercholesterolemia	86.5% 192/222	86.6% 194/224
Chronic Angina	6.8% 15/221)	7.2% (16/223)

Patient Characteristics	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Ischemic Heart Disease	27.1% 59/218	28.6% 64/224
Myocardial Infarction	22.4% (49/219)	21.0% (46/219)
Percutaneous Coronary Intervention (PCI)	34.8% (77/221)	32.9% (73/222)
Coronary Artery Bypass Graft (CABG)	19.8% 44/222	21.5% 48/223
Transient Ischemic Attack (TIA)	4.5% (10/221)	5.4% (12/221)
Cerebrovascular Accident (CVA)	6.8% 15/221)	10.8% 24/223
CVA Type		
Ischemic	33.3% (5/15)	41.7% (10/24)
Hemorrhagic	0.0% (0/15)	8.3% 2/24
Unknown	66.7% (10/15)	50.0% (12/24)
Congestive Heart Failure (CHF)	10.4% (23/221)	9.0% (20/222)
Chronic Renal Insufficiency	22.5% (50/222)	10.8% 24/223
Renal Failure	2.7% (6/221)	0.4% (1/224)
Previous Lower Extremity Artery Revascularization	31.5% (70/222)	36.8% 82/223
History of Deep Venous Thromboembolism	4.1% (9/220)	3.6% 8/224)
Thromboembolism Type		
Deep Venous Thromboembolism	100.0% (9/9)	75.0% 6/8)
Pulmonary Embolism	0.0% (0/9)	12.5% 1/8)
Unknown	0.0% (0/9)	12.5% 1/8)
History of Lower Limb Amputation	0.5% (1/222)	0.0% (0/224)
Family History of Peripheral Artery Disease (PAD)	7.6% (13/170)	11.1% 18/162
Family History of Coronary Artery Disease (CAD)	47.0% 87/185	50.3% 89/177

Table 11 presents the baseline lesion characteristics, procedural characteristics, and post procedure measurements for the TRANSCEND study.

Table 11: Angiographic Core Lab Baseline, Procedural, Post-procedure Reported Lesion Characteristics

Characteristics	SurVeil DCB (N=222 Subjects L=222 Lesions)	IN.PACT Admiral DCB (N=224 Subjects L=224 Lesions)
Pre-Procedure Morphology		
Vessel Location		
SFA		
Proximal	11.8% 26/221	9.9% (22/223)
Mid	40.3% 89/221	40.4% (90/223)
Distal	42.5% (94/221)	41.3% (92/223)
Ostial	0.0% (0/221)	1.8% 4/223)
Popliteal		
Proximal	3.6% 8/221)	5.4% (12/223)
Mid	1.8% 4/221)	0.9% (2/223)

Characteristics	SurVeil DCB (N=222 Subjects L=222 Lesions)	IN.PACT Admiral DCB (N=224 Subjects L=224 Lesions)
Distal	0.0% (0/221)	0.4% (1/223)
Lesion Length (mm)		
Mean ± SD (N)	72.5±48.4 (221)	70.0±50.5 (223)
Median (Q1,Q3)	60.6 (33.1,99.0)	55.7 (28.2,99.0
Range (Min,Max)	(10.5,215.0)	(9.8,232.8)
Eccentric	21.7% 48/221	25.1% (56/223)
Bend		
<45 degrees	100.0% (221/221)	100.0% (223/223)
≥45 degrees to <90 degrees	0.0% (0/221)	0.0% (0/223)
≥90 degrees	0.0% (0/221)	0.0% (0/223)
Thrombus	0.0% (0/221)	0.4% (1/223)[1]
Calcification		
None/Mild	50.7% (112/221)	48.0% (107/223)
Moderate	36.2% 80/221	41.3% (92/223)
Severe	13.1% (29/221)	10.8% 24/223
Ulcerated	7.7% (17/221)	5.4% (12/223)
Aneurysm	0.0% (0/221)	0.0% (0/223)
Ectasia	5.0% (11/221)	4.5% (10/223)
Blood Flow		
Normal	73.8% 163/221	72.2% (161/223)
Decreased	3.6% 8/221)	2.7% (6/223)
No Flow	22.6% (50/221)	25.1% (56/223)
Collaterals	24.0% (53/221)	27.8% 62/223
Collateral Grade		
1-Minimal	1.9% (1/53)	1.6% (1/62)
2-Moderate	22.6% (12/53)	33.9% (21/62)
3-Good	75.5% (40/53)	64.5% (40/62)
Occluded[2]	22.2% (49/221)	26.5% (59/223)
Pre-Procedure Quantitative Vascular Angiography		
Reference Vessel Diameter (RVD) (mm)[3]		
Mean ± SD (N)	5.3±0.9 (221)	5.3±0.7 (223)
Median (Q1,Q3)	5.2 (4.6,5.8)	5.2 (4.7,5.8)
Range (Min,Max)	3.2,8.4	(3.7,8.4
Minimum Lumen Diameter (MLD) (mm)[4]		
Mean ± SD (N)	1.4±1.1 (221)	1.3±1.0 (223)
Median (Q1,Q3)	1.5 (0.5,2.2)	1.3 (0.0,2.0)
Range (Min,Max)	(0.0,4.4)	(0.0,4.3)
Diameter Stenosis (%)[5]		
Mean ± SD (N)	72.9±18.8 (221)	75.8±18.1 (223)
Median (Q1,Q3)	71.1 (58.0,87.5	74.4 (60.5,100.0)
Range (Min,Max)	(22.0,100.0)	(31.2,100.0)

Characteristics	SurVeil DCB (N=222 Subjects L=222 Lesions)	IN.PACT Admiral DCB (N=224 Subjects L=224 Lesions)
Post-Procedure		
Thrombus	0.0% (0/217)	0.0% (0/223)
Spasm	0.0% (0/217)	0.0% (0/223)
Abrupt Closure	0.0% (0/217)	0.0% (0/223)
No Reflow	0.0% (0/217)	0.0% (0/223)
Distal Embolization	0.0% (0/217)	0.0% (0/222)
Perforation		
0	100.0% (217/217)	100.0% (223/223)
I	0.0% (0/217)	0.0% (0/223)
II	0.0% (0/217)	0.0% (0/223)
III	0.0% (0/217)	0.0% (0/223)
Blood Flow		
Normal	100.0% (217/217)	100.0% (223/223)
Decreased	0.0% (0/217)	0.0% (0/223)
No Flow	0.0% (0/217)	0.0% (0/223)
Dissection		
None	41.9% (91/217)	48.0% 107/223
A	11.5% (25/217)	11.2% (25/223)
B	24.9% (54/217)	25.1% (56/223)
C	17.1% (37/217)	11.2% (25/223)
D	4.6% (10/217)	4.5% (10/223)
E	0.0% (0/217)	0.0% (0/223)
F	0.0% (0/217)	0.0% (0/223)
Staining	0.0% (0/215)	0.0% (0/222)
Post-Procedure Quantitative Vascular Angiography		
RVD (mm)[1]		
Mean ± SD (N)	5.3±0.9 (217)	5.3±0.8 (223)
Median (Q1,Q3)	5.3 (4.7,5.9)	5.3 (4.8,5.8)
Range (Min,Max)	3.4,8.4	(3.7,8.4
MLD (mm)[2]		
Mean ± SD (N)	4.3±0.8 (217)	4.3±0.7 (223)
Median (Q1,Q3)	4.3 (3.9,4.8)	4.2 (3.8,4.8)
Range (Min,Max)	(2.5,6.6)	(2.6,6.9)
Diameter Stenosis (%)[3]		
Mean ± SD (N)	18.7±9.6 (217)	18.9±9.3 (223)
Median (Q1,Q3)	17.9 (11.4,25.6)	18.8 (13.1,24.7
Range (Min,Max)	(-1.6,45.0)	(-3.5,47.1)
Procedural Characteristics		
Pre-dilatation Performed	100.0% (222/222)	100.0% (224/224)
Post-dilatation Performed	18.0% 40/222 [6]	17.4% (39/224)
Bailout Stenting Performed	8.1% 18/222)	6.7% (15/224)

Characteristics	SurVeil DCB (N=222 Subjects L=222 Lesions)	IN.PACT Admiral DCB (N=224 Subjects L=224 Lesions)
Device Success[7]	92.1% (199/216)	93.7% 208/222
Technical Success[8]	100.0% (217/217)	100.0% (223/223)
Procedure Success[9]	99.5% 217/218	99.6% (222/223)

[1] Per the angiographic core laboratory, subject 115-009 had thrombus in the target vessel.

[2] Occluded was defined as 100% diameter stenosis.

[3] RVD was calculated as the average of the distal and proximal user-defined target lesion normal references from 2 projections.

[4] MLD is based on the average of 2 projections.

[5] Percent diameter stenosis was calculated as follows: (1−minimum lumen diameter/RVD ×100.

[6]SurVeil DCB subject 117-019 had post-dilatation performed using 2 post dilatation balloons.

[7] Device Success: defined as successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below rated burst pressure, and achievement of <50% residual stenosis of the target lesion (by core lab-assessed QA) without flow-limiting arterial dissection, using only the study device.

[8] Technical Success: defined as achievement of a final residual diameter stenosis of <50% without flow-limiting arterial dissection at the end of the procedure.

[9] Procedure Success: defined as evidence of both acute technical success and absence of PARC MAEs (e.g., death, stroke, myocardial infarction, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and or need for urgent/ emergent vascular surgery) within 72 hours of the index procedure.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT full study cohort of 222 SurVeil DCB subjects and 224 IN.PACT Admiral DCB subjects available for the 12- month evaluation. **Table 12** presents the primary safety results for the full study cohort. The SurVeil™ Drug-Coated Balloon was concluded to be non-inferior to the IN.PACT® Admiral® Drug-Coated Balloon for the primary safety endpoint if the one-sided lower 97.5% confidence bound on the difference between groups (SurVeil DCB vs. IN.PACT DCB) in is less than 10% (non-inferiority margin). In the ITT group, using multiple imputation, the rate of the primary safety endpoint was 91.7% in the Surveil DCB group compared to 89.6% in the IN.PACT Admiral DCB group. The difference in rates between the groups was 2.1% with one-sided lower 97.5% CL of -4.0%. Since this is higher than the pre-specified noninferiority margin of -10.0%, noninferiority is met (P-value for noninferiority <0.0001) and the SurVeil DCB is declared noninferior to the IN.PACT Admiral DCB with regards to the primary safety endpoint. A complete case analysis was carried out as a sensitivity analysis on ITT subjects with available data (i.e., subjects who experienced the primary safety composite or had at least 335 days of follow-up) and provided similar results. Kaplan-Meier plot of primary safety through 395 days is presented in **Figure 5**.

Table 12: Primary Safety – Full Cohort, Intent-to-Treat (N=446)

Primary Safety Endpoint	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)	Difference [One-sided Lower 97.5% CL]	Non-inferiority Test P-value[1]
Composite of freedom from device- and procedure-related death through 30 days and freedom from major target limb amputation and clinically-driven TVR through 12 months (ITT – Multiple Imputations)	**91.7% (87.9%,95.5 %)**	**89.6% (85.5%,93.7%)**	**2.1% [-4.0%]**	**<0.0001**
Composite of freedom from device- and procedure-related death through 30 days and freedom from major target limb amputation and clinically-driven TVR through 12 months (ITT - Complete Case)	92.0% (183/199)	89.9% (195/217)	2.1% [-4.0%]	<0.0001
Freedom from device- and procedure-related death through 30 days[2]	99.5% (217/218)	100.0% (223/223)		
Freedom from clinically-driven TVR through 12 months[3]	92.4% (183/198)	89.9% (195/217)		
Freedom from major target limb amputation through 12 months[4]	100.0% (196/196)	100.0% (215/215)		

[1] P-value is derived from one-sided Farrington-Manning test with noninferiority margin of 10% and a one-sided significance level of 0.025.
[2] Denominators include subjects with at least 28 days of follow-up or subjects experiencing device- or procedure-related death through 30 days.
[3] Denominators include subjects with at least 335 days of follow-up or subjects experiencing clinically-driven TVR through 365 days.
[4] Denominators include subjects with at least 335 days of follow-up or subjects experiencing target limb amputation through 365 days.

Primary Safety Endpoint	0	[1, 90]	[91, 180]	[181, 270]	[271, 365]
SurVeil DCB (N=222 Subjects)					
# Entered	222	222	209	202	193
# Censored	0	9	5	5	53
# Events	0	4	2	4	6
Event-free [%]	100.0%	98.1%	97.2%	95.2%	92.0%
Greenwood SE [%]	0.0%	0.9%	1.1%	1.5%	1.9%
IN.PACT Admiral DCB (N=224 Subjects)					
# Entered	224	223	220	217	209
# Censored	1	1	1	1	48
# Events	0	2	2	7	11
Event-free [%]	100.0%	99.1%	98.2%	95.0%	89.9%
Greenwood SE [%]	0.0%	0.6%	0.9%	1.5%	2.0%
Tests Between Groups	Test	Chi-Square	Degree of Freedom	P-value	
	Log-Rank	0.5455	1	0.460	

Note: The p-value should be interpreted with caution because a hypothesis test for the survival endpoint was not pre-specified and was not adjusted for multiplicity

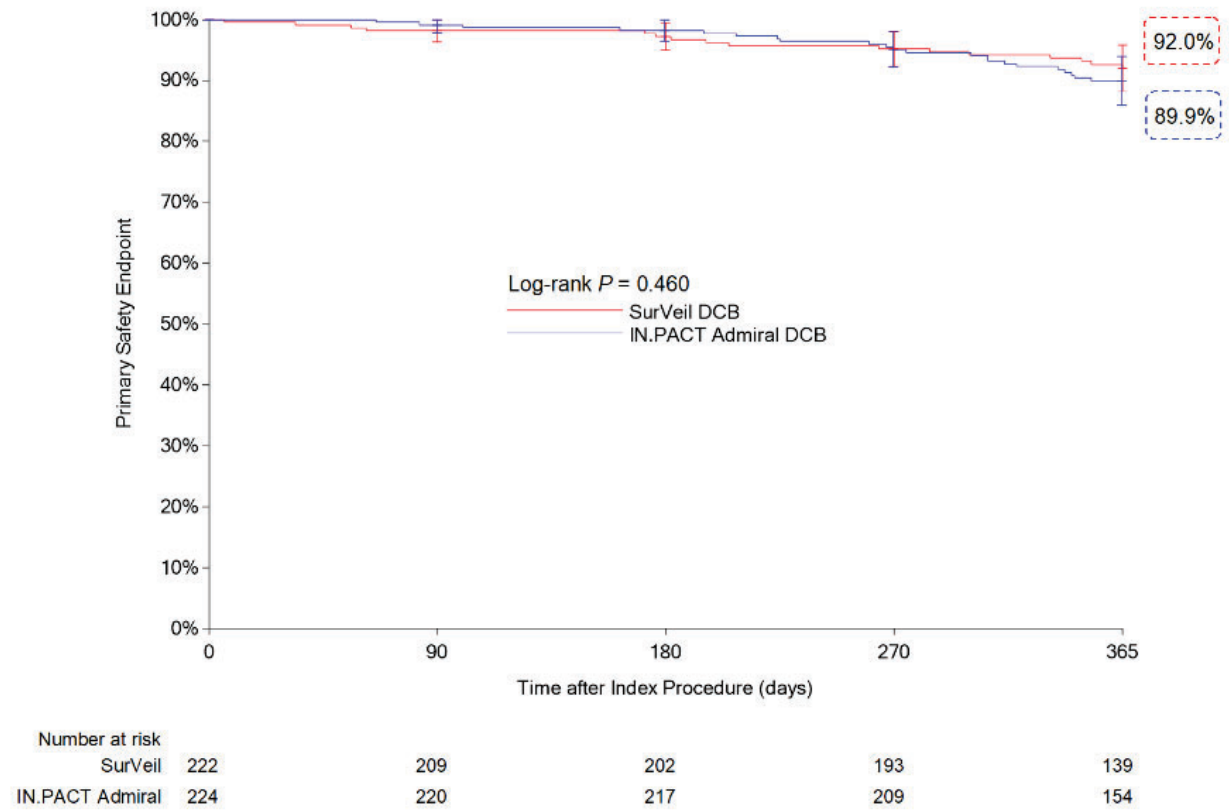


Figure 5: Kaplan-Meier Curve for the Primary Safety Endpoint to 12 Months - ITT Analysis Population (N=446)

Adverse effects that occurred in the PMA clinical study:

Table 13 displays the rates of site reported Serious Adverse Events (SAEs) classified by the MedDRA System Organ Class (SOC) and preferred term. An SAE was defined as an adverse event that leads to:

1. Death
2. A serious deterioration in the health of the subject that either results in:
   a. life-threatening illness or injury or
   b. a permanent impairment of a body structure or a body function or
   c. in-patient hospitalization or prolongation of existing hospitalization or
   d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
3. Fetal distress, fetal death, or congenital abnormality or birth defect.

Table 13: Summary of All Site-Reported Serious Adverse Events through 12 Months – ITT Analysis Population (N=446)

Serious Adverse Events	SurVeil DCB (N=222 Subjects)		IN.PACT Admiral DCB (N=224 Subjects)	
	Events	Rate of Subjects with Event	Events	Rate of Subjects with Event
Any Serious Adverse Event	**176**	**44.6% (99/222)**	**193**	**37.9% (85/224)**
Blood and lymphatic system disorders	**6**	**2.7% (6/222)**	**1**	**0.4% (1/224)**
Anaemia	2	0.9% (2/222)	1	0.4% (1/224)
Haemorrhagic anaemia	3	1.4% (3/222)	0	0.0% (0/224)
Microcytic anaemia	1	0.5% (1/222)	0	0.0% (0/224)
Cardiac disorders	**27**	**9.5% (21/222)**	**31**	**10.7% (24/224)**
Acute myocardial infarction	5	2.3% (5/222)	7	3.1% (7/224)
Angina pectoris	4	1.8% 4/222)	2	0.9% (2/224)
Angina unstable	2	0.9% (2/222)	1	0.4% (1/224)
Aortic valve stenosis	0	0.0% (0/222)	1	0.4% (1/224)
Atrial fibrillation	1	0.5% (1/222)	1	0.4% (1/224)
Atrial flutter	1	0.5% (1/222)	1	0.4% (1/224)
Atrioventricular block	0	0.0% (0/222)	1	0.4% (1/224)
Atrioventricular block second degree	0	0.0% (0/222)	2	0.9% (2/224)
Cardiac arrest	1	0.5% (1/222)	2	0.9% (2/224)
Cardiac failure	0	0.0% (0/222)	1	0.4% (1/224)
Cardiac failure acute	0	0.0% (0/222)	1	0.4% (1/224)
Cardiac failure congestive	8	1.8% 4/222)	3	1.3% (3/224)
Coronary artery disease	1	0.5% (1/222)	3	0.4% (1/224)
Coronary artery occlusion	0	0.0% (0/222)	1	0.4% (1/224)
Coronary artery stenosis	2	0.9% (2/222)	1	0.4% (1/224)
Myocardial ischaemia	1	0.5% (1/222)	0	0.0% (0/224)
Sinus node dysfunction	0	0.0% (0/222)	1	0.4% (1/224)
Ventricular extrasystoles	1	0.5% (1/222)	0	0.0% (0/224)
Ventricular fibrillation	0	0.0% (0/222)	2	0.9% (2/224)
Eye disorders	**2**	**0.9% (2/222)**	**1**	**0.4% (1/224)**
Glaucoma	1	0.5% (1/222)	0	0.0% (0/224)
Retinal artery occlusion	0	0.0% (0/222)	1	0.4% (1/224)
Vitreous haemorrhage	1	0.5% (1/222)	0	0.0% (0/224)
Gastrointestinal disorders	**7**	**2.3% (5/222)**	**10**	**4.0% (9/224)**
Abdominal hernia	1	0.5% (1/222)	0	0.0% (0/224)
Barrett's oesophagus	0	0.0% (0/222)	1	0.4% (1/224)
Dysphagia	0	0.0% (0/222)	1	0.4% (1/224)

Serious Adverse Events	SurVeil DCB (N=222 Subjects)		IN.PACT Admiral DCB (N=224 Subjects)	
	Events	Rate of Subjects with Event	Events	Rate of Subjects with Event
Gastric ulcer haemorrhage	0	0.0% (0/222)	1	0.4% (1/224)
Gastritis	0	0.0% (0/222)	1	0.4% (1/224)
Gastrointestinal haemorrhage	3	0.9% (2/222)	1	0.4% (1/224)
Inguinal hernia	0	0.0% (0/222)	1	0.4% (1/224)
Intestinal obstruction	1	0.5% (1/222)	0	0.0% (0/224)
Lower gastrointestinal haemorrhage	0	0.0% (0/222)	1	0.4% (1/224)
Nausea	0	0.0% (0/222)	1	0.4% (1/224)
Retroperitoneal fibrosis	1	0.5% (1/222)	0	0.0% (0/224)
Umbilical hernia	1	0.5% (1/222)	1	0.4% (1/224)
Vomiting	0	0.0% (0/222)	1	0.4% (1/224)
General disorders and administration site conditions	**12**	**5.0% (11/222)**	**7**	**2.7% (6/224)**
Catheter site discharge	2	0.9% (2/222)	0	0.0% (0/224)
Catheter site haematoma	3	1.4% (3/222)	0	0.0% (0/224)
Catheter site haemorrhage	0	0.0% (0/222)	1	0.4% (1/224)
Death	1	0.5% (1/222)[1]	0	0.0% (0/224)
Drug withdrawal syndrome	1	0.5% (1/222)	0	0.0% (0/224)
Fatigue	0	0.0% (0/222)	1	0.4% (1/224)
Non-cardiac chest pain	3	1.4% (3/222)	2	0.4% (1/224)
Pyrexia	0	0.0% (0/222)	1	0.4% (1/224)
Vascular stent occlusion	1	0.5% (1/222)	1	0.4% (1/224)
Vascular stent restenosis	1	0.5% (1/222)	1	0.4% (1/224)
Hepatobiliary disorders	**1**	**0.5% (1/222)**	**0**	**0.0% (0/224)**
Cholelithiasis	1	0.5% (1/222)	0	0.0% (0/224)
Immune system disorders	**1**	**0.5% (1/222)**	**1**	**0.4% (1/224)**
Anaphylactic reaction	1	0.5% (1/222)	1	0.4% (1/224)
Infections and infestations	**16**	**6.3% (14/222)**	**24**	**5.8% (13/224)**
Bronchitis	0	0.0% (0/222)	2	0.4% (1/224)
Bronchitis bacterial	0	0.0% (0/222)	1	0.4% (1/224)
Cellulitis	1	0.5% (1/222)	0	0.0% (0/224)
Diverticulitis	0	0.0% (0/222)	1	0.4% (1/224)
Endocarditis bacterial	0	0.0% (0/222)	1	0.4% (1/224)
Enterococcal bacteraemia	0	0.0% (0/222)	1	0.4% (1/224)
Epididymitis	1	0.5% (1/222)	0	0.0% (0/224)
Gastroenteritis	0	0.0% (0/222)	1	0.4% (1/224)
Infected skin ulcer	0	0.0% (0/222)	1	0.4% (1/224)
Infection	1	0.5% (1/222)	0	0.0% (0/224)

Serious Adverse Events	SurVeil DCB (N=222 Subjects) Events	SurVeil DCB (N=222 Subjects) Rate of Subjects with Event	IN.PACT Admiral DCB (N=224 Subjects) Events	IN.PACT Admiral DCB (N=224 Subjects) Rate of Subjects with Event
Infective exacerbation of chronic obstructive airways disease	0	0.0% (0/222)	1	0.4% (1/224)
Influenza	0	0.0% (0/222)	1	0.4% (1/224)
Localised infection	0	0.0% (0/222)	1	0.4% (1/224)
Lung infection	1	0.5% (1/222)	0	0.0% (0/224)
Osteomyelitis	0	0.0% (0/222)	1	0.4% (1/224)
Pneumonia	6	2.7% (6/222)	8	2.7% (6/224)
Postoperative wound infection	1	0.5% (1/222)	0	0.0% (0/224)
Pyelonephritis	1	0.5% (1/222)	0	0.0% (0/224)
Pyelonephritis acute	1	0.5% (1/222)	0	0.0% (0/224)
Sepsis	1	0.5% (1/222)	2	0.9% (2/224)
Septic shock	0	0.0% (0/222)	1	0.4% (1/224)
Staphylococcal infection	1	0.5% (1/222)	0	0.0% (0/224)
Urinary tract infection	1	0.5% (1/222)	0	0.0% (0/224)
Wound infection	0	0.0% (0/222)	1	0.4% (1/224)
Injury, poisoning and procedural complications	**22**	**9.0% (20/222)**	**16**	**6.7% (15/224)**
Ankle fracture	2	0.9% (2/222)	0	0.0% (0/224)
Arterial bypass thrombosis	0	0.0% (0/222)	1	0.4% (1/224)
Femoral neck fracture	1	0.5% (1/222)	2	0.9% (2/224)
Hip fracture	1	0.5% (1/222)	0	0.0% (0/224)
Meniscus injury	0	0.0% (0/222)	1	0.4% (1/224)
Overdose	1	0.5% (1/222)	0	0.0% (0/224)
Peripheral artery restenosis	9	3.6% 8/222)	6	2.2% (5/224)
Procedural hypotension	1	0.5% (1/222)	0	0.0% (0/224)
Pubis fracture	0	0.0% (0/222)	1	0.4% (1/224)
Rib fracture	1	0.5% (1/222)	0	0.0% (0/224)
Scar	0	0.0% (0/222)	1	0.4% (1/224)
Spinal compression fracture	0	0.0% (0/222)	1	0.4% (1/224)
Transplant failure	0	0.0% (0/222)	1	0.4% (1/224)
Upper limb fracture	1	0.5% (1/222)	0	0.0% (0/224)
Vascular access site pseudoaneurysm	3	1.4% (3/222)	2	0.9% (2/224)
Vascular pseudoaneurysm	2	0.9% (2/222)	0	0.0% (0/224)
Investigations	**0**	**0.0% (0/222)**	**1**	**0.4% (1/224)**
Blood pressure systolic increased	0	0.0% (0/222)	1	0.4% (1/224)
Metabolism and nutrition disorders	**2**	**0.9% (2/222)**	**3**	**0.4% (1/224)**
Dehydration	0	0.0% (0/222)	2	0.4% (1/224)
Hyperkalaemia	0	0.0% (0/222)	1	0.4% (1/224)

Serious Adverse Events	SurVeil DCB (N=222 Subjects)		IN.PACT Admiral DCB (N=224 Subjects)	
	Events	Rate of Subjects with Event	Events	Rate of Subjects with Event
Hyperlipidaemia	1	0.5% (1/222)	0	0.0% (0/224)
Hypoglycaemia	1	0.5% (1/222)	0	0.0% (0/224)
Musculoskeletal and connective tissue disorders	**7**	**3.2% (7/222)**	**11**	**4.9% (11/224)**
Arthralgia	1	0.5% (1/222)	0	0.0% (0/224)
Back disorder	0	0.0% (0/222)	1	0.4% (1/224)
Back pain	0	0.0% (0/222)	1	0.4% (1/224)
Compartment syndrome	0	0.0% (0/222)	1	0.4% (1/224)
Dupuytren's contracture	1	0.5% (1/222)	0	0.0% (0/224)
Haemarthrosis	0	0.0% (0/222)	1	0.4% (1/224)
Intervertebral disc protrusion	1	0.5% (1/222)	0	0.0% (0/224)
Lumbar spinal stenosis	1	0.5% (1/222)	2	0.9% (2/224)
Muscle spasms	1	0.5% (1/222)	0	0.0% (0/224)
Osteoarthritis	0	0.0% (0/222)	1	0.4% (1/224)
Pain in extremity	1	0.5% (1/222)	2	0.9% (2/224)
Rotator cuff syndrome	0	0.0% (0/222)	1	0.4% (1/224)
Spinal osteoarthritis	1	0.5% (1/222)	0	0.0% (0/224)
Spondylolysis	0	0.0% (0/222)	1	0.4% (1/224)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4**	**1.8% (4/222)**	**6**	**2.7% (6/224)**
Carcinoid tumour of the small bowel	0	0.0% (0/222)	1	0.4% (1/224)
Cholesteatoma	1	0.5% (1/222)	0	0.0% (0/224)
Gastrooesophageal cancer	0	0.0% (0/222)	1	0.4% (1/224)
Laryngeal cancer metastatic	0	0.0% (0/222)	1	0.4% (1/224)
Lung neoplasm malignant	1	0.5% (1/222)	0	0.0% (0/224)
Neoplasm skin	0	0.0% (0/222)	1	0.4% (1/224)
Papillary thyroid cancer	0	0.0% (0/222)	1	0.4% (1/224)
Salivary gland neoplasm	1	0.5% (1/222)	0	0.0% (0/224)
Squamous cell carcinoma	1	0.5% (1/222)	0	0.0% (0/224)
Squamous cell carcinoma of lung	0	0.0% (0/222)	1	0.4% (1/224)
Nervous system disorders	**8**	**3.2% (7/222)**	**10**	**4.0% (9/224)**
Carotid artery stenosis	1	0.5% (1/222)	2	0.9% (2/224)
Cerebrovascular accident	0	0.0% (0/222)	1	0.4% (1/224)
Embolic stroke	1	0.5% (1/222)	1	0.4% (1/224)
Encephalopathy	0	0.0% (0/222)	2	0.9% (2/224)
Epidural lipomatosis	1	0.5% (1/222)	0	0.0% (0/224)
Haemorrhagic stroke	1	0.5% (1/222)	0	0.0% (0/224)
Metabolic encephalopathy	0	0.0% (0/222)	3	1.3% (3/224)

Serious Adverse Events	SurVeil DCB (N=222 Subjects) Events	SurVeil DCB (N=222 Subjects) Rate of Subjects with Event	IN.PACT Admiral DCB (N=224 Subjects) Events	IN.PACT Admiral DCB (N=224 Subjects) Rate of Subjects with Event
Post herpetic neuralgia	1	0.5% (1/222)	0	0.0% (0/224)
Presyncope	1	0.5% (1/222)	1	0.4% (1/224)
Syncope	1	0.5% (1/222)	0	0.0% (0/224)
Transient ischaemic attack	1	0.5% (1/222)	0	0.0% (0/224)
Product issues	**0**	**0.0% (0/222)**	**1**	**0.4% (1/224)**
Device malfunction	0	0.0% (0/222)	1	0.4% (1/224)
Psychiatric disorders	**0**	**0.0% (0/222)**	**2**	**0.9% (2/224)**
Completed suicide	0	0.0% (0/222)	1	0.4% (1/224)
Mental disorder	0	0.0% (0/222)	1	0.4% (1/224)
Renal and urinary disorders	**3**	**1.4% (3/222)**	**4**	**1.8% (4/224)**
Acute kidney injury	1	0.5% (1/222)	3	1.3% (3/224)
Chronic kidney disease	0	0.0% (0/222)	1	0.4% (1/224)
Nephrolithiasis	1	0.5% (1/222)	0	0.0% (0/224)
Renal mass	1	0.5% (1/222)	0	0.0% (0/224)
Reproductive system and breast disorders	**1**	**0.5% (1/222)**	**1**	**0.4% (1/224)**
Genital erosion	1	0.5% (1/222)	0	0.0% (0/224)
Vaginal prolapse	0	0.0% (0/222)	1	0.4% (1/224)
Respiratory, thoracic and mediastinal disorders	**3**	**1.4% (3/222)**	**17**	**4.0% (9/224)**
Acute respiratory failure	0	0.0% (0/222)	3	1.3% (3/224)
Aspiration	1	0.5% (1/222)	0	0.0% (0/224)
Chronic obstructive pulmonary disease	1	0.5% (1/222)	4	0.4% (1/224)
Dyspnoea	1	0.5% (1/222)	1	0.4% (1/224)
Emphysema	0	0.0% (0/222)	1	0.4% (1/224)
Epistaxis	0	0.0% (0/222)	2	0.4% (1/224)
Hypoxia	0	0.0% (0/222)	1	0.4% (1/224)
Pulmonary mass	0	0.0% (0/222)	1	0.4% (1/224)
Respiratory failure	0	0.0% (0/222)	4	1.3% (3/224)
Skin and subcutaneous tissue disorders	**1**	**0.5% (1/222)**	**0**	**0.0% (0/224)**
Neuropathic ulcer	1	0.5% (1/222)	0	0.0% (0/224)
Vascular disorders	**53**	**18.9% (42/222)**	**46**	**15.2% (34/224)**
Aortic aneurysm	1	0.5% (1/222)	1	0.4% (1/224)
Arterial spasm	1	0.5% (1/222)	0	0.0% (0/224)
Arteriovenous fistula	0	0.0% (0/222)	1	0.4% (1/224)

Serious Adverse Events	SurVeil DCB (N=222 Subjects)		IN.PACT Admiral DCB (N=224 Subjects)	
	Events	Rate of Subjects with Event	Events	Rate of Subjects with Event
Deep vein thrombosis	1	0.5% (1/222)	1	0.4% (1/224)
Haematoma	1	0.5% (1/222)	0	0.0% (0/224)
Haemorrhage	1	0.5% (1/222)	0	0.0% (0/224)
Hypertension	1	0.5% (1/222)	0	0.0% (0/224)
Hypertensive emergency	0	0.0% (0/222)	1	0.4% (1/224)
Hypotension	1	0.5% (1/222)	1	0.4% (1/224)
Iliac artery occlusion	0	0.0% (0/222)	1	0.4% (1/224)
Orthostatic hypotension	0	0.0% (0/222)	1	0.4% (1/224)
Peripheral arterial occlusive disease	2	0.9% (2/222)	2	0.9% (2/224)
Peripheral artery aneurysm	3	0.5% (1/222)	0	0.0% (0/224)
Peripheral artery dissection	1	0.5% (1/222)	1	0.4% (1/224)
Peripheral artery occlusion	12	4.5% (10/222)	17	5.8% 13/224)
Peripheral artery stenosis	23	9.9% (22/222)	15	5.4% (12/224)
Peripheral embolism	1	0.5% (1/222)	1	0.4% (1/224)
Peripheral ischaemia	1	0.5% (1/222)	0	0.0% (0/224)
Peripheral vascular disorder	1	0.5% (1/222)	0	0.0% (0/224)
Peripheral venous disease	0	0.0% (0/222)	1	0.4% (1/224)
Subclavian steal syndrome	0	0.0% (0/222)	1	0.4% (1/224)
Varicose vein	2	0.5% (1/222)	1	0.4% (1/224)

This table presents serious adverse events starting from the index procedure through 365 days post procedure.
[1]One Subject expired at home of unknown cause.

2. Effectiveness Results

The analysis of effectiveness was based on the ITT full study cohort of 222 SurVeil DCB subjects and 224 IN.PACT Admiral DCB subjects available for the 12- month time point. **Table 14** presents the primary effectiveness results for the full study cohort. The SurVeil™ Drug-Coated Balloon was concluded to be non-inferior to the IN.PACT® Admiral® Drug-Coated Balloon for the primary effectiveness endpoint of primary patency if the one-sided lower 97.5% confidence bound on the difference between groups (SurVeil DCB vs. IN.PACT DCB) is less than 15% (non-inferiority margin). In the ITT group, using multiple imputation, the rate of primary patency at 12 months was 81.7% in the Surveil DCB group compared to 85.9% in the IN.PACT Admiral DCB group. The difference in rates between the groups was -4.2% with one-sided lower 97.5% CL of -12.0%. Since this is higher than the pre-specified noninferiority margin of -15.0%, noninferiority is met (P-value for noninferiority 0.0035) and the SurVeil DCB is declared noninferior to IN.PACT Admiral DCB with respect to the primary effectiveness endpoint. A complete case analysis was carried out as a sensitivity analysis on ITT subjects with available data (i.e., subjects who experienced the primary effectiveness composite or had at least 335 days of follow-up) and provided

similar results. Kaplan-Meier plot of primary patency through 12 months is presented in **Figure 6**.

Table 14: Primary Effectiveness – Full Cohort, Intent-to-Treat (N=446)

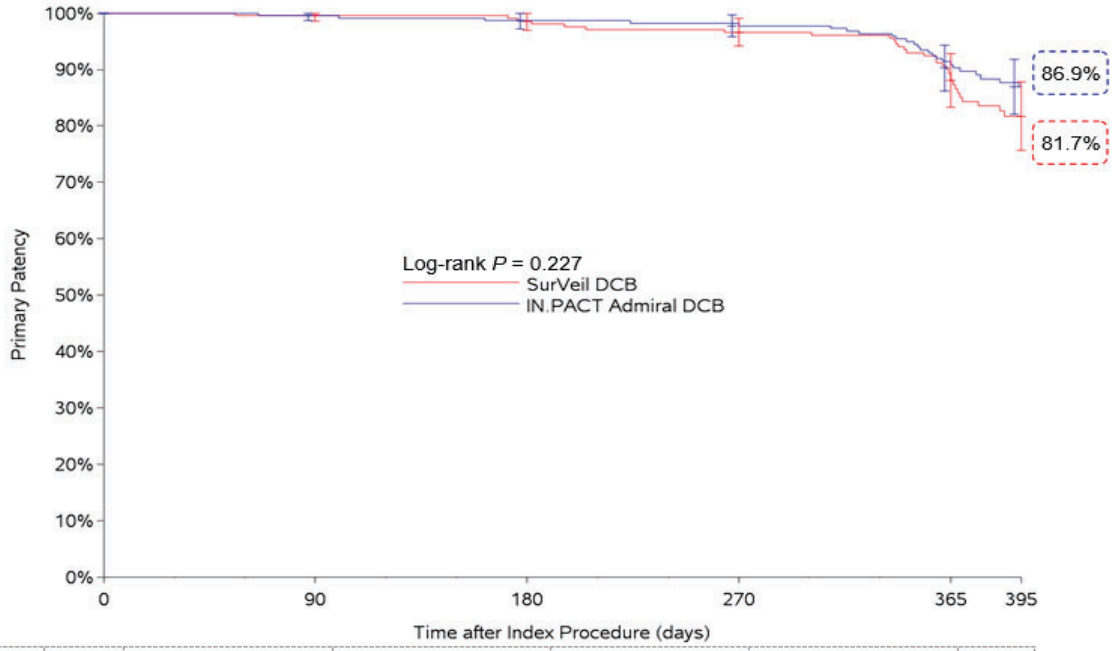
Primary Effectiveness Endpoint	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)	Difference [One-sided Lower 97.5% CL]	Non-inferiority Test P-value[1]
Primary patency through 12 months (ITT – Multiple Imputation)	**81.7% (75.9%,87.4%)**	**85.9% (80.9%,90.9%)**	**-4.2% [-12.0%]**	**0.0035**
Primary patency through 12 months (ITT - Complete Case)	82.2% (139/169)	86.7% (163/188)	-4.5% [-12.3%]	0.0041
Freedom from clinically driven TLR through 12 months[2]	91.9% (182/198)	94.4% (203/215)		
Freedom from binary restenosis through 12 months[3]	88.0% (139/158)	91.2% (165/181)		

[1] P-value is derived from one-sided Farrington-Manning test with noninferiority margin of 15% and a one-sided significance level of 0.025.
[2] Denominators include subjects with at least 335 days of follow-up or subjects experiencing clinically-driven TLR through 395 days.
[3] Denominators include subjects with evaluable 12-month DUS (within or outside the visit window of 365±30 days) or subjects whose stenosis status could have been imputed from later assessments.

Primary Patency Failure	0	[1, 90]	[91, 180]	[181, 270]	[271, 365]	[366-395]
SurVeil DCB (N=222 Subjects)						
# Entered	222	222	211	204	195	128
# Censored	0	10	5	5	52	31
# Events	0	1	2	4	15	8
Event-free [%]	100.0%	99.5%	98.6%	96.6%	88.0%	81.7%
Greenwood SE [%]	0.0%	0.5%	0.8%	1.3%	2.4%	3.1%
IN.PACT Admiral DCB (N=224 Subjects)						
# Entered	224	223	221	218	214	152
# Censored	1	1	1	2	47	30
# Events	0	1	2	2	15	5
Event-free [%]	100.0%	99.6%	98.7%	97.7%	90.3%	86.9%
Greenwood SE [%]	0.0%	0.4%	0.8%	1.0%	2.1%	2.5%
Tests Between Groups	Test	Chi-Square	Degree of Freedom	P-value		
	Log-Rank	1.4592	1	0.227		

The time to primary patency failure was defined as the time to binary restensosis based on date of 12-month DUS or clinically-driven TLR event date, whichever was earlier. For those who did not have primary patency failure, follow-up days were used.

Note: The p-value should be interpreted with caution because a hypothesis test for the survival endpoint was not pre-specified and was not adjusted for multiplicity



Number at risk						
SurVeil	222	211	204	195	133	89
IN.PACT Admiral	224	221	218	214	157	117

Figure 6: Kaplan-Meier Curve for Primary Patency to 395 days - ITT Analysis Population (N=446)

3. Secondary Endpoints

Secondary endpoints for the full ITT cohort for device/technical/procedure success, freedom from all-cause death, major target limb amputation and TVR through 30 days, target vessel patency (freedom from clinically driven TVR and freedom from binary restenosis), sustained clinical improvement, clinically driven TVR, historical MAEs, major target limb amputation, thrombosis at the target lesion, change in target limb Rutherford class from baseline, change in target limb PARC class from baseline, hemodynamic improvement as assessed by changes in resting target limb Ankle-Brachial Index (ABI) from baseline, change in Walking Impairment Questionnaire score from baseline, change in Six Minute Walk Test (6-MWT) from baseline, and change in Peripheral Artery Questionnaire (PAQ) from baseline are presented in **Table 15-Table 21**.

Table 15: Secondary Endpoints – Clinical Endpoints through 12 Months - ITT Analysis Population (N=446)

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Freedom from all-cause death, major target limb amputation and TVR At 30 days	99.5% 217/218	100.0% (223/223)
Target vessel patency[1] At 12 months	79.0% (139/176)	80.7% 159/197
Sustained clinical improvement[2]		

At 6 months	75.6% 158/209	77.5% (172/222)
At 12 months	61.1% 121/198	63.9% (140/219)
Clinically-driven TLR		
At 6 months	1.4% (3/209)	1.4% (3/222)
At 12 months	5.6% 11/198)	4.7% (10/215)
Historical MAE[3]		
At 6 months	2.8% 6/212)	1.8% 4/223)
At 12 months	8.4% 17/203)	7.8% 17/219)
Major target limb amputation		
At 6 months	0.0% 0/208)	0.0% (0/222)
At 12 months	0.0% (0/196)	0.0% (0/215)
Thrombosis at the target lesion		
At 6 months	0.0% 0/208)	0.0% (0/222)
At 12 months	0.0% (0/196)	0.0% (0/215)

Denominators for 30-day outcomes include subjects with at least 28 days of follow-up or subjects experiencing the event through 30 days.

Denominators for 6-month outcomes include subjects with at least 150 days of follow-up or subjects experiencing the event through 180 days.

Denominators for 12-month outcomes include subjects with at least 335 days of follow-up or subjects experiencing the event through 365 days, with the exception of target vessel patency, where TVRs through 395 days were counted.

[1] Target vessel patency, defined as freedom from clinically-driven TVR and freedom from binary restenosis (restenosis defined as DUS PSVR ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs), within 12 months. No angiograms were used to determine binary restenosis.

[2] Sustained clinical improvement, defined as freedom from major target limb amputation, TVR and worsening target limb Rutherford class, within 6 and 12 months.

[3] Historical MAEs, defined as composite of all-cause death, clinically-driven TLR, major target limb amputation, or thrombosis at the target lesion, within 6 and 12months.

Table 16: Change in Rutherford Classification from Baseline through 12 Months – ITT Analysis Population (N=446)

	SurVeil DCB (N=222 Subjects)	**IN.PACT Admiral DCB (N=224 Subjects)**
Change in Rutherford Classification from Baseline to 1 Month		
Grade ≥+3 Markedly improved	48.1% 101/210	40.9% (90/220)
Grade +2 Moderately improved	30.0% (63/210)	35.5% 78/220
Grade +1 Mildly improved	13.3% 28/210	13.2% (29/220)
No change	7.6% (16/210)	9.1% (20/220)
Grade -1 Mildly worsening	0.5% (1/210)	0.9% (2/220)
Grade -2 Moderately worsening	0.0% (0/210)	0.0% (0/220)
Grade ≤-3 Markedly worsening	0.5% (1/210)	0.5% (1/220)
Change in Rutherford Classification from Baseline to 6 Months		
Grade ≥+3 Markedly improved	51.8% 101/195	45.5% (95/209)
Grade +2 Moderately improved	33.3% (65/195)	33.5% (70/209)

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Grade +1 Mildly improved	7.7% (15/195)	14.4% (30/209)
No change	5.6% (11/195)	5.7% (12/209)
Grade -1 Mildly worsening	0.5% (1/195)	1.0% (2/209)
Grade -2 Moderately worsening	0.5% (1/195)	0.0% (0/209)
Grade ≤-3 Markedly worsening	0.5% (1/195)	0.0% (0/209)
Change in Rutherford Classification from Baseline to 12 Months		
Grade ≥+3 Markedly improved	44.8% 82/183	36.3% (74/204)
Grade +2 Moderately improved	27.3% 50/183	37.3% (76/204)
Grade +1 Mildly improved	15.3% 28/183	16.2% (33/204)
No change	9.8% 18/183)	7.8% 16/204)
Grade -1 Mildly worsening	2.7% 5/183)	1.5% (3/204)
Grade -2 Moderately worsening	0.0% 0/183)	1.0% (2/204)
Grade ≤-3 Markedly worsening	0.0% 0/183)	0.0% (0/204)

The denominator represents the number of subjects for whom Rutherford classification was available.

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Table 17: Change in Target Limb PARC Clinical Symptom Classification from Baseline through 12 Months – ITT Analysis Population (N=446)

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Change in PARC Classification from Baseline to 1 Month		
Grade ≥+3 Markedly improved	47.1% (99/210)	40.3% 89/221
Grade +2 Moderately improved	28.1% 59/210	35.3% 78/221
Grade +1 Mildly improved	14.8% 31/210	14.0% (31/221)
Grade 0 No change	8.6% 18/210)	8.1% 18/221)
Grade -1 Mildly worsening	1.0% (2/210)	1.8% 4/221)
Grade -2 Moderately worsening	0.0% (0/210)	0.0% (0/221)
Grade ≤-3 Markedly worsening	0.5% (1/210)	0.5% (1/221)
Change in PARC Classification from Baseline to 6 Months		
Grade ≥+3 Markedly improved	50.8% 99/195	44.2% 92/208
Grade +2 Moderately improved	33.3% (65/195)	33.7% 70/208
Grade +1 Mildly improved	8.2% 16/195)	14.4% 30/208
Grade 0 No change	6.2% (12/195)	6.7% 14/208)
Grade -1 Mildly worsening	0.5% (1/195)	1.0% 2/208)
Grade -2 Moderately worsening	0.5% (1/195)	0.0% 0/208)
Grade ≤-3 Markedly worsening	0.5% (1/195)	0.0% 0/208)
Change in PARC Classification from Baseline to 12 Months		

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Grade ≥+3 Markedly improved	43.7% 80/183	34.0% (69/203)
Grade +2 Moderately improved	29.0% 53/183	39.4% 80/203
Grade +1 Mildly improved	14.8% 27/183	15.3% (31/203)
Grade 0 No change	9.3% 17/183)	8.4% 17/203)
Grade -1 Mildly worsening	3.3% 6/183)	2.0% (4/203)
Grade -2 Moderately worsening	0.0% 0/183)	0.5% (1/203)
Grade ≤-3 Markedly worsening	0.0% 0/183)	0.5% (1/203)

The denominator represents the number of subjects for whom PARC clinical classification was available.

Table 18: Change in Ankle Brachial Index and Toe Brachial Index from Baseline through 12 Months – ITT Analysis Population (N=446)

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Change from Baseline to 6 Months		
Resting ABI		
Mean ± SD (N)	0.2±0.2 (183)	0.2±0.2 (199)
Median (Q1, Q3)	0.2 (0.1,0.4)	0.2 (0.1,0.3)
Range (min, max)	(-0.5,0.8)	(-0.8,1.1)
Resting ABI reduction ≥0.15	3.3% 6/183)	4.0% 8/199)
Resting TBI		
Mean ± SD (N)	0.2±0.2 (9)	0.2±0.2 (10)
Median (Q1, Q3)	0.3 (-0.1,0.3)	0.1 (0.1,0.2)
Range (min, max)	(-0.1,0.4)	(-0.0,0.7)
Resting TBI reduction ≥0.15	0.0% (0/9)	0.0% (0/10)
Change from Baseline to 12 Months		
Resting ABI		
Mean ± SD (N)	0.2±0.2 (174)	0.2±0.2 (189)
Median (Q1, Q3)	0.2 (0.0,0.3)	0.2 (0.1,0.4)
Range (min, max)	(-0.4,0.8)	(-0.7,0.9)
Resting ABI reduction ≥0.15	8.6% 15/174)	3.2% 6/189)
Resting TBI		
Mean ± SD (N)	0.1±0.2 (11)	0.0±0.2 (8
Median (Q1, Q3)	0.0 (-0.1,0.2)	0.1 (-0.0,0.2)
Range (min, max)	(-0.2,0.4)	(-0.4,0.3)
Resting TBI reduction ≥0.15	18.2% 2/11)	12.5% 1/8)

The denominator represents the number of subjects for whom the specific information was available.

Table 19: Secondary Endpoints – Change in Walking Impairment Questionnaire from Baseline through 12 Months – ITT Analysis Population

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Change in WIQ Score from Baseline to 1 Month		
Walking Impairment Score		
Mean ± SD (N)	39.8±37.8 (204)	39.5±38.2 (219)
Median (Q1, Q3)	50.0 (25.0,75.0)	50.0 (25.0,75.0)
Range (min, max)	(-75.0,100.0)	(-75.0,100.0)
Walking Distance Score		
Mean ± SD (N)	34.2±40.0 (203)	28.9±39.1 (218)
Median (Q1, Q3)	37.6 (1.8,70.3	23.4 (0.1,65.0)
Range (min, max)	(-90.6,99.4)	(-98.9,99.9
Walking Speed Score		
Mean ± SD (N)	20.8±32.1 (198)	18.9±29.0 (215)
Median (Q1, Q3)	15.2 (0.0,43.5)	15.2 (0.0,34.8
Range (min, max)	(-90.2,96.7)	(-81.5,100.0
Stair Climbing Score		
Mean ± SD (N)	24.1±37.9 (200)	19.4±38.8 (217)
Median (Q1, Q3)	20.8 (0.0,54.2	12.5 (0.0,45.8
Range (min, max)	(-100.0,95.8	(-100.0,100.0)
Change in WIQ Score from Baseline to 12 Months		
Walking Impairment Score		
Mean ± SD (N)	34.3±42.3 (181)	38.3±42.0 (205)
Median (Q1, Q3)	25.0 (0.0,75.0)	50.0 (25.0,75.0)
Range (min, max)	(-75.0,100.0)	(-75.0,100.0)
Walking Distance Score		
Mean ± SD (N)	29.9±38.2 (181)	30.9±40.3 (204)
Median (Q1, Q3)	26.3 (0.0,62.9)	27.7 (1.1,66.9)
Range (min, max)	(-89.5,99.4	(-98.2,100.0
Walking Speed Score		
Mean ± SD (N)	19.2±33.4 (178)	21.2±34.7 (205)
Median (Q1, Q3)	17.4 (0.0,43.5)	17.4 (0.0,43.5)
Range (min, max)	(-87.0,96.7	(-96.7,100.0)
Stair Climbing Score		
Mean ± SD (N)	20.7±38.0 (180)	24.1±40.5 (205)
Median (Q1, Q3)	20.8 (-4.2,47.9)	20.8 (0.0,54.2
Range (min, max)	(-100.0,100.0)	(-100.0,100.0)

The denominator represents the number of subjects for whom the specific score was available.

Table 20: Analysis of Secondary Endpoints – Change in 6-minute Walk Test from Baseline to 12 Months - ITT Analysis Population

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
Change in 6-MWT from Baseline to 12 Months		
Walking Distance (m)		
Mean ± SD (N)	45.8±118.8 163	60.7±113.6 180
Median (Q1, Q3)	44.0 (-10.0,108.2)	45.3 (-5.0,125.4)
Range (min, max)	(-233.0,692.1)	(-234.1,500.0)

The denominator represents the number of subjects for whom the specific information was available.

Table 21: Secondary Endpoints – Improvement in Peripheral Artery Questionnaire Scores from Baseline through 12 Months – ITT Analysis Population (N=446)

	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)
1 Month		
Physical Function Score Improvement	78.7% 140/178	81.6% 160/196
Stability Score Improvement	74.9% (152/203)	75.8% 166/219
Symptom Score Improvement	85.2% 173/203	84.5% 185/219
Treatment Satisfaction Score Improvement	34.7% (70/202)	36.5% 80/219
Quality of Life Score Improvement	84.2% 171/203	86.8% 190/219
Social Limitation Score Improvement	76.3% (135/177)	81.2% 164/202
Summary Score Improvement	89.2% 181/203	90.0% (197/219)
12 Months		
Physical Function Score Improvement	75.8% 122/161	79.2% 141/178
Stability Score Improvement	41.1% 74/180	42.4% 87/205
Symptom Score Improvement	82.2% 148/180	80.5% 165/205
Treatment Satisfaction Score Improvement	34.6% (62/179)	34.6% (71/205)
Quality of Life Score Improvement	85.6% 154/180	82.4% 169/205
Social Limitation Score Improvement	75.9% (123/162)	75.4% 138/183
Summary Score Improvement	86.1% 155/180	83.4% 171/205

Improvement is defined as increase in score of >0.

4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: age, smoking, gender, diabetes, chronic renal insufficiency, lesion length, lesion calcification, lesion type, bailout stenting, and residual stenosis. The TRANSCEND study results have been analyzed by different pre-defined sub-groups to investigate the consistency of results through 12 months. The primary safety endpoint at 12 months (**Table 22**) and primary effectiveness endpoint of primary patency at 12 months (**Table 23**) are illustrated for each subgroup in the tables below. Primary safety endpoint results were consistent across all subgroups

except for the age subgroup, where results differed between subjects younger than 65 years and subjects older than 65 years (P=0.0624 <0.15; the prespecified level of significance for the subgroup analysis was 0.15). Primary effectiveness endpoint results were consistent across all subgroups as evidenced by P for interaction >0.15.

Table 22: Subgroup Analysis: Primary Safety Endpoint - ITT Analysis Population (N=446)

Primary Safety Endpoint	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)	Difference [95% CI]	P-value for Interaction of Treatment and Subgroup[1]
Age				0.0624
Age ≤65	87.0% 60/69)	91.6% 87/95)	-4.6%[-14.3%,5.1%]	
Age >65	94.6% (123/130)	88.5% 108/122	6.1%[-0.8%,12.9%]	
Smoking				0.2576
Current smoker	95.1% 78/82)	89.0% 73/82)	6.1%[-2.1%,14.3%]	
Former smoker	90.7% 78/86)	88.9% 88/99)	1.8%[-6.9%,10.5%]	
Never smoked	87.1% 27/31)	94.4% (34/36)	-7.3%[-21.3%,6.6%]	
Gender				0.6976
Male	92.6% (113/122)	89.7% 122/136	2.9%[-4.0%,9.8%]	
Female	90.9% (70/77)	90.1% 73/81)	0.8%[-8.3%,9.9%]	
Diabetes Mellitus				0.5935
Diabetics	89.4% 76/85)	88.6% 78/88)	0.8%[-8.5%,10.1%]	
Non-diabetics	93.9% (107/114)	90.7% (117/129)	3.2%[-3.5%,9.8%]	
Chronic Renal Insufficiency				0.6561
Chronic renal insufficiency	95.5% (42/44)	91.7% (22/24)	3.8%[-8.9%,16.4%]	
Non-chronic renal insufficiency	91.0% (141/155)	89.6% 172/192	1.4%[-4.9%,7.6%]	
Lesion Length				0.4027
Total lesion length ≤90mm	93.3% (112/120)	93.5% 129/138	-0.1%[-6.2%,5.9%]	
Total lesion length >90mm	89.9% 71/79)	83.5% 66/79)	6.3%[-4.2%,16.9%]	
Lesion Calcification[2]				0.3226
None/mildly calcified	91.3% (94/103)	92.2% (94/102)	-0.9%[-8.4%,6.7%]	
Moderately/severely calcified	92.7% 89/96)	87.7% 100/114	5.0%[-3.0%,12.9%]	
Lesion Type				0.9719
de novo lesion	92.2% (177/192)	89.6% 189/211	2.6%[-3.0%,8.2%]	
Restenotic lesion	85.7% 6/7)	100.0% (6/6)	-14.3%[-40.2%,11.6%]	
Bailout Stenting				0.5923
Subjects with bailout stents	93.8% 15/16)	85.7% 12/14)	8.0%[-13.8%,29.9%]	
Subjects without bailout stents	91.8% 168/183	90.1% 183/203	1.7%[-4.1%,7.4%]	
Residual Stenosis after Pre-dilatation				0.9132
<50%	92.7% (140/151)	90.7% (146/161)	2.0%[-4.1%,8.1%]	
≥50%	89.7% 35/39)	86.0% 43/50)	3.7%[-9.8%,17.3%]	

[1] P-value is derived from logistic regression on the primary safety endpoint with treatment, subgroup, and interaction of treatment and subgroup as covariates.

[2] Calcification is based on angiographic core laboratory data.

Table 23: Subgroup Analysis: Primary Effectiveness Endpoint - ITT Analysis Population (N=446)

Primary Effectiveness Endpoint	SurVeil DCB (N=222 Subjects)	IN.PACT Admiral DCB (N=224 Subjects)	Difference [95% CI]	P-value for Interaction of Treatment and Subgroup[1]
Age				0.4973
Age ≤65	82.3% 51/62)	89.3% 75/84)	-7.0%[-18.6%,4.6%]	
Age >65	82.2% 88/107	84.6% 88/104	-2.4%[-12.4%,7.7%]	
Smoking				0.9977
Current smoker	86.3% 63/73)	90.1% (64/71)	-3.8%[-14.3%,6.7%]	
Former smoker	81.4% 57/70)	86.7% 72/83)	-5.3%[-17.0%,6.4%]	
Never smoked	73.1% (19/26)	79.4% (27/34)	-6.3%[-28.1%,15.5%]	
Gender				0.7177
Male	82.9% 87/105	88.1% 104/118	-5.3%[-14.6%,4.0%]	
Female	81.3% 52/64)	84.3% 59/70)	-3.0%[-15.8%,9.8%]	
Diabetes Mellitus				0.6602
Diabetics	72.7% 48/66)	81.1% 60/74)	-8.4%[-22.3%,5.6%]	
Non-diabetics	88.3% (91/103)	90.4% (103/114)	-2.0%[-10.2%,6.2%]	
Chronic Renal Insufficiency				0.9681
Chronic renal insufficiency	81.6% 31/38)	86.4% 19/22)	-4.8%[-23.7%,14.1%]	
Non-chronic renal insufficiency	82.4% 108/131	86.7% 143/165	-4.2%[-12.6%,4.1%]	
Lesion Length				0.6228
Total lesion length ≤90mm	88.5% 92/104	90.1% (109/121)	-1.6%[-9.7%,6.5%]	
Total lesion length >90mm	72.3% (47/65)	80.6% 54/67)	-8.3%[-22.7%,6.1%]	
Lesion Calcification[2]				0.8860
None/mildly calcified	82.6% 76/92)	86.5% 77/89)	-3.9%[-14.4%,6.6%]	
Moderately/severely calcified	81.8% 63/77)	86.9% 86/99)	-5.1%[-15.9%,5.8%]	
Lesion Type				0.2236
de novo lesion	84.0% 136/162	86.8% 158/182	-2.9%[-10.4%,4.6%]	
Restenotic lesion	42.9% (3/7)	83.3% 5/6)	-40.5%[-87.7%,6.8%]	
Bailout Stenting				0.7828
Subjects with bailout stents	84.6% 11/13)	91.7% (11/12)	-7.1%[-32.1%,18.0%]	
Subjects without bailout stents	82.1% 128/156	86.4% 152/176	-4.3%[-12.2%,3.6%]	
Residual Stenosis after Pre-dilatation				0.9893
<50%	84.9% 107/126	87.9% 123/140	-2.9%[-11.2%,5.3%]	
≥50%	77.1% (27/35)	81.4% 35/43)	-4.3%[-22.4%,13.9%]	

[1] P-value is derived from logistic regression on the primary effectiveness endpoint with treatment, subgroup, and interaction of treatment and subgroup as covariates.

[2] Calcification is based on angiographic core laboratory data.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 72 principal investigators and 185 sub-investigators, of which none were full-time or part-time employees of the sponsor and one (1) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None of the investigators
- Significant payment of other sorts: One (1) investigator
- Proprietary interest in the product tested held by the investigator: None of the investigators
- Significant equity interest held by investigator in sponsor of covered study: None of the investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

PREVEIL Early Feasibility Study - Pharmacokinetics

The pharmacokinetic (PK) profile of paclitaxel following treatment with SurVeil DCB was evaluated in 13 patients receiving 1300 – 3800 µg of paclitaxel. Mean plasma concentration peaked immediately post-procedure (Cmax 2.25 ± 2.5 ng/mL) and was undetectable at 30 days. The AUC0-last was 3.74 ± 3.2 hr·ng/mL. These data indicate that treatment with the SurVeil DCB provides low systemic exposure of paclitaxel.

Late Mortality

Previous meta-analyses of randomized controlled trials of paclitaxel-coated balloons and paclitaxel-eluting stents used to treat peripheral arterial disease in the femoropopliteal arteries have identified an increased risk of late mortality at 2 years and beyond (1,2). The TRANSCEND Study was not included in these analyses. The magnitude and mechanism for the increased risk in mortality is currently unclear. Because there is limited follow-up data at 3 years from the TRANSCEND Study, in order to demonstrate that the Surveil DCB does not represent an unacceptable risk of late mortality compared to the currently marketed devices, additional analyses were performed.

The TRANSCEND trial is ongoing through 5 years, and in order to demonstrate that the SurVeil DCB does not represent an unacceptable risk of late mortality compared to the currently marketed IN.PACT Admiral DCB, additional exploratory analyses were performed including: 1) Bayesian predictive modeling to estimate 2- and 3-year mortality

rates and 2) Kaplan-Meier (KM) analyses. Both analyses were conducted based on all available data provided by the sponsor. Vital status is known at a time point if a subject completed the visit for that time point or later, or if a vitality assessment was completed for an exited subject confirming the subject was alive beyond that time point, or if the subject died prior to the time point. The analysis data set included data through June 30, 2022.

Table 24: TRANSCEND Predictive Mortality Analysis Vital Status

Time	SurVeil DCB (n)		IN.PACT Admiral DCB (n)		Total (n)	
	Unknown	Known	Unknown	Known	Unknown	Known
Randomization	0	222	0	224	0	446
6-Months (180 days)	2	220	0	224	2	444
1-Year (365 days)	4	218	0	224	4	442
2-Years (730 days)	8	214	1	223	9	437
3-Years (1095 days)	12	170	5	189	17	359

Kaplan Meier Analysis:

Figure 7 summarizes of the results of the 3-year mortality analyses for the SurVeil DCB.

	Time after Procedure (days)				
All-Cause Survival	**0**	**180**	**365**	**730**	**1095**
SurVeil DCB					
# Entered	222	216	212	200	156
# Censored	-	2	3	4	42
# Events	-	4	7	18	24
Survival Rate [%]	-	98.2%	96.8%	91.8%	89.0%
Greenwood SE [%]	-	0.90%	1.19%	1.86%	2.13%
95% Confidence Interval[1]	-	[96.4, 100.0%]	[94.5, 99.2%]	[88.2, 95.5%]	[84.9, 93.2%]
IN.PACT Admiral DCB					
# Entered	224	223	217	208	164
# Censored	-	0	0	0	33
# Events	-	1	7	16	27
Survival Rate [%]	-	99.6%	96.9%	92.9%	87.8%
Greenwood SE [%]	-	0.45%	1.16%	1.72%	2.21%

	Time after Procedure (days)				
All-Cause Survival	**0**	**180**	**365**	**730**	**1095**
95% Confidence Interval[1]	-	[98.7, 100.0%]	[94.6, 99.2%]	[89.5, 96.3%]	[83.5, 92.2%]
[1]Log Confidence Intervals					

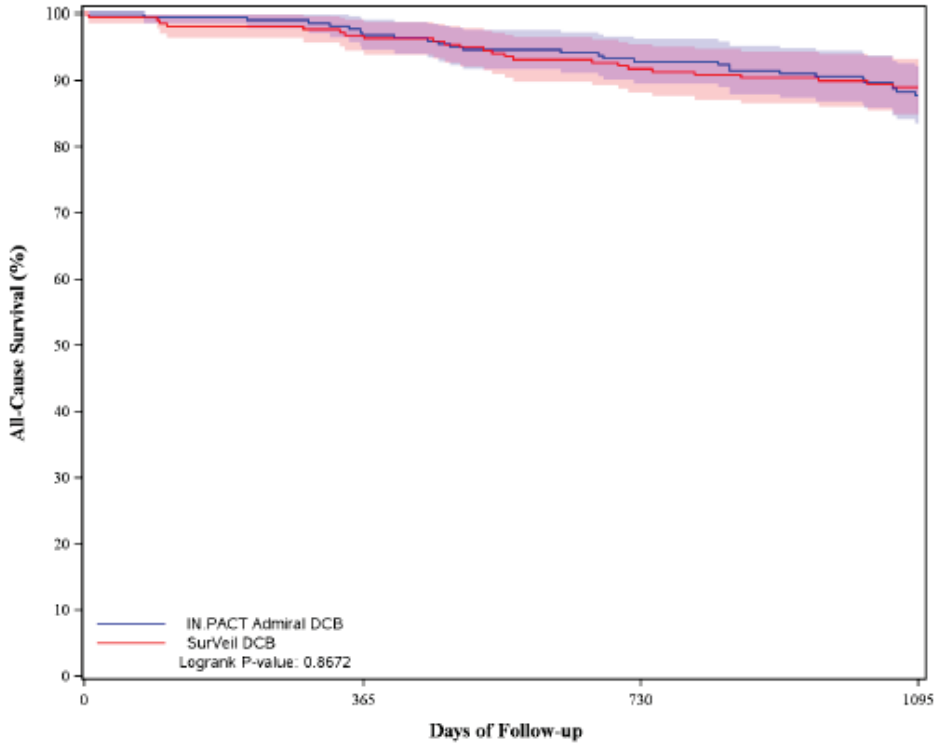

Figure 7: Kaplan-Meier estimates of survival through 3 years by arm

Bayesian Predictive Modeling:
A Bayesian piecewise constant hazard model was used for estimation and prediction of unobserved survival times through 3 years comparing the SurVeil DCB arm to the IN.PACT Admiral DCB arm from the TRANSCEND trial. The predictions of survival are based on Kaplan-Meier estimates of 2-and 3-year survival calculated with observed and predicted future data for the randomized groups. The Kaplan Meier estimate of the survival rate was 91.8% and 89.0% in the SurVeil DCB group and 92.9% and 87.8% in the IN.PACT Admiral DCB group at 2 and 3 years, respectively. For both the 2-and 3-year, the predictive analysis demonstrates that the mortality risk of the SurVeil DCB treatment group is comparable to that of the IN.PACT Admiral DCB group.

Based on the totality of the data provided, the SurVeil DCB does not appear to present an unacceptable mortality risk at 3 years, compared to currently marketed paclitaxel-coated device IN.PACT Admiral DCB.

The TRANSCEND trial results were not included in any of these published meta-analyses. The magnitude and mechanism for the increased risk in mortality is currently unclear.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The TRANSCEND Study is a global, prospective, multi-center, single-blind, randomized, controlled trial to evaluate the noninferiority of the SurVeil DCB compared to the Food and Drug Administration (FDA)-approved Medtronic IN.PACT Admiral DCB. Subjects with a stenosed femoral and/or popliteal artery were randomized in a 1:1 ratio to either the SurVeil DCB or the IN.PACT Admiral DCB.

The TRANSCEND Study met its primary effectiveness endpoint, with the SurVeil DCB demonstrating noninferior patency compared to the IN.PACT Admiral DCB.

The 12-month primary patency rate was 81.7% in the Surveil DCB group and 85.9% in the IN.PACT Admiral DCB group. Target vessel patency (79.0% SurVeil DCB and 80.7% IN.PACT Admiral DCB), sustained clinical improvement (61.1% and 63.9%, respectively), CD-TLR (5.6% and 4.7%, respectively), and historical MAE 8.4% and 7.8%, respectively) are comparable, with no statistical or clinical difference shown.

Secondary endpoints were also comparable for device success, CD-TLR, functional outcomes, and quality of life measures.

Subjects in the Surveil DCB group demonstrated comparable results in secondary endpoints and patient outcome measures (e.g. Rutherford, PARC classification, 6-minute walk test, etc.) to subjects in the IN.PACT Admiral DCB group at 12 months. These results support the clinical benefit of the SurVeil DCB for the treatment of stenotic lesions in femoral and popliteal arteries.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. Pre-clinical studies have shown some elevated risk of toxicity at higher dosages, but this risk is mitigated through inclusion of labeling restricting use to not more than 200 mm of total balloon length. The TRANSCEND Study met its primary safety endpoint at 12 months, with the SurVeil DCB demonstrating non-inferior safety compared to the IN.PACT Admiral DCB. No safety or toxicity concerns were noted in the clinical study.

The TRANSCEND Study met its primary safety endpoint, with the SurVeil DCB demonstrating noninferior safety compared to the IN.PACT Admiral DCB.

The 12-month freedom from the primary safety composite was 91.7% in the SurVeil DCB group and 89.6% in the IN.PACT Admiral DCB group. Through 12 months, there were no target limb amputations and no target lesion thromboses.

Overall, the type and frequency of AEs observed during the TRANSCEND study are expected for this patient population and therapeutic area. The most common device-related SAEs were peripheral artery restenosis, occlusion, or stenosis. There were no unanticipated adverse device effects identified or reported.

The mortality rates through 12 months were similar for both groups. The Kaplan Meier mortality estimate at 1 year is 3.4% (95% CI: 0.9%, 5.8% CI) for the SurVeil DCB and 3.3% (95% CI: 0.9%, 5.6%) for the IN.PACT Admiral DCB. Because there is limited follow up data at 2 and 3 years from the TRANSCEND trial, in order to demonstrate that the SurVeil DCB does not represent an unacceptable risk of late mortality compared to the currently marketed IN.PACT Admiral DCB, additional analyses were performed including: 1) Bayesian predictive modeling to estimate 2- and 3-year mortality rates and 2) Kaplan-Meier (KM) analyses. Both analyses were conducted based on all available data. Based on the totality of the data provided, the SurVeil DCB does not appear to present an unacceptable 2- and 3-year mortality risk compared to currently marketed paclitaxel-coated IN.PACT Admiral DCB.

These results support the safety of the SurVeil DCB for the treatment of stenotic lesions in femoral and popliteal arteries.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval, as described above. Benefits of the SurVeil DCB include non-inferior patency and clinically-driven target lesion revascularization, sustained clinical improvement, and improved quality of life.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Risks of the SurVeil DCB include adverse effects related to the SurVeil DCB and procedure, including the potential for drug-related toxicity. FDA has determined that, when used in accordance with the indications for use, the probability of experiencing drug-related toxicity is low. Risk mitigation regarding drug-related toxicity has been included as a labeling warning, which further reduces the probability of this harm.

The probable benefit of the SurVeil DCB, including reducing re-interventions and improving patients' symptoms and quality of life, outweigh the probable risks associated with use of the device. Additional factors considered in determining probable risks and benefits for the SurVeil DCB device included:

- The clinical study provided adequate follow-up (12 months) to evaluate safety and effectiveness, with measures taken to assess the impact of missing data. Longer-term follow-up is ongoing.

- The device is intended for use in subjects with peripheral arterial disease of the femoral and popliteal arteries in lesion lengths ≤180 mm. The results adequately support use in the identified population.

- There are alternative treatments available for this disease, such as percutaneous transluminal angioplasty (PTA) alone and other drug coated balloons. This product has shown similar safety and effectiveness results to these approved products.

- The frequency and types of adverse events reported throughout the pivotal clinical study are in alignment with what is expected in the studied patient population and therapeutic area. No unanticipated adverse device effects were identified or reported in the study.

- In considerations of the mortality signal observed in patients after 2 years post-treatment with paclitaxel-coated devices used to treat femoropopliteal atherosclerotic disease, predictive modeling of SurVeil DCB mortality data was evaluated to predict that the SurVeil DCB does not represent an unacceptable or increased risk of late mortality compared to marketed devices.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives, or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

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

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The results from the TRANSCEND study provides evidence of the safety and effectiveness of the SurVeil DCB. The device is appropriate for its intended use. The data demonstrates that the SurVeil DCB provides clinical benefit with an acceptable safety profile that is noninferior to the IN.PACT Admiral DCB.

XIV. CDRH DECISION

CDRH issued an approval order on 6/16/2023. The final conditions of approval cited in the approval order are described below.

Non-Clinical

1. You will continue to collect particulate data for new batches manufactured of the SurVeil DCB. Within 1 year of the Approval Order, you must submit a PMA report providing complete particulate data for the new batches along with the batch details (lot numbers, manufacturing date, number of units used for testing, etc.). As appropriate, data should be pooled with previous particulate data to review the particulate specification. Within this report, you should provide a scientific rationale based on the expanded dataset to support the continued use of the current particulate specifications. If the new dataset does not demonstrate that the current particulate specifications adequately control the quality of your product, you must submit a PMA supplement to propose new particulate specifications based on this expanded dataset.

2. Long-term drug stability studies will be completed on three total finished product batches representing the commercial process each year, evaluating one lot of the largest-longest device size (i.e., 7x150 mm), one intermediate size (i.e., one of four proposed intermediate sizes), and one lot of the shortest-smallest device size (i.e., 4x40 mm). Batches for these studies will be stored at Long Term Conditions of 25°C ± 2°C/60% RH ± 5%, per ICH Q1A(R2). Testing will occur at 0, 3, 6, 9, 12, 18, and 24 months using an alternative matrixing approach defined in Table 46 of P210025/A001. Be advised that failure to comply with any post-approval requirement, including test protocol, sampling size, sampling plan, and acceptance criteria, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2 .

Clinical

1. *The TRANSCEND Continued Follow-Up Study:* This study will evaluate the long-term safety and effectiveness of the SurVeil DCB in 446 subjects from the premarket study. The TRANSCEND Study was designed as a global, multicenter, single blind, randomized (1:1 SurVeil DCB to IN.PACT Admiral DCB) trial. Subjects will be followed annually through 5 years post-procedure, and all efforts must be made to minimize the amount of missing long-term data (a minimum of 75% of subjects should be evaluable for the primary efficacy endpoint at 3 years, and a minimum of 90% of subjects should have a documented mortality status at 5 years).

   The primary effectiveness endpoint is primary patency, defined as a composite of freedom from binary restenosis (restenosis defined as duplex ultrasound [DUS] peak systolic velocity ratio [PSVR] ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs) and clinically-driven target lesion revascularization (TLR) through 12 months post-index procedure.

The primary safety endpoint is a composite of freedom from device- and procedure-related death through 30 days post-index procedure and freedom from major target limb amputation (above the ankle) and clinically-driven target vessel revascularization (TVR) through 12 months post-index procedure.

The endpoints to be assessed through 3 years post-procedure are rate of: (1) major adverse events (MAE), (2) clinically-driven target lesion revascularization (CD-TLR), and (3) major target limb amputation. Mortality is to be assessed through 5 years post-procedure.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Food and Drug Administration June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee. Available Online: https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-19-20-2019-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting.

2. Katsanos, K., S. Spiliopoulos, P. Kitrou, M. Krokidis, and D. Karnabatidis. 2018. 'Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials', J Am Heart Assoc, 7: e011245.