SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Peripheral Transluminal Angioplasty Catheter
Device Trade Name:	Ranger™ Paclitaxel-Coated PTA Balloon Catheter
Device Procode:	ONU
Applicant's Name and Address:	Boston Scientific Corporation Three Scimed Place Maple Grove, MN 55311
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P190019
Date of FDA Notice of Approval:	October 30, 2020

II. INDICATIONS FOR USE

The Ranger Paclitaxel-Coated PTA Balloon Catheter is indicated for percutaneous transluminal angioplasty (PTA) of de novo or restenotic lesions up to 180 mm in length located in native superficial femoral and proximal popliteal arteries (SFA/PPA) with reference vessel diameters of 4 - 7 mm.

III. CONTRAINDICATIONS

The Ranger Paclitaxel-Coated PTA Balloon Catheter is contraindicated for use in patients

- With known hypersensitivity to paclitaxel (or structurally-related compounds).
- Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children
- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system

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 future device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients.

Additional warnings and precautions can be found in the Ranger™ Paclitaxel-Coated PTA Balloon Catheter labeling.

V. DEVICE DESCRIPTION

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

- Uncoated PTA Balloon Catheter: Percutaneous transluminal angioplasty 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

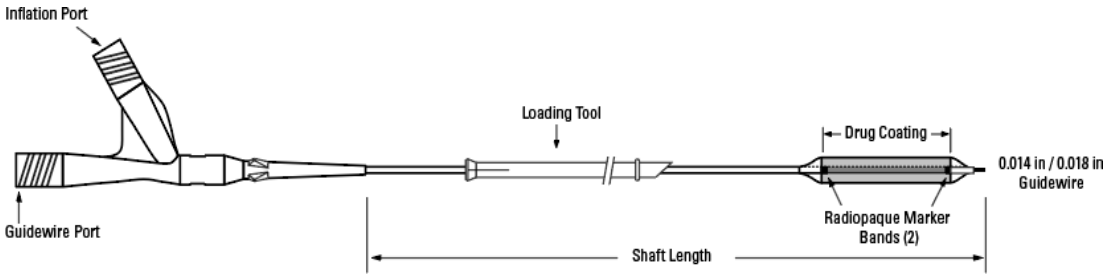


Figure 1: Schematic of the Ranger DCB PTA Catheter Component

The Ranger DCB is available in multiple balloon sizes and catheter working lengths, as listed in **Table 1**, and is compatible with 0.014" / 0.018" guidewires.

Table 1: Ranger DCB Product Matrix

Balloon Diameter (mm)	Balloon Length (mm)							
	30	40	60	80	100	120	150	200
4.0	X	X	X	X	X	X	X	X
5.0	X	X	X	X	X	X	X	X
6.0	X	X	X	X	X	X	X	X
7.0	X	X	X	X	X	X	X	X

Note: Catheters are available in working lengths of 80 and 135 cm (balloon lengths 30 – 100 mm) and 90 and 150 cm (balloon lengths 120 – 200 mm)

Drug Component

The proprietary Ranger DCB TransPax™ coating consists of active pharmaceutical paclitaxel at a nominal drug dose density of 2 μg/mm^2 of balloon surface, and acetyl tributyl citrate (ATBC) excipient which provides drug coating durability and drug transfer to the vessel wall upon balloon expansion.

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

Table 2: Nominal Paclitaxel Content by Balloon Size

Balloon Diameter (mm)	Balloon Length (mm)							
	30	40	60	80	100	120	150	200
4.0	782 μg	1043 μg	1564 μg	2086 μg	2607 μg	3100 μg	3878 μg	5165 μg
5.0	975 μg	1301 μg	1951 μg	2601 μg	3251 μg	3978 μg	4942 μg	6592 μg
6.0	1100 μg	1467 μg	2200 μg	3108 μg	3889 μg	4809 μg	5975 μg	7966 μg
7.0	1283 μg	1711 μg	2714 μg	3626 μg	4538 μg	5564 μg	6958 μg	9266 μg

Active Pharmaceutical Ingredient (API) – Paclitaxel

The API of the Ranger DCB is paclitaxel. The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division. The CAS Registry number of paclitaxel is 33069-62-4. The systematic IUPAC chemical name is (2aR-(2aα,4β,4aβ,6β,9α(α R*,βS*),11α,12α,12bα))-β-(Benzoylamino)- α-hydroxybenzenepropanoic acid 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester, and the chemical formula is $C_{47}H_{51}NO_{14}$. The chemical structure of paclitaxel is illustrated in **Figure 2**.

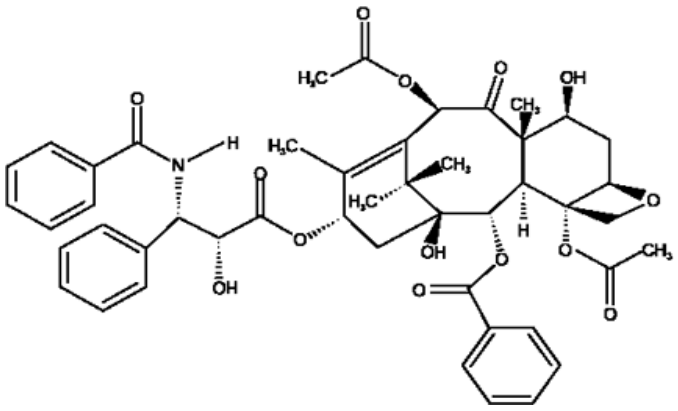


Figure 2: Paclitaxel Chemical Structure

Excipient – Acetyl Tributyl Citrate (ATBC)

The plasticizer ATBC is used as an excipient to facilitate delivery and transfer of the active pharmaceutical ingredient (paclitaxel) from the balloon to the arterial vessel wall upon balloon expansion. The chemical structure of ATBC is shown in **Figure 3** below.

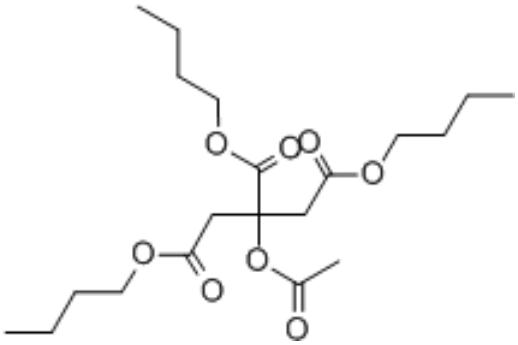


Figure 3: ATBC Chemical Structure

Mechanism of Action

The primary mode of action for the Ranger DCB is mechanical dilatation of de novo 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 arterial vessel wall.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

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

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

VII. MARKETING HISTORY

The Ranger Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) has been available for distribution in the European Union (EU) since receiving CE Mark in July 2014 for balloon lengths 30 to 100 mm, with balloon lengths 120 to 200 mm receiving CE Mark in July 2017. The Ranger DCB has not been withdrawn from marketing from any region.

The Ranger DCB is available for commercial distribution in the 69 countries listed in **Table 3** with a general peripheral indication.

Table 3: Commercial Availability of the Ranger DCB

Argentina	Armenia	Australia	Austria	Bahrain	Bangladesh
Belgium	Brunei	Bulgaria	Canada	Chile	Colombia
Costa Rica	Croatia	Czech Republic	Denmark	Dominican Republic	Egypt
El Salvador	Finland	France	Germany	Great Britain	Greece
Hong Kong	Hungary	India	Indonesia	Ireland	Israel
Italy	Jordan	Kuwait	Latvia	Lebanon	Lithuania
Macedonia	Malaysia	Malta	Mexico	Morocco	Netherlands
New Zealand	Norway	Oman	Pakistan	Palestinian territories	Panama
Paraguay	Peru	Philippines	Poland	Portugal	Romania
Saudi Arabia	Singapore	Slovakia	Slovenia	South Africa	South Korea
Spain	Sweden	Switzerland	Taiwan	Thailand	Turkey
United Arab Emirates	Uruguay	Vietnam			

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) which may be associated with the use of Ranger Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) include, but are not limited to:

- Allergic reaction (device, contrast medium, medications)
- Arteriovenous fistula
- Death
- Hemorrhage / Bleeding
- Hypotension / Hypertension
- Infection / Sepsis
- Pseudoaneurysm
- Thromboembolic episodes
- Vascular thrombosis
- Vessel injury (e.g., dissection, perforation, rupture)
- Vessel occlusion
- Vessel spasm

Potential adverse effects, not captured above, that may be due to systemic administration of paclitaxel, include, but are not limited to, the following:

- Allergic / immunologic reaction to drug (paclitaxel or structurally-related compounds) or coating or its individual components
- Alopecia
- Anemia
- Blood product transfusion
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
- Myalgia/Arthralgia
- Peripheral neuropathy

Apart from hypersensitivity reactions (allergic / immunologic reactions), the likelihood of paclitaxel related adverse events is low, due to the low exposure.

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A series of non-clinical laboratory studies related to the product were performed to evaluate the device, including: biocompatibility studies, *in vitro* engineering testing, coating characterization testing, analytical pharmaceutical testing, packaging testing, stability and shelf life testing, sterilization, and Good Laboratory Practice (GLP) animal studies. A summary for each of the evaluations is provided below.

A. Biocompatibility Studies

Biocompatibility testing of the Ranger Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) was conducted separately on uncoated Ranger PTA balloon catheters and on isolated balloon components containing drug coating. For the purposes of this testing, the uncoated Ranger PTA balloon catheter was categorized as an externally communicating device with limited contact duration (<24 hours) with circulating blood, and the balloon component with drug coating was categorized as an implant device with permanent blood contact (>30 days). In addition, chemical characterization was conducted *in vitro* on both uncoated and drug-coated balloon components.

The endpoints of sub-acute (sub-chronic) toxicity, chronic toxicity, and implantation were evaluated using coated Ranger PTA balloon catheters as part of *in vivo* studies conducted to evaluate the safety and effectiveness of the device in porcine iliofemoral artery model, as described in Section IX.H, Animal Studies, below. These additional animal studies demonstrated a lack of inflammation and toxicity when the product was used in a clinically-relevant vascular location.

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 Ranger DCB is biocompatible for its intended use. A summary of the biocompatibility testing and results can be found in **Table 4**.

Table 4: Summary of Biocompatibility Testing

Test / ISO Reference	Test Name	Uncoated Catheter	Coated Balloon	Results
Cytotoxicity ISO 10993-5	MEM Endpoint Dilution Assay	X	X	Non-cytotoxic for uncoated catheter; acceptable response for coated balloon*
	Direct Cytotoxicity	--	X	Non-cytotoxic
Sensitization ISO 10993-10	Guinea Pig Maximization	X	X	Non-sensitizing
Irritation	Intracutaneous	X	X	Non-irritant

ISO 10993-10	Reactivity			
Systemic Toxicity ISO 10993-11	Acute Systemic Toxicity	X	X	Non-toxic
	Sub-acute (Sub-chronic) Systemic Toxicity	Catheter + drug-coated balloon		Non-toxic#
	Chronic Systemic Toxicity	Catheter + drug-coated balloon		Non-toxic#
Pyrogenicity ISO 10993-11	Material-Mediated Rabbit Pyrogenicity	X	X	Non-pyrogenic
Implantation ISO 10993-6	Implantation	Catheter + drug-coated balloon		Acceptable local tissue response#
Hemocompatibility ISO 10993-4	Hemolysis Direct Contact	X	X	Non-hemolytic
	Hemolysis Extract Method	X	X	Non-hemolytic
	Complement Activation C3a and SC5b-9	X	X	Not a complement activator
	In vivo thrombogenicity	Catheter + drug-coated balloon		Non-thrombogenic#
Chemical Characterization ISO 10993-18	Exhaustive Extraction and Analysis by GC/MS, LC/MS, ICP/MS	X (balloon only)	X	Extractables do not pose toxicity concerns for the endpoints of carcinogenicity, genotoxicity, and subchronic/chronic systemic toxicity.

***** Cytotoxic response from the neat extract of the balloon, but considered acceptable after extract dilution and based on acceptable implantation response from the GLP safety study, noted in Section H below.

Endpoint was assessed in the GLP safety study, as noted in Section H below.

B. *In Vitro* Bench Testing

An overview of the functional engineering testing performed on the Ranger DCB is provided in **Table 5**. The table includes the test performed, the objective of the tests, the acceptance criteria (as applicable), and the result of the test.

Table 5: Summary of Functional Testing Performed

Test	Testing Objective	Acceptance Criteria (Specification)	Pass / Fail
Catheter Profiles	Demonstrate the catheter inner diameter (ID) and outer diameter (OD) meets the	OD: The catheter profiles (mm) must be:	Pass

Balloon Diameter	Max Crossing Profile	Shaft Profile
4	≤ 1.78	Characterization only

<table>
<tr><th>Test</th><th>Testing Objective</th><th>Acceptance Criteria (Specification)</th><th>Pass / Fail</th></tr>
<tr><td></td><td>labeled values</td><td>
<table>
<tr><td>5</td><td>≤ 1.78</td><td>Characterization only</td></tr>
<tr><td>6</td><td>≤ 1.88</td><td>Characterization only</td></tr>
<tr><td>7</td><td>≤ 2.20</td><td>Characterization only</td></tr>
</table>
ID: The device accommodates 0.018” guidewires
</td><td></td></tr>
<tr><td>Catheter Working Length</td><td>Demonstrate the catheter working length (manifold strain relief to distal end) meets the labeled value</td><td>80, 90, 135, 150 ± 2.5 cm</td><td>Pass</td></tr>
<tr><td>Balloon Body Length</td><td>Demonstrate the balloon working body length meets the labeled value when inflated to nominal pressure</td><td>The balloon working length (mm) must be:
<table>
<tr><th>Nominal Balloon Length</th><th>Min</th><th>Max</th></tr>
<tr><td>30</td><td>28</td><td>32</td></tr>
<tr><td>40</td><td>38</td><td>42</td></tr>
<tr><td>60</td><td>57</td><td>63</td></tr>
<tr><td>80</td><td>76</td><td>84</td></tr>
<tr><td>100</td><td>95</td><td>105</td></tr>
<tr><td>120 (4mm diameter)</td><td>114</td><td>126</td></tr>
<tr><td>120 (all others)</td><td>116</td><td>124</td></tr>
<tr><td>150 (4mm diameter)</td><td>142.5</td><td>157.5</td></tr>
<tr><td>150 (all others)</td><td>145</td><td>155</td></tr>
<tr><td>200</td><td>195</td><td>205</td></tr>
</table>
</td><td>Pass</td></tr>
<tr><td>Balloon Preparation, Deployment and Retraction</td><td>Demonstrate the catheter can be safely and reliably prepared, inflated/deflated, and retracted using the recommended techniques in the Instructions for Use without damage to the product</td><td>Devices must be prepared, tracked through an anatomically relevant model, inflated/deflated, and withdrawn without damage to the catheter</td><td>Pass</td></tr>
<tr><td>Balloon Rated Burst Pressure</td><td>Demonstrate the catheter can withstand inflation pressures that exceed the labeled balloon burst pressures</td><td>No part of the device shall fail at or below the rated burst pressure (atm):
<table>
<tr><th>Balloon Diameter</th><th>Rated Burst Pressure</th></tr>
<tr><td>4 – 7 mm</td><td>14</td></tr>
</table>
</td><td>Pass</td></tr>
<tr><td>Repeat Inflation</td><td>Demonstrate the catheter can withstand</td><td>The catheter must withstand 10 repeat inflations to rated burst pressure without failure</td><td>Pass</td></tr>
</table>

<table>
<tr><th>Test</th><th>Testing Objective</th><th>Acceptance Criteria (Specification)</th><th>Pass / Fail</th></tr>
<tr><td></td><td>multiple inflations to RBP</td><td></td><td></td></tr>
<tr><td>Balloon Compliance</td><td>Demonstrate the balloon diameter meets the labeled compliance values with increasing pressure</td><td>The balloon diameters must be:<table><tr><th>Balloon Diameter</th><th>Difference from Labelled</th></tr><tr><td>4 – 5 mm</td><td>≤ 18%</td></tr><tr><td>6 – 7 mm</td><td>≤ 15%</td></tr></table></td><td>Pass</td></tr>
<tr><td>Balloon Inflation / Deflation Time</td><td>Demonstrate the balloon inflates and deflates within clinically acceptable time limits</td><td>Inflation: This test is for characterization only

Deflation: The deflation time from rated burst pressure must be ≤ 60 seconds</td><td>Pass</td></tr>
<tr><td>Bond Tensile Strength:
a) Manifold
b) Proximal Balloon
c) Outer Shaft at Tack Weld
d) Tip</td><td>Demonstrate the catheter can withstand tensile strength requirements of the catheter bonds after pre-conditioning</td><td>The catheter must withstand the tensile forces (lbf):<table><tr><th>Balloon Diameter / Length</th><th>Shaft Type</th><th>Manifold</th><th>Proximal Balloon & Tack Weld</th><th>Tip</th></tr><tr><td>4 x all</td><td rowspan="4">4F</td><td rowspan="4">≥ 2.95</td><td rowspan="4">≥ 3.14</td><td rowspan="4">0.5</td></tr><tr><td>5 x ≤100</td></tr><tr><td>6 x ≤60</td></tr><tr><td>7 x ≤40</td></tr><tr><td>5 x ≥120</td><td rowspan="3">4/5F Hybrid</td><td rowspan="3">≥ 3.18</td><td rowspan="3">≥ 3.38</td><td rowspan="3">0.5</td></tr><tr><td>6 x ≥80</td></tr><tr><td>7 x ≥60</td></tr></table></td><td>Pass</td></tr>
<tr><td>Kink Resistance</td><td>Demonstrate the catheter can withstand flexural forces without kinking after pre-conditioning</td><td>The shaft must not kink at the specified diameter (mm):<table><tr><th>Balloon Diameter / Length</th><th>Shaft Type</th><th>Kink Diameter</th></tr><tr><td>4 x all</td><td rowspan="4">4F</td><td rowspan="4">≥ 18.0</td></tr><tr><td>5 x ≤100</td></tr><tr><td>6 x ≤60</td></tr><tr><td>7 x ≤40</td></tr><tr><td>5 x ≥120</td><td rowspan="3">4/5F Hybrid</td><td rowspan="3">≥30.0</td></tr><tr><td>6 x ≥80</td></tr><tr><td>7 x ≥60</td></tr></table></td><td>Pass</td></tr>
<tr><td>Kink to Failure</td><td>Demonstrate the minimum diameter at which the catheter will kink</td><td>This test is for characterization only</td><td>N/A</td></tr>
<tr><td>Torque Strength</td><td>Demonstrate the catheter maintains</td><td>This test is for characterization only</td><td>N/A</td></tr>
</table>

Test	Testing Objective	Acceptance Criteria (Specification)	Pass / Fail
	integrity when subjected to torsional forces		
Torque to Failure	Demonstrate the failure point of the catheter while applying torque	This test is for characterization only	N/A
Radiopacity	Demonstrate the marker bands are fluoroscopically visible	The marker bands must be visible under fluoroscopy imaging	Pass

C. Coating Characterization Testing

Analytical testing was performed to evaluate characteristics of the Ranger DCB drug coating as summarized in **Table 6** below.

Table 6: Summary of Ranger DCB Coating Characterization

Test	Description
Particulates (Simulated Use)	Characterize the total counts and sizes of particulates generated from the drug coated balloon in simulated use conditions
Particulate Identity and Crystallinity Characterization	Characterize chemical composition and crystallinity of particulates
Drug Coating Thickness	Characterize coating thickness of the balloon at multiple locations along the length and circumference of the balloon
Drug Coating Circumferential Uniformity	Measure the uniformity of drug content of multiple circumferential segments of finished Ranger DCB
Drug Coating Longitudinal Uniformity	Measure the uniformity of drug content of multiple longitudinal segments, depending on balloon length, of finished Ranger DCB
Drug Coating Durability	Durability and any performance impact to durability, is manifested in an assessment of drug content. Cohesion and adhesion of the coating is assessed in the measurement of drug content after the following steps: 1. Insertion through a guide sheath 2.Track through simulated anatomy
Crystallinity Characterization	Characterize degree of crystallinity of the coating
Drug Coating Integrity	Characterize drug coating Integrity including quantification of coated area

D. Chemistry, Manufacturing and Controls (CMC) Testing

The established requirements for ongoing Ranger DCB release batch and stability testing are summarized in **Table 7**.

Table 7: Ranger DCB CMC Testing Requirements

Test	Description	Acceptance Criteria
Appearance	Packaging securement and appearance of the balloon coating appearance is evaluated by visual inspection	Must meet visual standard
Drug Identity	The identity of the drug substance, paclitaxel, is confirmed by HPLC analysis and its UV spectrum	Identity must be confirmed via two different tests
Drug Content Assay	Paclitaxel content is quantified by high performance liquid chromatography (HPLC) to ensure product contains the labeled dose	90 – 110% of label claim
Drug Content Uniformity	Paclitaxel content is quantified by HPLC to ensure individual devices contain the labeled dose	USP <905>
Drug Degradants and Impurities	The levels of drug degradants and impurities are quantified by HPLC to ensure they remain within acceptable levels	ICH Q3B(R2)
Residual Acetone Content	The residual acetone from the manufacturing process is quantified gas chromatography – flame ionization detector (GC-FID) to ensure it remains within acceptable levels	Residual acetone levels must be within limits
Drug Release	The release paclitaxel quantified by HPLC to ensure it is within limits	USP <711>
Device Sterility	The sterility of the single-use device is evaluated per USP <71>	USP <71>
Endotoxins	Endotoxin levels are evaluated per AAMI ST72 to ensure they are within established safety guidelines	AAMI ST72
Particulates	The release particulate matter is evaluated by USP <788> to ensure it is within limits	Particulate sizes and counts must be within limits

E. Packaging Testing

Packaging verification testing was performed to demonstrate that the Ranger DCB packaging can withstand the hazards of the distribution environment, and that the sterility of the device is maintained throughout the labeled shelf life. 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.

F. Stability/Shelf Life Testing

A stability study was conducted according to International Conference on Harmonization (ICH) guidelines on Ranger DCB finished product to establish shelf life. The testing included drug coating appearance, drug assay, drug impurities and degradants, drug release, particulates, sterility, and endotoxin.

Shelf life engineering and packaging testing was also performed on aged product to demonstrate the device and packaging performs within specifications throughout the product shelf life.

The data generated from the stability and shelf life studies currently supports the 18-month labeled shelf life.

G. Sterilization

The Ranger DCB is sterilized using ethylene oxide (EO) gas and has been validated per AAMI / ANSI / ISO 11135:2007, Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices. Results from the sterilization studies demonstrate the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6} and residual EO levels were within acceptable ranges in accordance with EN ISO 10993-7:2008, Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals.

H. Animal Studies

The following *in vivo* animal testing was conducted in a porcine iliofemoral artery model to evaluate the safety of the Ranger DCB:

- One pharmacokinetic (PK) study was completed evaluating drug content in blood (time points from 0.5 hours to 60 days), treated iliofemoral arterial tissue, and downstream muscle/organ specimens (time points from 4 hours to 60 days) in swine.
- One safety study was completed (time points from 7 to 180 days) providing evidence of drug delivery, tissue response, and safety in swine iliofemoral arteries.
- One acute performance study was completed evaluating device performance and the potential for thrombus formation in swine iliofemoral arteries.

All animal studies were conducted in accordance with 21 CFR 58 (Good Laboratory Practices). In addition to the principal endpoints noted for each study, all animals were carefully evaluated for general health (i.e. vital signs, behavior, nutritional condition, gait, etc.) and clinical responses to treatment.

A list and description of the animal studies conducted is presented in **Table 8**.

Table 8: Summary of *In Vivo* Ranger DCB Animal Studies

Study ID	Number & Animal Type	Local Drug Dose	Balloon Size	Time Points	Major Endpoints	Endpoints Met
15-018G Pharmacokinetic	n=36 Domestic Swine	1x	5-7 x 80 mm	Tissue 4 hours, 1/3/5/7/14/ 21/42/60 days Blood Baseline, 30 minutes, 1/4/8/hours, 1/2/3/5/7/14/21/42/60 days	• Quantitative Angiography • Clinical Health • Arterial, Non-Target Tissue, and Blood levels	Yes
15-017G Vascular Response	n=54 Domestic Swine	1x, 3x	5-8 x 80 mm	7/30/90/180 days	• Quantitative Angiography • Clinical Safety • Histological Morphometric and Morphologic analysis • SEM Analysis	Yes
16-041G Acute Performance	n=2 Domestic Swine	1x	6-7 x 80 mm	Acute	• Clinical Safety and Device Performance	Yes

The preclinical studies conducted demonstrate and confirm the safety of treatment with the Ranger DCB. The GLP safety evaluation study of the Ranger DCB demonstrated favorable safety parameters as defined by the following:

- Successful delivery of the device to the target treatment location without major procedural or device related complications, such as acute thrombosis, major bleeding, or flow-limiting dissection.
- No morbidity or mortality device-related complications during the treatment procedures and in-life phases of the experiments.
- No major angiographic differences observed between test and control treatment groups. No major vessel abnormalities were reported. Angiographic flow and stenosis were similar across treatment arms (1X, 3X, and Uncoated Balloon).
- The histological morphometric assessments of the treated iliofemoral arteries were generally comparable across treatment arms (1X, 3X, and Uncoated Balloon) including EEL, IEL, lumen, medial, and neointimal areas, neointimal thickness and percent stenosis. There were no incidences of thrombotic occlusion or aneurysmal formation out to 180 days.
- Comparable histological indicators of vessel wall healing such as: injury, inflammation, and fibrosis with the test articles (1X, 3X) when compared to

control tissue sections. The extent of endothelial coverage as determined by light microscopy and/or scanning electron microscopy (SEM) in tissue sections were comparable between arms with endothelization nearly complete by 30 days and no abnormal findings on any endothelial surface.

- Downstream non-target tissues including skeletal muscle and organs showed no clinically relevant device related events.

The preclinical pharmacokinetic study demonstrated effective drug delivery and uptake into the arterial tissues at the therapeutic dose density (2.0 μg/mm^2) with no evidence of drug toxicity demonstrated as follows:

- Successful delivery of the device to the target treatment location without major procedural or device related complications, such as acute thrombosis, major bleeding, or flow-limiting dissection.
- No morbidity or mortality device-related complications during the treatment procedures and in-life phases of the experiments. No major vessel abnormalities were reported.
- Arterial paclitaxel concentrations were highest at the early time points and decreased to low but detectable through 60 days. Pharmacokinetic parameters of arterial tissue demonstrated a C_{max} of 99.6 ng/mg.
- Blood paclitaxel concentrations reached their maximum at 4 hours post-device deployment followed by a rapid elimination profile, reaching levels below quantification by 14 days post-procedure.
- The presence of paclitaxel in major organs or muscles was not associated with any adverse clinical reactions. Systemic concentrations in non-target tissues exhibited much lower paclitaxel concentrations relative to the treated arteries at the earlier time points and further decreased to almost non-detectable levels over 60 days. Results indicate limited systemic and non-target tissue drug exposure to paclitaxel with treatment using Ranger DCB.

Acute performance data demonstrated acceptable clinical safety (including no thrombus formation) and device performance. Pharmacokinetic data demonstrated localization of paclitaxel with limited systemic and non-target tissue exposure. Histopathology data demonstrated an acceptable drug dose and embolic load safety margin (3X safety margin) for the intended therapeutic dose of 2.0 μg/mm^2 and range of allowable balloon sizes.

X. SUMMARY OF PRIMARY CLINICAL STUDY

RANGER II SFA Trial

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of percutaneous balloon angioplasty with the Ranger Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB), after pre-dilatation, of de novo and restenotic lesions in native superficial femoral and popliteal arteries with the Ranger DCB in the US, Canada, Europe (Austria and Belgium), Japan, and New Zealand under IDE # G160172. Data from this clinical study were the basis for the PMA approval decision. A summary of the pivotal study is presented below.

A. Study Design

Patients were treated between March 2, 2017 and August 30, 2018. The database for this PMA reflected data collected through November 19, 2019 and included 376 patients randomized 3:1 to the Ranger DCB (n=278) or the control PTA device (n=98). There were 67 enrolling investigational sites.

The RANGER II SFA clinical study (NCT03064126) compares Ranger DCB vs. standard balloon angioplasty for the treatment of superficial femoral arteries (SFA) and proximal popliteal arteries (PPA). The RANGER II SFA study is a global, prospective, multi-center, single-blind, superiority, 3:1 (Ranger DCB vs. standard PTA) randomized controlled trial (RCT). It also includes a concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) sub study and a concurrent, non-blinded, non-randomized, Long Balloon (LB) Sub Study.

Data collected for the full cohort of 376 RCT subjects for study visits through November 19, 2019 is included in this summary.

A subject was randomized once they had been consented, met eligibility criteria, and underwent successful pre-dilatation.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the RANGER II SFA trial was limited to the following inclusion criteria:

   - Subject (or Legal Guardian) is willing and able to provide consent before any study-specific tests or procedures are performed and agree to attend all required follow-up visits;
   - Subject at least 20 years of age;
   - Chronic symptomatic lower limb ischemia defined as Rutherford classification 2, 3, or 4;
   - Target lesion is in the native SFA and/or PPA down to the P1 segment;
   - Patent popliteal and infrapopliteal arteries, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot;
   - Reference vessel diameter ≥ 4 mm and ≤ 8 mm by visual estimate (use of a

radiopaque ruler is recommended); and

- Angiographic evidence that target lesion consists of a single de novo, non-stented and non-atherectomy treated or restenotic lesion (or tandem lesions or a combination lesion as defined below) that is:
  - ≥ 70% -99% stenotic with total lesion length up to 180 mm by visual estimate (use of a radiopaque ruler is recommended).
  - Occluded with total lesion length ≤ 100 mm by visual estimate (use of a radiopaque ruler is recommended).
  - If lesion is restenotic, most recent PTA treatment must be > 3 months prior to enrollment.

  Notes:

  Combination lesions (a non-occlusive lesion that includes a totally occluded segment along its length) are eligible provided that the combined total lesion length is ≤180 mm.

  Tandem (or "adjacent") lesions may be enrolled providing they meet all of the following criteria:

  - Separated by a gap of ≤ 30 mm (3 cm);
  - Total combined lesion length meets requirements (angiographic inclusion criteria including 30 mm gap);
  - Able to be treated as a single lesion.

Patients were <u>not</u> permitted to enroll into the RANGER II SFA trial if they meet any of the following exclusion criteria:

- Life expectancy, documented in the Investigator's opinion, of less than 12 months;
- Hemorrhagic stroke or cardiac event (e.g. STEMI, unstable angina) within 6 months prior to enrollment;
- Known allergies or sensitivities to heparin, aspirin, other anticoagulant/antiplatelet therapies, and/or paclitaxel;
- Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated;
- Chronic renal insufficiency with serum creatinine > 2.0 mg/dL within 30 days of index procedure or treatment with dialysis;
- Platelet count <80,000 mm^3 or >600,000 mm^3 or history of bleeding diathesis;
- Receiving immunosuppressive therapy;
- Septicemia at the time of enrollment;
- Any major (e.g., cardiac, peripheral, abdominal) intervention (including in the

contralateral SFA/PPA) planned within 30 days post index procedure;

- Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of enrollment;
- Failure to successfully cross the target lesion with a guidewire (successful crossing means tip of the crossing device is distal to the target lesion in the absence of flow-limiting dissections or perforations);
- Failure to successfully pre-dilate the target vessel;
- Patient has lesion that requires the use of adjunctive primary treatment modalities (i.e. laser, atherectomy, scoring/cutting balloon, other debulking devices, etc.) during the index procedure;
- History of major amputation in the target limb;
- Target lesion or vessel has ever been previously treated with stent (e.g. in-stent restenosis) or surgery. Target lesion or vessel has been treated with atherectomy or a DCB in the past 12 months;
- Pregnant or breast feeding;
- Presence of aneurysm in the target vessel;
- Acute ischemia and/or acute thrombosis of the SFA/PPA prior to enrollment;
- Patient has significant inflow disease which cannot be treated prior to the target lesion treatment;
- Patient has perforated targeted vessel as evidenced by extravasation of contrast media;
- Patient has severe calcification that renders the lesion undilatable;
- Current participation in another investigational drug or device clinical trial that has not completed the primary endpoint at the time of randomization/enrollment or that clinically interferes with the current trial endpoints.

  Note: Studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies.

2. Follow-Up Schedule

   All patients are to be scheduled for evaluations at 1, 6, 12, 24, 36, 48, and 60 months. The 48 and 60 month visits can occur in office/clinic or by telephone. A subgroup of patients enrolled in a pharmacokinetics sub-study had blood drawn at 24 or 48 hours, 7, and 30 days post-procedure, as well as the required assessments through 60 months.

   Preoperatively, a screening was performed. A peri-procedure assessment was also performed. **Table 9** below summarizes the objective parameters and key timepoints

of the RANGER II SFA trial.

Table 9: RANGER II SFA Data Collection Schedule

Procedure/Assessment	Pre-procedure [2]	During Index Procedure	Pre-Discharge	Day 1 or 2[6]	Day 7 (±1 day)	1-month (30 ± 7 days)	6-month (182 ± 30 days)	12-month (365 ± 30 days)	24-month (730 ± 30 days)	36-month (1095 ± 30 days)	48-month[5] (1460 ± 30 days)	60-month[5] (1825 ± 30 days)
Informed Consent[1]	X											
Confirm Inclusion/Exclusion	X	X										
Demographics and Medical History, Height and Weight	X											
Pregnancy Test[2]	X											
Physical Exam[3]	X		X			X	X	X	X	X		
Complete Blood Count (CBC) and platelet count	X											
Serum Creatinine	X											
ABI Measurements	X					X	X	X	X	X		
Rutherford Classification	X					X	X	X	X	X		
Walking Impairment Questionnaire (WIQ)	X					X	X	X	X	X		
EQ-5D Questionnaire	X					X	X	X	X	X		
6 Minute Walk Test (6MWT)	X						X	X				
Angiogram[4]		X										
Randomization/Enrollment		X										
PK venous draw	X	X[6]	X	X	X	X						
Duplex Ultrasound[4]						X	X	X	X	X		
Medication Assessment	X	X	X			X	X	X	X	X	X	X
Adverse Events Assessment		X	X			X	X	X	X[7]	X[7]	X[7]	X[7]

[1] Subject's consent obtained and informed consent form signed prior to obtaining any study-specific tests or procedures. Testing (CBC, platelets, ABI, and Rutherford Classification) completed as a part of the subject's standard of care, within 30 days of the index procedure and that meets the study (inclusion/exclusion) criteria, are not required to be repeated.

[2] Performed within 30 days of procedure, except urine or blood pregnancy test required for females of childbearing potential performed within 24 hrs of procedure

[3] Physical exam includes obtaining Vital signs (B/P, HR, RR*), Rutherford Classification and ABI at 1 mth, 6 mth, 12 mth, 24 mth and 36 mth follow up visits. Pre-discharge: Vital signs only.
* Respiratory rate is not mandatory if not local standard of care.

[4] Angiograms and Ultrasounds will be sent to the respective core lab for analysis.

[5] The 48 month and 60 month visit may be conducted in the office/clinic or by telephone.

[6] PK venous draw at screening, 10 min, 30 min, 1 hr, 3 hr, 6 hr, 24 or 48 hr after last Ranger DCB removal, Day 7 and Day 30 post index procedure.

[7] Reporting required through the end of trial for SAEs, UADEs and ADEs/Device Deficiencies. AEs not related to the investigational device or procedure reported only through 12 month follow-up visit.

3. Clinical Endpoints

Primary Safety Endpoint: The primary safety endpoint assessed the occurrence of Major Adverse Events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization (TLR) through 12 months. This safety endpoint was designed to demonstrate that the 12-month MAE-free rate for the Ranger DCB treatment group is non-inferior to the Standard PTA control group.

Primary Effectiveness Endpoint: The RCT primary effectiveness endpoint assessed primary patency at 12 months post-procedure. This effectiveness endpoint was designed to demonstrate that the 12-month primary patency for the Ranger DCB treatment group is superior to the Standard PTA control group. Primary vessel patency was defined as the percentage of lesions (target stented segments) that reached the endpoint without a hemodynamically significant stenosis on duplex ultrasound (DUS) (Peak Systolic Velocity Ratio {PSVR} is ≤ 2.4), and without clinically-driven TLR or bypass of the target lesion before or on the DUS follow up visit.

Secondary Endpoints: The secondary endpoints that will be evaluated, but are not necessarily powered to make statistically based conclusions, for the RANGER II SFA study are listed below:

- Technical success defined as successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP)
- Procedural success defined as residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used)
- Clinical success defined as procedural success without procedural complications (i.e. death, major target limb amputation, thrombosis of the target lesion, or clinically-driven TLR) prior to discharge
- Major Adverse Events (MAE) through 60 months. MAEs are defined as all-cause death post-index procedure, TLR, and major target limb amputation
- Death of any cause within 30 days, 6, 12, 24, 36, 48 and 60 months
- TVR rates at 6, 12, 24, 36, 48 and 60 months
- TLR rates at 6, 12, 24, 36, 48 and 60 months
- Rate of Primary and Secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline at 1, 6, 12, 24 and 36 months post-procedure
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1, 6, 12, 24 and 36 months post-

procedure

- Duplex-defined binary restenosis (PSVR > 2.4) of the target lesion at 1, 6, 12, 24 and 36 months
- Walking Improvement (distance) at 6 months and 12 months as assessed by changes in the Six Minute Hall Walk Test (6MWT) from baseline
- Walking Improvement and Patient Utility Values assessed at 1, 6, 12, 24 and 36 months as assessed by change in Walking Impairment Questionnaire (WIQ) and EQ-5D™ from baseline
- Changes in healthcare utilization over time
- PK parameters calculated for subjects in the PK substudy

B. Accountability of Full PMA Cohort

Sixty-seven (67) centers located in the United States, Japan, New Zealand, Europe (Belgium and Austria) and Canada recruited 376 RCT subjects requiring treatment of lesions in the femoropopliteal arteries. Fifty-eight (58%) percent of all subjects were enrolled in the United States (56% in the RCT, 100% in the PK sub-study).

As of the database snapshot on November 19, 2019, a total of 343 RCT subjects completed the 12-month follow-up visit as required by the RANGER II SFA protocol. **Table 10** displays the subject disposition at each follow-up visit for the RCT.

Table 10: Subject Disposition Through 12 Months – RCT, Intent-to-Treat (N=376)

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)	Overall (N=376 Subjects)
Intent to Treat (All Enrolled Subjects)	278	98	376
Eligible for 1-Month Clinical Follow-up	277	98	375
Not Eligible for 1-Month Clinical Follow-up	1	0	1
Death ≤ 37 Days with no 1-Month Clinical Follow- up Performed	1	0	1
Withdrawal	0	0	0
Adverse Event	0	0	0
Investigator Discretion	0	0	0
Lost to Follow-up	0	0	0
Withdrew Consent	0	0	0
Failed Angioplasty attempt	0	0	0
Other	0	0	0
1-Month Visit Missed	5	1	6
1-Month Visit Window Not Open	0	0	0
1-Month Visit Window Still Open	0	0	0
1-Month Visit Pending Data Entry	0	0	0
1-Month Clinical Follow-up Performed	272	97	369
1-Month Clinical Follow-up or Death (Evaluable)	273	97	370

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)	Overall (N=376 Subjects)
1-Month Clinical Follow-up Compliance[1]	98.2% (272/277)	99.0% (97/98)	98.4% (369/375)
1-Month Duplex Ultrasound Follow-up Compliance[1,2]	96.4% (267/277)	98.0% (96/98)	96.8% (363/375)
Eligible for 6-Month Clinical Follow-up	272	93	365
Not Eligible for 6-Month Clinical Follow-up	6	5	11
Death ≤ 212 Days with no 6-Month Clinical Follow-up Performed	3	2	5
Withdrawal	3	3	6
Adverse Event	0	0	0
Investigator Discretion	0	0	0
Lost to Follow-up	0	0	0
Withdrew Consent	3	3	6
Failed Angioplasty attempt	0	0	0
Other	0	0	0
6-Month Visit Missed	9	2	11
6-Month Visit Window Not Open	0	0	0
6-Month Visit Window Still Open	0	0	0
6-Month Visit Pending Data Entry	0	0	0
6-Month Clinical Follow-up Performed	263	91	354
6-Month Clinical Follow-up or Death (Evaluable)	266	93	359
6-Month Clinical Follow-up Compliance[1]	95.6% (263/275)	94.8% (91/96)	95.4% (354/371)
6-Month Duplex Ultrasound Follow-up Compliance[1,2]	94.9% (261/275)	93.8% (90/96)	94.6% (351/371)
Eligible for 12-Month Clinical Follow-up	263	92	355
Not Eligible for 12-Month Clinical Follow-up	15	6	21
Death ≤ 395 Days with no 12-Month Clinical Follow-up Performed	6	2	8
Withdrawal	9	4	13
Adverse Event	0	0	0
Investigator Discretion	1	0	1
Lost to Follow-up	0	0	0
Withdrew Consent	7	4	11
Failed Angioplasty attempt	0	0	0
Other	1	0	1
12-Month Visit Missed	11	1	12
12-Month Visit Window Not Open	0	0	0
12-Month Visit Window Still Open	0	0	0
12-Month Visit Pending Data Entry	0	0	0
12-Month Clinical Follow-up Performed	252	91	343
12-Month Clinical Follow-up or Death (Evaluable)	258	93	351
12-Month Clinical Follow-up Compliance[1]	92.6% (252/272)	94.8% (91/96)	93.2% (343/368)
12-Month Duplex Ultrasound Follow-up Compliance[1,2]	92.3% (251/272)	93.8% (90/96)	92.7% (341/368)

[1] Death prior to the visit window or within the visit window with no clinical follow-up does not contribute to the denominators and numerators of the compliance rate.

[2] All site-reported duplex ultrasounds apply, including anyone without interpretable images.

C. Study Population Demographics and Baseline Characteristics

Patient Population

Table 11 provides a summary of baseline demographics and medical history for subjects enrolled into the RANGER II SFA Randomized Controlled Trial (RCT).

Table 11: Baseline Demographics and Medical History - RCT (N=376)

Subject Characteristic	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
Demographics		
Age (Year)	70.6 ± 9.5 (278) (43.0, 89.0)	69.1 ± 10.3 (98) (47.0, 88.0)
Gender		
Male	62.2% (173/278)	68.4% (67/98)
Female	37.8% (105/278)	31.6% (31/98)
Intersex	0.0% (0/278)	0.0% (0/98)
Unknown	0.0% (0/278)	0.0% (0/98)
Race/Ethnicity		
Hispanic or Latino	7.6% (21/278)	8.2% (8/98)
Caucasian	55.8% (155/278)	60.2% (59/98)
Asian	27.7% (77/278)	25.5% (25/98)
Japanese	27.7% (77/278)	25.5% (25/98)
Chinese	0.0% (0/278)	0.0% (0/98)
Korean	0.0% (0/278)	0.0% (0/98)
Other Asian	0.0% (0/278)	0.0% (0/98)
Black, or African heritage	7.2% (20/278)	4.1% (4/98)
Native Hawaiian or other Pacific Islander	0.0% (0/278)	0.0% (0/98)
American Indian or Alaska Native	0.4% (1/278)	0.0% (0/98)
Other	0.4% (1/278)	0.0% (0/98)
Not Disclosed	1.1% (3/278)	2.0% (2/98)
General Medical History		
History of Smoking		
Current	31.3% (87/278)	45.9% (45/98)
Previous	54.0% (150/278)	38.8% (38/98)
Never	14.4% (40/278)	15.3% (15/98)
Unknown	0.4% (1/278)	0.0% (0/98)
Current Diabetes Mellitus	42.4% (118/278)	43.9% (43/98)
Type 1	1.7% (2/118)	0.0% (0/43)
Type 2	96.6% (114/118)	100.0% (43/43)
Unknown	1.7% (2/118)	0.0% (0/43)
Current Method of Treatment		
Diet	26.3% (31/118)	27.9% (12/43)
Diet(only)	5.1% (6/118)	11.6% (5/43)
Medically Treated	94.1% (111/118)	88.4% (38/43)
Oral Agent	73.7% (87/118)	74.4% (32/43)
Insulin	36.4% (43/118)	39.5% (17/43)
Other	1.7% (2/118)	0.0% (0/43)

Subject Characteristic	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
Unknown	0.8% (1/118)	0.0% (0/43)
History of Hyperlipidemia requiring medication	75.9% (211/278)	79.6% (78/98)
History of Hypertension requiring medication	90.3% (251/278)	81.6% (80/98)
History of Chronic Obstructive Pulmonary Disease	18.9% (52/275)	21.4% (21/98)
Cardiac History		
History of Coronary Artery Disease	47.5% (131/276)	44.9% (44/98)
History of Myocardial Infarction (MI)	16.6% (46/277)	14.4% (14/97)
History of Congestive Heart Failure	9.4% (26/277)	9.2% (9/98)
New York Heart Assoc. (NYHA) Classification		
I	38.5% (10/26)	0.0% (0/9)
II	23.1% (6/26)	66.7% (6/9)
III	3.8% (1/26)	0.0% (0/9)
IV	0.0% (0/26)	0.0% (0/9)
Unknown	34.6% (9/26)	33.3% (3/9)
History of Percutaneous Coronary Intervention (PCI)	29.6% (81/274)	34.7% (34/98)
History of Coronary Artery Bypass Graft (CABG) Surgery	12.6% (35/277)	15.5% (15/97)
Current Anginal Status		
Stable Angina	12.6% (35/278)	13.3% (13/98)
Unstable Angina	0.4% (1/278)	0.0% (0/98)
None	87.1% (242/278)	86.7% (85/98)
Unknown	0.0% (0/278)	0.0% (0/98)
Neurologic/Renal History		
History of Transient Ischemic Attacks (TIA)	5.1% (14/275)	7.2% (7/97)
History of Cerebrovascular Accident (CVA)	13.0% (36/276)	11.2% (11/98)
History of Renal Insufficiency	10.8% (30/278)	5.2% (5/97)
History of Renal Percutaneous Intervention	2.2% (6/275)	1.0% (1/97)
ABI (mmHg ratio)	0.8 ± 0.2 (276) (0.3, 1.7)	0.8 ± 0.2 (93) (0.2, 1.5)
Rutherford Category		
2	39.2% (109/278)	33.7% (33/98)
3	51.4% (143/278)	59.2% (58/98)
4	9.4% (26/278)	7.1% (7/98)

Lesion Characteristics

Baseline lesion characteristics, procedural characteristics, and post-procedure measurements for the RCT are summarized in **Table 12**

Table 12: Baseline, Procedure and Post-procedure Reported Lesion Characteristics - RCT (N=376)

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
Baseline Angiographic Core Lab Reported Lesion Characteristics		
Treated Limb		
Right leg	48.9% (136/278)	53.1% (52/98)
Left leg	51.1% (142/278)	46.9% (46/98)
Lesion Location		
pSFA	17.3% (48/278)	18.4% (18/98)
mSFA	52.5% (146/278)	44.9% (44/98)
dSFA	24.8% (69/278)	32.7% (32/98)
pPopliteal	4.3% (12/278)	4.1% (4/98)
mPopliteal	1.1% (3/278)	0.0% (0/98)
dPopliteal	0.0% (0/278)	0.0% (0/98)
Not Available	0.0% (0/278)	0.0% (0/98)
Lesion Length (mm)	82.5 ± 48.9 (278) (9.2, 232.5)	79.9 ± 49.3 (98) (13.6, 232.1)
Lesion Type		
Eccentric Lesion	77.0% (214/278)	74.5% (73/98)
Concentric Lesion	23.0% (64/278)	25.5% (25/98)
Not Available	0.0% (0/278)	0.0% (0/98)
Thrombus		
None	97.8% (272/278)	99.0% (97/98)
Possible	0.0% (0/278)	1.0% (1/98)
Small	0.0% (0/278)	0.0% (0/98)
Moderate	0.0% (0/278)	0.0% (0/98)
Large	0.4% (1/278)	0.0% (0/98)
Total occlusion	0.4% (1/278)	0.0% (0/98)
Not Available	1.4% (4/278)	0.0% (0/98)
PACSS Calcification		
Grade 0	35.3% (98/278)	22.4% (22/98)
Grade 1	12.6% (35/278)	14.3% (14/98)
Grade 2	2.5% (7/278)	1.0% (1/98)
Grade 3	36.3% (101/278)	52.0% (51/98)
Grade 4	11.5% (32/278)	10.2% (10/98)
NA	1.8% (5/278)	0.0% (0/98)
Ulceration (Present)	4.3% (12/278)	3.1% (3/98)
Aneurysm (Present)	0.7% (2/278)	3.1% (3/98)
TIMI Flow		
Grade 0	16.9% (47/278)	23.5% (23/98)
Grade 1	1.8% (5/278)	2.0% (2/98)
Grade 2	0.7% (2/278)	0.0% (0/98)
Grade 3	67.6% (188/278)	63.3% (62/98)

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
Not Available	12.9% (36/278)	11.2% (11/98)
TASC II Type		
A	59.4% (165/278)	61.2% (60/98)
B	30.2% (84/278)	30.6% (30/98)
C	9.0% (25/278)	6.1% (6/98)
D	1.4% (4/278)	2.0% (2/98)
Not Available	0.0% (0/278)	0.0% (0/98)
Minimum Lumen Diameter (MLD, mm)	1.4 ± 0.9 (278) (0.0, 4.5)	1.2 ± 1.1 (98) (0.0, 4.3)
Reference Vessel Diameter (RVD, mm)	5.1 ± 0.9 (278) (3.0, 8.7)	5.1 ± 0.9 (98) (3.2, 8.3)
% Diameter Stenosis	73.7 ± 16.9 (278) (26.1, 100.0)	78.2 ± 18.4 (98) (35.8, 100.0)
100% (Occlusion)	18.3% (51/278)	29.6% (29/98)
Angiographic Core Lab Reported Post-Procedure Measurements		
Dissection		
None	24.5% (68/278)	35.7% (35/98)
Grade A	0.0% (0/278)	0.0% (0/98)
Grade B	45.3% (126/278)	37.8% (37/98)
Grade C	16.5% (46/278)	16.3% (16/98)
Grade D	12.9% (36/278)	5.1% (5/98)
Grade E	0.0% (0/278)	0.0% (0/98)
Grade F	0.0% (0/278)	0.0% (0/98)
Not Available	0.7% (2/278)	5.1% (5/98)
In-Segment Percent Diameter Stenosis (% DS)	25.0 ± 12.2 (277) (-7.5, 61.7)	24.5 ± 12.9 (93) (-12.1, 59.1)
In-Segment Minimum Lumen Diameter (MLD, mm)	3.8 ± 0.7 (277) (1.8, 5.8)	3.8 ± 0.8 (93) (2.1, 6.5)
Procedural Characteristics		
Pre-dilatation[a]		
Pre-dilatation Performed	100.0% (278/278)	100.0% (98/98)
Post-dilatation[a]		
Post-dilatation Performed	13.3% (37/278)	21.4% (21/98)
Bare Metal Stent bailout[a]	5.0% (14/278)	9.2% (9/98)[b]
Technical Success[1a]	99.6% (277/278)	NA
Procedural Success[2]	96.8% (269/278)	99.0% (97/98)
Clinical Success[3]	96.0% (267/278)	98.0% (96/98)

Sites may report more than one lesion location.

[a] Site reported data.

[b] One Standard PTA subject received a bailout drug-eluting stent not allowed per protocol.

[1] Technical Success: successful delivery, balloon inflation and deflation and retrieval of the intact trial device without burst below the rated burst pressure (RBP). Device deficiency data was collected only for Ranger DCB.

[2] Procedural Success: residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core laboratory evaluation (if core laboratory assessment is not available then the site-reported estimate is used).

[3] Clinical Success: procedural success without procedural complications (i.e. death, major target limb amputation, thrombosis of the target lesion, or clinically-driven TLR) prior to discharge.

D. Safety and Effectiveness Results

1. Primary Safety Results - RCT

Primary results for the full RCT cohort are presented below. Ranger DCB will be concluded to be non-inferior to Standard PTA regarding the primary safety endpoint, 12-month MAE-free rate, if the one-sided lower 97.5% confidence bound on the difference between treatment groups (Ranger DCB vs. Standard PTA) in 12- month MAE-free rate is greater than -0.1 (or -10%). Based on the intent-to-treat (ITT) population, the MAE-free rate at 12 months was 94.1% (241/256) in the Ranger DCB group and 83.5% (76/91) in the Standard PTA group respectively, with the one-sided lower 97.5% confidence bound on the difference to be 2.48% (non-inferiority p-value <.0001). The primary safety endpoint was also evaluated based on the Per-Protocol (PP) cohort which consisted of randomized subjects who met the eligibility criteria and received the assigned treatment, and had similar results to the ITT analysis. Therefore, the primary safety endpoint was met and Ranger DCB is concluded to be non-inferior to Standard PTA for the primary safety endpoint. The primary safety results for this study are presented below in **Table 13**. Kaplan-Meier plot of freedom from MAE through 365 days is presented in **Figure 4**.

Table 13: Primary Safety Endpoint – Full Cohort RCT, Intent-to-Treat (N=376), Per Protocol (N=370)

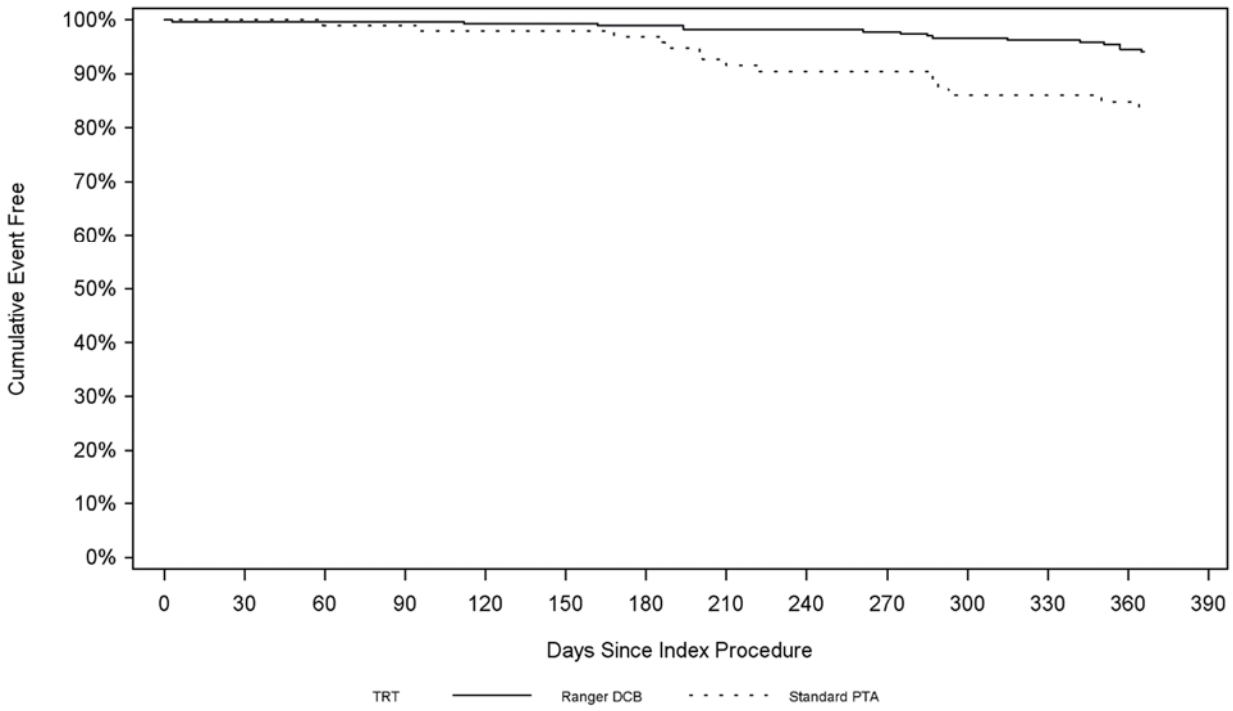
Intent-To-Treat (N=376)	**Ranger DCB (N=278 Subjects)**	**Standard PTA (N=98 Subjects)**	**Difference [95% CI]**	**One-sided 97.5% Lower CI**	**P-value[2]**
12-Month MAE[1]-Free	94.1% (241/256)	83.5% (76/91)	10.6% [2.5%, 18.8%]	2.48%	<.0001
Per-Protocol (N=370)	**Ranger DCB (N=274 Subjects)**	**Standard PTA (N=96 Subjects)**	**Difference [95% CI]**	**One-sided 97.5% Lower CI**	**P-value[2]**
12-Month MAE[1]-Free	94.8% (239/252)	84.3% (75/89)	10.6% [2.5%, 18.6%]	2.53%	<.0001

[1] Primary Safety: Twelve-Month Major Adverse Events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization through 12 months.

[2] P-value is adjusted for non-inferiority margin (-10%).

Note:

- The success criteria for 12M safety endpoint hypothesis is the one-sided 97.5% lower bound greater than non-inferiority margin (i.e.>-10%).
- The success criteria for 12M effectiveness endpoint hypothesis is the one-sided 97.5% lower bound greater than zero (i.e.>0).
- All events were adjudicated by the independent Clinical Events Committee and all DUS and angiographic measurements were made by the independent core laboratories.



	Time from Index Procedure (Days)							
Number of Subjects with Ranger DCB Balloon	**0**	**1-30**	**31-60**	**61-90**	**91-120**	**121-182**	**183-270**	**271-365**
Entered	278	277	276	274	274	271	269	255
Censored	1	0	2	0	2	1	11	41
Events	0	1	0	0	1	1	3	9
Event Rate	0%	0.4%	0.4%	0.4%	0.7%	1.1%	2.2%	5.9%
Event Free	100%	99.6%	99.6%	99.6%	99.3%	98.9%	97.8%	94.1%
Std Error	0%	0.4%	0.4%	0.4%	0.5%	0.6%	0.9%	1.5%
Number of Subjects with Standard PTA Balloon	**0**	**1-30**	**31-60**	**61-90**	**91-120**	**121-182**	**183-270**	**271-365**
Entered	98	98	98	96	96	94	91	83
Censored	0	0	1	0	1	2	2	11
Events	0	0	1	0	1	1	6	6
Event Rate	0%	0%	1.0%	1.0%	2.1%	3.1%	9.6%	16.4%
Event Free	100%	100%	99.0%	99.0%	97.9%	96.9%	90.4%	83.6%
Std Error	0%	0%	1.0%	1.0%	1.4%	1.8%	3.0%	3.9%

Subjects event-free at 365 days or later are censored at greater than 365 days.
Event rate and standard error estimates are for interval end. Standard errors by Greenwood formula.

Figure 4: Kaplan-Meier Plot – Freedom from Major Adverse Event Through 12 Months, Intent- to-Treat (N=376 Subjects)

Table 14 shows the individual components of the primary safety endpoint: all causes of death through 1 month, target limb major amputation through 12 months and target lesion revascularization (TLR) through 12 months for the full RCT cohort.

Table 14: Safety Endpoints through 12 Months – Full Cohort RCT, Intent-to-Treat (N=376)

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)	Difference [95% CI]
Primary Safety Endpoint			
12-Month MAE[1]-Free	94.1% (241/256)	83.5% (76/91)	10.6% [2.5%, 18.8%]
12-Month MAE[1] and Components			
12-Month MAE[1] (Composite Endpoint)	5.9% (15/256)	16.5% (15/91)	
All Causes of Deaths at 1 Month	0.4% (1/256)	0.0% (0/91)	
Target Limb Major Amputation	0.0% (0/256)	0.0% (0/91)	
Target Lesion Revascularization	5.5% (14/256)	16.5% (15/91)	
Clinically-Driven	5.5% (14/256)	16.5% (15/91)	
Non-Clinically-Driven	0.0% (0/256)	0.0% (0/78)	
[1] Twelve-Month Major Adverse Events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization through 12 months			

Table 15 displays the frequency of Serious Adverse Events (SAE) by MedDRA System/Organ Class that were reported as of the data snapshot date of November 19, 2019, observed in the RANGER II SFA pivotal trial for the full RCT cohort. A serious adverse event is defined as an event that led to death or led to a serious deterioration in the health of the subject; resulted in a life-threatening illness or injury; resulted in a permanent impairment of a body structure or a body function; required in-subject hospitalization or prolongation of existing hospitalization; or resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

Table 15: Frequency of Site-Reported Serious Adverse Events to 12 Months – Full Cohort - Intent-to- Treat (N=376 Subjects)

Serious Adverse Event		Ranger DCB (N=278 Subjects)		Standard PTA (N=98 Subjects)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**
Total	Total	228	45.7% (127/278)	94	48.0% (47/98)
Vascular disorders	Total	87	21.2% (59/278)	36	27.6% (27/98)
	Peripheral artery stenosis	36	10.4% (29/278)	19	14.3% (14/98)
	Intermittent claudication	19	6.1% (17/278)	6	5.1% (5/98)
	Peripheral artery occlusion	11	2.9% (8/278)	4	4.1% (4/98)
	Peripheral arterial occlusive disease	9	2.2% (6/278)	2	1.0% (1/98)

Serious Adverse Event		Ranger DCB (N=278 Subjects)		Standard PTA (N=98 Subjects)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**
	Peripheral ischemia	3	1.1% (3/278)	0	0.0% (0/98)
	Hematoma	2	0.7% (2/278)	0	0.0% (0/98)
	Hypotension	2	0.7% (2/278)	0	0.0% (0/98)
	Peripheral vascular disorder	1	0.4% (1/278)	1	1.0% (1/98)
	Essential hypertension	1	0.4% (1/278)	0	0.0% (0/98)
	Lower limb artery perforation	1	0.4% (1/278)	0	0.0% (0/98)
	Peripheral coldness	1	0.4% (1/278)	0	0.0% (0/98)
	Thrombophlebitis superficial	1	0.4% (1/278)	0	0.0% (0/98)
	Deep vein thrombosis	0	0.0% (0/278)	1	1.0% (1/98)
	Hypertensive crisis	0	0.0% (0/278)	1	1.0% (1/98)
	Orthostatic hypotension	0	0.0% (0/278)	1	1.0% (1/98)
	Peripheral embolism	0	0.0% (0/278)	1	1.0% (1/98)
Cardiac disorders	Total	30	7.6% (21/278)	14	8.2% (8/98)
	Atrial fibrillation	4	1.1% (3/278)	1	1.0% (1/98)
	Cardiac failure congestive	4	1.1% (3/278)	1	1.0% (1/98)
	Angina pectoris	4	1.4% (4/278)	0	0.0% (0/98)
	Coronary artery disease	3	1.1% (3/278)	5	3.1% (3/98)
	Angina unstable	3	1.1% (3/278)	2	2.0% (2/98)
	Coronary artery stenosis	3	1.1% (3/278)	1	1.0% (1/98)
	Acute myocardial infarction	2	0.7% (2/278)	1	1.0% (1/98)
	Cardiac arrest	1	0.4% (1/278)	0	0.0% (0/98)
	Cardiac failure	1	0.4% (1/278)	0	0.0% (0/98)
	Cardiac failure acute	1	0.4% (1/278)	0	0.0% (0/98)
	Coronary artery occlusion	1	0.4% (1/278)	0	0.0% (0/98)
	Ischemic cardiomyopathy	1	0.4% (1/278)	0	0.0% (0/98)
	Myocardial infarction	1	0.4% (1/278)	0	0.0% (0/98)
	Ventricular tachycardia	1	0.4% (1/278)	0	0.0% (0/98)
	Aortic valve incompetence	0	0.0% (0/278)	1	1.0% (1/98)
	Atrioventricular block	0	0.0% (0/278)	1	1.0% (1/98)
	Mitral valve incompetence	0	0.0% (0/278)	1	1.0% (1/98)
Injury, poisoning and procedural complications	Total	20	6.8% (19/278)	10	7.1% (7/98)
	Vascular procedure complication	11	4.0% (11/278)	4	4.1% (4/98)
	Vascular pseudoaneurysm	4	1.4% (4/278)	1	1.0% (1/98)
	Anemia postoperative	1	0.4% (1/278)	0	0.0% (0/98)
	Contusion	1	0.4% (1/278)	0	0.0% (0/98)
	Extradural hematoma	1	0.4% (1/278)	0	0.0% (0/98)
	Peripheral artery bypass graft stenosis	1	0.4% (1/278)	0	0.0% (0/98)
	Subdural hematoma	1	0.4% (1/278)	0	0.0% (0/98)

Serious Adverse Event		Ranger DCB (N=278 Subjects)		Standard PTA (N=98 Subjects)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**
	Ankle fracture	0	0.0% (0/278)	2	1.0% (1/98)
	Humerus fracture	0	0.0% (0/278)	2	1.0% (1/98)
	Cervical vertebral fracture	0	0.0% (0/278)	1	1.0% (1/98)
Infections and infestations	Total	17	6.1% (17/278)	6	5.1% (5/98)
	Pneumonia	4	1.4% (4/278)	2	2.0% (2/98)
	Cellulitis	2	0.7% (2/278)	1	1.0% (1/98)
	Diverticulitis	2	0.7% (2/278)	1	1.0% (1/98)
	Post procedural infection	2	0.7% (2/278)	0	0.0% (0/98)
	Bronchitis	1	0.4% (1/278)	0	0.0% (0/98)
	Bronchopulmonary aspergillosis	1	0.4% (1/278)	0	0.0% (0/98)
	Cystitis	1	0.4% (1/278)	0	0.0% (0/98)
	Device related infection	1	0.4% (1/278)	0	0.0% (0/98)
	Enteritis infectious	1	0.4% (1/278)	0	0.0% (0/98)
	Sepsis	1	0.4% (1/278)	0	0.0% (0/98)
	Urinary tract infection	1	0.4% (1/278)	0	0.0% (0/98)
	Osteomyelitis	0	0.0% (0/278)	1	1.0% (1/98)
	Pyelonephritis	0	0.0% (0/278)	1	1.0% (1/98)
General disorders and administration site conditions	Total	12	4.0% (11/278)	1	1.0% (1/98)
	Catheter site hematoma	5	1.4% (4/278)	0	0.0% (0/98)
	Non-cardiac chest pain	2	0.7% (2/278)	0	0.0% (0/98)
	Accidental death	1	0.4% (1/278)	0	0.0% (0/98)
	Chest pain	1	0.4% (1/278)	0	0.0% (0/98)
	Device related thrombosis	1	0.4% (1/278)	0	0.0% (0/98)
	Implant site inflammation	1	0.4% (1/278)	0	0.0% (0/98)
	Oedema peripheral	1	0.4% (1/278)	0	0.0% (0/98)
	Death	0	0.0% (0/278)	1	1.0% (1/98)
Respiratory, thoracic and mediastinal disorders	Total	11	3.2% (9/278)	4	4.1% (4/98)
	Acute respiratory failure	3	0.7% (2/278)	0	0.0% (0/98)
	Respiratory failure	2	0.7% (2/278)	2	2.0% (2/98)
	Chronic obstructive pulmonary disease	2	0.7% (2/278)	0	0.0% (0/98)
	Dyspnea	1	0.4% (1/278)	0	0.0% (0/98)
	Hemothorax	1	0.4% (1/278)	0	0.0% (0/98)
	Pleural effusion	1	0.4% (1/278)	0	0.0% (0/98)
	Pulmonary embolism	1	0.4% (1/278)	0	0.0% (0/98)
	Pneumothorax	0	0.0% (0/278)	2	2.0% (2/98)
Gastrointestinal	Total	9	3.2% (9/278)	5	4.1% (4/98)

Serious Adverse Event		Ranger DCB (N=278 Subjects)		Standard PTA (N=98 Subjects)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**
disorders					
	Constipation	1	0.4% (1/278)	1	1.0% (1/98)
	Abdominal pain upper	1	0.4% (1/278)	0	0.0% (0/98)
	Diarrhea	1	0.4% (1/278)	0	0.0% (0/98)
	Enteritis	1	0.4% (1/278)	0	0.0% (0/98)
	Gastrointestinal hemorrhage	1	0.4% (1/278)	0	0.0% (0/98)
	Large intestinal stenosis	1	0.4% (1/278)	0	0.0% (0/98)
	Lower gastrointestinal hemorrhage	1	0.4% (1/278)	0	0.0% (0/98)
	Retroperitoneal hematoma	1	0.4% (1/278)	0	0.0% (0/98)
	Upper gastrointestinal hemorrhage	1	0.4% (1/278)	0	0.0% (0/98)
	Inguinal hernia	0	0.0% (0/278)	3	3.1% (3/98)
	Pancreatitis acute	0	0.0% (0/278)	1	1.0% (1/98)
Renal and urinary disorders	Total	8	2.5% (7/278)	6	3.1% (3/98)
	Acute kidney injury	3	1.1% (3/278)	4	2.0% (2/98)
	Renal failure	2	0.7% (2/278)	0	0.0% (0/98)
	Haematuria	1	0.4% (1/278)	1	1.0% (1/98)
	Calculus urinary	1	0.4% (1/278)	0	0.0% (0/98)
	Urinary bladder polyp	1	0.4% (1/278)	0	0.0% (0/98)
	Urinary retention	0	0.0% (0/278)	1	1.0% (1/98)
Musculoskeletal and connective tissue disorders	Total	7	2.5% (7/278)	4	4.1% (4/98)
	Back pain	2	0.7% (2/278)	0	0.0% (0/98)
	Pain in extremity	2	0.7% (2/278)	0	0.0% (0/98)
	Osteoarthritis	1	0.4% (1/278)	2	2.0% (2/98)
	Intervertebral disc protrusion	1	0.4% (1/278)	0	0.0% (0/98)
	Myalgia	1	0.4% (1/278)	0	0.0% (0/98)
	Cervical spinal stenosis	0	0.0% (0/278)	1	1.0% (1/98)
	Plantar fasciitis	0	0.0% (0/278)	1	1.0% (1/98)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Total	7	2.5% (7/278)	1	1.0% (1/98)
	Benign lung neoplasm	1	0.4% (1/278)	0	0.0% (0/98)
	Invasive ductal breast carcinoma	1	0.4% (1/278)	0	0.0% (0/98)
	Lung neoplasm malignant	1	0.4% (1/278)	0	0.0% (0/98)
	Malignant neoplasm of renal pelvis	1	0.4% (1/278)	0	0.0% (0/98)
	Prostate cancer	1	0.4% (1/278)	0	0.0% (0/98)
	Squamous cell carcinoma of	1	0.4% (1/278)	0	0.0% (0/98)

Serious Adverse Event		Ranger DCB (N=278 Subjects)		Standard PTA (N=98 Subjects)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**
	lung				
	Transitional cell carcinoma	1	0.4% (1/278)	0	0.0% (0/98)
	Bladder cancer	0	0.0% (0/278)	1	1.0% (1/98)
Nervous system disorders	Total	7	2.2% (6/278)	0	0.0% (0/98)
	Cerebral infarction	2	0.7% (2/278)	0	0.0% (0/98)
	Cerebrovascular accident	2	0.4% (1/278)	0	0.0% (0/98)
	Dementia with Lewy bodies	1	0.4% (1/278)	0	0.0% (0/98)
	Headache	1	0.4% (1/278)	0	0.0% (0/98)
	Syncope	1	0.4% (1/278)	0	0.0% (0/98)
Blood and lymphatic system disorders	Total	3	1.1% (3/278)	1	1.0% (1/98)
	Anemia	2	0.7% (2/278)	1	1.0% (1/98)
	Iron deficiency anemia	1	0.4% (1/278)	0	0.0% (0/98)
Metabolism and nutrition disorders	Total	3	0.7% (2/278)	0	0.0% (0/98)
	Decreased appetite	1	0.4% (1/278)	0	0.0% (0/98)
	Hyperglycemia	1	0.4% (1/278)	0	0.0% (0/98)
	Hyponatraemia	1	0.4% (1/278)	0	0.0% (0/98)
Skin and subcutaneous tissue disorders	Total	2	0.7% (2/278)	3	2.0% (2/98)
	Skin ulcer	2	0.7% (2/278)	1	1.0% (1/98)
	Diabetic foot	0	0.0% (0/278)	1	1.0% (1/98)
	Drug eruption	0	0.0% (0/278)	1	1.0% (1/98)
Eye disorders	Total	1	0.4% (1/278)	1	1.0% (1/98)
	Cataract	1	0.4% (1/278)	1	1.0% (1/98)
Psychiatric disorders	Total	1	0.4% (1/278)	1	1.0% (1/98)
	Delirium	1	0.4% (1/278)	0	0.0% (0/98)
	Mental status changes	0	0.0% (0/278)	1	1.0% (1/98)
Ear and labyrinth disorders	Total	1	0.4% (1/278)	0	0.0% (0/98)
	Vertigo	1	0.4% (1/278)	0	0.0% (0/98)
Hepatobiliary disorders	Total	1	0.4% (1/278)	0	0.0% (0/98)
	Cholelithiasis	1	0.4% (1/278)	0	0.0% (0/98)
Reproductive system and breast disorders	Total	1	0.4% (1/278)	0	0.0% (0/98)
	Uterine polyp	1	0.4% (1/278)	0	0.0% (0/98)
Investigations	Total	0	0.0% (0/278)	1	1.0% (1/98)
	Hemoglobin decreased	0	0.0% (0/278)	1	1.0% (1/98)

Serious Adverse Event		Ranger DCB (N=278 Subjects)		Standard PTA (N=98 Subjects)	
MedDRA System Organ Class	MedDRA Preferred Term	Events	Rate of Subjects with Event	Events	Rate of Subjects with Event
"Events" numbers are total episodes of each type of event among all subjects. "Rate of Subjects with Event" numbers are percent of subjects who experienced one or more episodes of the event. "Events" numbers for "TOTAL" are the sum of the individual event category totals. "Rate of Subjects with Event" numbers for "TOTAL" is the percent of subjects who experienced an adverse event.					

2. Primary Effectiveness Results – RCT

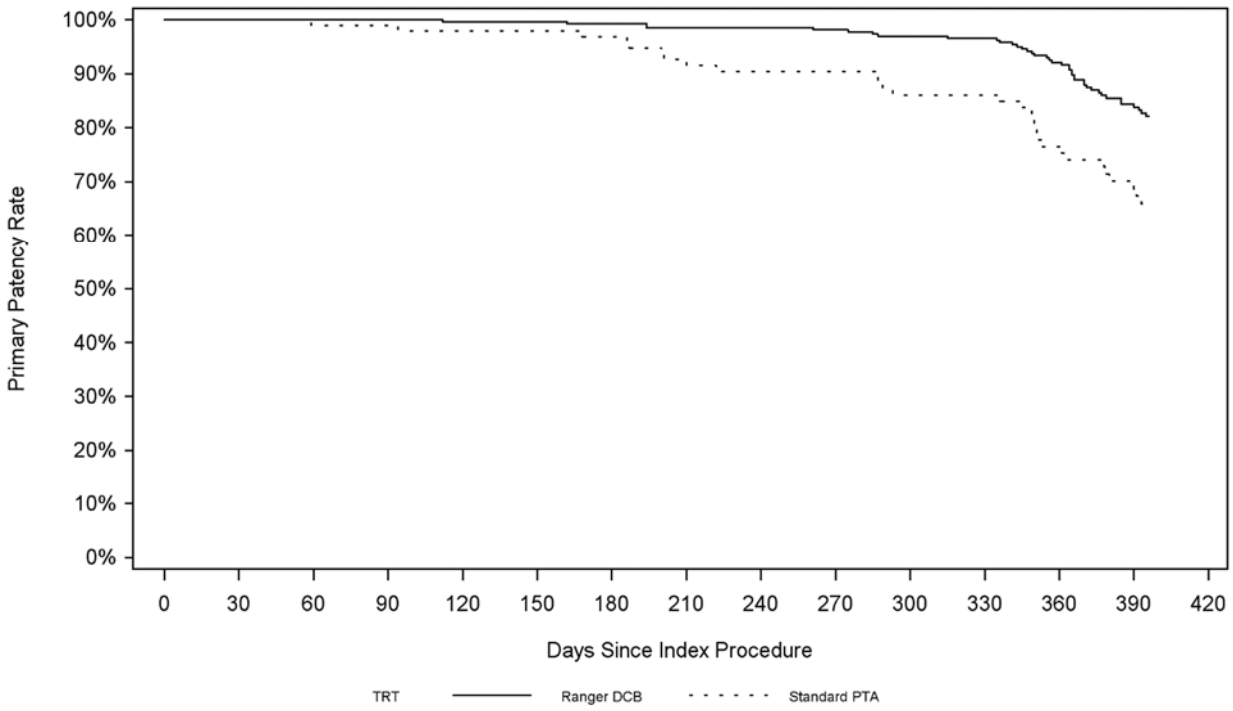
Primary effectiveness results for the full RCT cohort are presented in the section below. Based on the ITT population, primary patency at 12 months was 82.9% (194/234) in the Ranger DCB group and 66.3% (57/86) in the Standard PTA group respectively, with the one-sided lower 97.5% confidence bound on the difference to be 5.53% (p-value=0.0017). The primary effectiveness endpoint was also evaluated based on the PP population and had similar results. Therefore, the primary effectiveness endpoint was met and the Ranger DCB is concluded to be superior to Standard PTA for the primary effectiveness endpoint. Primary effectiveness results for the full cohort are provided in **Table 16**. Kaplan-Meier plot of primary patency through 13 months is presented in **Figure 5**.

Table 16: Primary Patency Endpoint through 12 Months – Full Cohort RCT, Intent- to-Treat (N=376), Per Protocol (N=370)

Intent-To-Treat (N=376)	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)	Difference [95% CI]	One- sided 97.5% Lower CI	P-value
12-Month Primary Patency[1]	82.9% (194/234)	66.3% (57/86)	16.6% [5.5%, 27.7%]	5.53%	0.0017
Per-Protocol (N=370)	**Ranger DCB (N=274 Subjects)**	**Standard PTA (N=96 Subjects)**	**Difference [95% CI]**	**One-sided 97.5% Lower CI**	**P-value**
12-Month Primary Patency[1]	83.1% (192/231)	66.7% (56/84)	16.5% [5.3%, 27.6%]	5.27%	0.0020

[1] Primary Patency: percentage (%) of lesions (target lesion segments) that reach endpoint without a hemodynamically significant stenosis on DUS and without clinically-driven TLR or, bypass of the target lesion before or on the DUS FU visit.

- Lesion patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment.
- PSVR >2.4 suggests >50% stenosis.



	Time from Index Procedure (Days)								
Number of Subjects with Ranger DCB Balloon	**0**	**1-30**	**31-60**	**61-90**	**91-120**	**121-182**	**183-270**	**271-365**	**366-395**
Entered	278	277	276	274	274	271	269	255	195
Censored	1	1	2	0	2	1	11	40	39
Events	0	0	0	0	1	1	3	20	15
Event Rate	0%	0%	0%	0%	0.4%	0.7%	1.9%	10.2%	17.9%
Event Free	100%	100%	100%	100%	99.6%	99.3%	98.1%	89.8%	82.1%
Std Error	0%	0%	0%	0%	0.4%	0.5%	0.8%	1.9%	2.6%
Number of Subjects with Standard PTA Balloon	**0**	**1-30**	**31-60**	**61-90**	**91-120**	**121-182**	**183-270**	**271-365**	**366-395**
Entered	98	98	98	96	96	94	91	83	59
Censored	0	0	1	0	1	2	2	10	9
Events	0	0	1	0	1	1	6	14	6
Event Rate	0%	0%	1.0%	1.0%	2.1%	3.1%	9.6%	26.0%	34.1%
Event Free	100%	100%	99.0%	99.0%	97.9%	96.9%	90.4%	74.0%	65.9%
Std Error	0%	0%	1.0%	1.0%	1.4%	1.8%	3.0%	4.7%	5.2%

Subjects event-free at 395 days or later are censored at greater than 395 days.
Event rate and standard error estimates are for interval end. Standard errors by Greenwood formula.

Figure 5: Kaplan-Meier Plot – Primary Patency Through 13 Months, Full Cohort, RCT Intent-to-Treat (N=376 Subjects)

3. Additional Secondary Analyses

Secondary endpoints for the full cohort for procedural / technical / clinical success, MAE rate through 60 months, non-serious non-device/procedure- related AE rates, rate of primary and secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline, walking improvement and patient utility values assessed by change in Walking Impairment Questionnaire and EQ-5D, rate of hemodynamic improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline, duplex-defined binary restenosis (PSVR >2.4), Walking Improvement at 6 and 12 months assessed by change in Six Minute Hall Walk (6MHW) from baseline, changes in healthcare utilization over time were evaluated, and PK parameters calculated for subjects in the PK substudy were observational.

The Ranger DCB group was observed to have higher percentages of subjects with hemodynamic improvement (ABI) and clinical improvement (Rutherford classification) compared to the Standard PTA group throughout the study. **Table 17** displays Hemodynamic improvement was achieved in 88.8% (230/259) of subjects in the Ranger DCB group and 75.9% (66/87) of subjects in the Standard PTA group at 6 months, and 80.0% (200/250) of subjects in the Ranger DCB group and 67.9% (57/84) of subjects in the Standard PTA group at 12 months. **Table 18** displays Primary Sustained Clinical Improvement at 12 months was achieved in the Ranger DCB group at 87.6% (220/251) and the Standard PTA group at 75.8% (69/91).

Table 17: Distribution of Ankle Brachial Index (ABI), Full Cohort RCT, Intent-to-Treat (N=376)

ABI Assessment	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
Hemodynamic Improvement	93.0% (252/271)	90.2% (83/92)
Hemodynamic Improvement (Including TLR)	93.0% (252/271)	90.2% (83/92)
6 Month		
Hemodynamic Improvement	88.8% (230/259)	75.9% (66/87)
Hemodynamic Improvement (Including TLR)	89.2% (231/259)	78.2% (68/87)
12 Month		
Hemodynamic Improvement	80.0% (200/250)	67.9% (57/84)
Hemodynamic Improvement (Including TLR)	83.6% (209/250)	79.8% (67/84)

Table 18: Rutherford Assessment, Full Cohort RCT, Intent-to-Treat (N=376)

Rutherford Assessment	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
1 Month		
Primary Sustained Clinical Improvement	94.1% (256/272)	93.8% (91/97)
Secondary Sustained Clinical Improvement	94.1% (256/272)	93.8% (91/97)
Clinical Deterioration	0.0% (0/272)	0.0% (0/97)
No Change from Baseline	5.9% (16/272)	6.2% (6/97)
6 Months		
Primary Sustained Clinical Improvement	94.7% (249/263)	91.2% (83/91)
Secondary Sustained Clinical Improvement	95.4% (251/263)	93.4% (85/91)
Clinical Deterioration	0.8% (2/263)	1.1% (1/91)
No Change from Baseline	3.8% (10/263)	5.5% (5/91)
12 Months		
Primary Sustained Clinical Improvement	87.6% (220/251)	75.8% (69/91)
Secondary Sustained Clinical Improvement	91.6% (230/251)	89.0% (81/91)
Clinical Deterioration	3.2% (8/251)	1.1% (1/91)
No Change from Baseline	5.2% (13/251)	9.9% (9/91)

Walking improvement was observed throughout the study, with an observed improvement in distance walked as measured by the 6 Minute Walk Test (6MWT) as shown in **Table 19**. Walking impairment was observed to be improved as assessed by the Walking Impairment Questionnaire (WIQ) in **Table 20** and an increase in the EQ-5D Index Value was observed as measured by the EQ-5D Questionnaire in **Table 21**.

Table 19: Six-Minute Walk Test, Full Cohort RCT, Intent-to-Treat (N=376)

Ranger DCB (N=278 Subjects)	Baseline	6-Month	12-Month
Total Walk Time (min)	5.7 ± 1.0 (273) (0.3, 6.0)	5.8 ± 0.8 (256) (1.0, 6.0)	5.7 ± 1.1 (239) (0.1, 6.0)
Total Distance Walk (m)	278.3 ± 192.3 (273) (6.1, 2200.0)	322.8 ± 128.9 (256) (30.5, 701.0)	319.7 ± 136.2 (239) (48.8, 792.5)
Standard PTA (N=98 Subjects)	**Baseline**	**6-Month**	**12-Month**
Total Walk Time (min)	5.3 ± 1.5 (96) (0.1, 6.0)	5.8 ± 0.8 (86) (1.3, 6.0)	5.7 ± 1.0 (89) (1.0, 6.0)
Total Distance Walk (m)	253.5 ± 127.4 (96) (3.0, 600.5)	320.2 ± 125.3 (85) (56.5, 600.0)	308.7 ± 136.5 (89) (30.5, 720.0)

Table 20: Walking Impairment Questionnaire (WIQ) Scoring Summary, Full Cohort RCT, Intent-to-Treat (N=376)

Ranger DCB (N=278 Subjects)	Baseline	1-Month	6-Month	12-Month
Walking Impairment	44.49 ± 30.68 (277) (0.00, 100.00)	77.95 ± 27.40 (271) (0.00, 100.00)	77.09 ± 28.40 (263) (0.00, 100.00)	76.71 ± 29.75 (248) (0.00, 100.00)
Change from Baseline		33.61 ± 35.78 (270) (-50.00, 100.00)	32.25 ± 37.07 (262) (-100.00, 100.00)	32.29 ± 39.40 (247) (-75.00, 100.00)
Standard PTA (N=98 Subjects)	**Baseline**	**1-Month**	**6-Month**	**12-Month**
Walking Impairment	40.72 ± 27.79 (97) (0.00, 100.00)	76.04 ± 28.31 (96) (0.00, 100.00)	73.61 ± 31.44 (90) (0.00, 100.00)	76.37 ± 28.71 (91) (0.00, 100.00)
Change from Baseline		34.47 ± 35.20 (95) (-50.00, 100.00)	31.18 ± 41.85 (89) (-75.00, 100.00)	34.72 ± 36.85 (90) (-50.00, 100.00)

Table 21: EQ-5D Assessment, Full Cohort RCT, Intent-to-Treat (N=376)

EQ-5D Assessment	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
1 Month		
Mobility Improvement	55.2% (149/270)	54.7% (52/95)
Self-Care Improvement	8.9% (24/270)	12.6% (12/95)
Usual Activities Improvement	39.6% (107/270)	46.3% (44/95)
Pain/Discomfort Improvement	52.2% (141/270)	64.2% (61/95)
Anxiety/Depression Improvement	20.4% (55/270)	24.2% (23/95)
6 Months		
Mobility Improvement	56.9% (149/262)	50.6% (45/89)
Self-Care Improvement	10.3% (27/262)	11.2% (10/89)
Usual Activities Improvement	38.9% (102/262)	42.7% (38/89)
Pain/Discomfort Improvement	48.1% (126/262)	52.8% (47/89)
Anxiety/Depression Improvement	23.3% (61/262)	27.0% (24/89)
12 Months		
Mobility Improvement	56.3% (139/247)	53.3% (48/90)
Self-Care Improvement	10.5% (26/247)	15.6% (14/90)
Usual Activities Improvement	38.1% (94/247)	45.6% (41/90)
Pain/Discomfort Improvement	53.4% (132/247)	56.7% (51/90)
Anxiety/Depression Improvement	23.9% (59/247)	24.4% (22/90)
"Improvement" is defined as improving at least one category from baseline.		

4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes. Boston Scientific has analyzed trial results by different pre-defined subgroups to investigate the consistency of results through 12 months in the RCT. Primary Safety Endpoint Event-Free Rate at 12 Months (**Table 22**), Primary Patency at 12 Months (**Table 23**), and Clinically-driven Target Lesion Revascularization at 12 Months (**Table 24**) are illustrated for each subgroup in the tables below. All data for the subgroup analyses trend in-favor of Ranger DCB over Standard PTA.

Table 22: Primary Safety Endpoint: Event-Free at 12 Months

	Ranger DCB (N=278 Subjects)	**Standard PTA (N=98 Subjects)**
Overall	94.1% (241/256)	83.5% (76/91)
Age ≥ 65	94.4% (187/198)	87.9% (58/66)
Age < 65	93.1% (54/58)	72.0% (18/25)
Medically-Treated Diabetes	91.1% (92/101)	80.0% (28/35)
Male Gender	94.4% (152/161)	87.3% (55/63)
Female Gender	93.7% (89/95)	75.0% (21/28)
Lesion length ≤ 5cm	95.0% (76/80)	93.5% (29/31)
Lesion length > 5cm and ≤ 10cm	92.4% (85/92)	81.3% (26/32)
Lesion length > 10cm	95.2% (80/84)	75.0% (21/28)

Table 23: Primary Patency at 12 Months

	Ranger DCB (N=278 Subjects)	**Standard PTA (N=98 Subjects)**
Overall	82.9% (194/234)	66.3% (57/86)
Age ≥ 65	83.5% (152/182)	71.9% (46/64)
Age < 65	80.8% (42/52)	50.0% (11/22)
Medically-Treated Diabetes	80.2% (73/91)	60.6% (20/33)
Male Gender	84.1% (122/145)	69.5% (41/59)
Female Gender	80.9% (72/89)	59.3% (16/27)
Lesion length ≤ 5cm	86.8% (66/76)	82.8% (24/29)
Lesion length > 5cm and ≤ 10cm	82.5% (66/80)	63.3% (19/30)
Lesion length > 10cm	79.5% (62/78)	51.9% (14/27)

Table 24: Clinically-Driven Target Lesion Revascularization at 12 Months

	Ranger DCB (N=278 Subjects)	**Standard PTA (N=98 Subjects)**
Overall	5.5% (14/256)	16.5% (15/91)
Age ≥ 65	5.6% (11/198)	12.1% (8/66)
Age < 65	5.2% (3/58)	28.0% (7/25)
Medically-Treated Diabetes	7.9% (8/101)	20.0% (7/35)
Male Gender	5.0% (8/161)	12.7% (8/63)

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
Female Gender	6.3% (6/95)	25.0% (7/28)
Lesion length ≤ 5cm	5.0% (4/80)	6.5% (2/31)
Lesion length > 5cm and ≤ 10cm	6.5% (6/92)	18.8% (6/32)
Lesion length > 10cm	4.8% (4/84)	25.0% (7/28)

Gender Analysis

There were 240 males and 136 females randomized in the pivotal study. Based on gender subgroup analyses, the Ranger DCB group was observed to have lower 12-month MAE rate and higher 12-month patency rate compared to the Standard PTA group for both males and females (**Table 25**). The results of an interaction analysis suggest no gender differences in the treatment effects regarding the primary safety and effectiveness endpoints between Ranger DCB and Standard PTA groups.

Table 25: Safety and Effectiveness Endpoints by Gender, Full RCT, Intent-to- Treat (N=376)

	Ranger DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)	P-value
Primary Safety Endpoint – MAE at 12 months[1]			
Gender			0.3779
Male (N=240)	5.6% (9/161)	12.7% (8/63)	
Female (N=136)	6.3% (6/95)	25.0% (7/28)	
Primary Effectiveness Endpoint – Primary Patency at 12 months[2]			
Gender			0.7087
Male (N=240)	84.1% (122/145)	69.5% (41/59)	
Female (N=136)	80.9% (72/89)	59.3% (16/27)	

[1] Primary Safety: Twelve-Month Major Adverse Events (MAEs) defined as all causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularization through 12 months.

All events were adjudicated by the independent Clinical Events Committee and all DUS and angiographic measurements were made by the independent core laboratories.

[2] Primary Patency: percentage (%) of lesions (target lesion segments) that reach endpoint without a hemodynamically significant stenosis on DUS and without clinically-driven TLR or, bypass of the target lesion before or on the DUS FU visit.

- Lesion patency is defined as freedom from more than 50% stenosis based on DUS PSVR comparing data within the treated segment to the proximal normal arterial segment.
- PSVR >2.4 suggests >50% stenosis.

5. Pharmacokinetic Sub-Study:

The Pharmacokinetic sub study is a prospective, multi-center, non-randomized study arm (Ranger DCB), conducted at multiple pre-specified investigational sites designed to evaluate the levels of paclitaxel in the systemic circulation of subjects at multiple time points after treatment with the Ranger DCB. Twelve (12) subjects were enrolled at three sites in the United States.

A summary of the pharmacokinetic parameters is presented in **Table 26** Summary of Pharmacokinetic Parameters. The pharmacokinetic sub-study demonstrated low systemic exposure with rapid clearance of paclitaxel.

Table 26: Summary of Pharmacokinetic Parameters

Parameter	Mean (N=12)	Standard Deviation
PTx Dose (µg)	6136.6	2554.3
C_{max} (ng/ml)	2.50	2.17
t_{max} (h)	0.17	-
AUC_{0-t} (ng*h/ml)	0.86	0.76
T_{max} (hr)	The timepoint where C_{max} is reached	
C_{max} (ng/mL)	Maximum plasma concentration	
AUC_{0-t} (ng*h/ml)	Area under the blood concentration versus time curve from time zero up to the time of the last quantifiable concentration, calculated by trapezoidal methods	

6. 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 68 principal investigators (318 sub investigators) of which none were full-time or part-time employees of the sponsor, and two (2) 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: Two (2) investigators
- 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: One (1) 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

RANGER SFA Trial

The Ranger Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) was initially evaluated in the RANGER SFA study. The RANGER SFA study was a prospective, randomized, multi-center clinical study of the Ranger DCB in comparison to uncoated PTA balloons in femoropopliteal lesions. The primary objective of the study was to evaluate the superior performance of the Ranger DCB for angioplasty of femoropopliteal artery lesions when compared to non-coated balloons at 6 months post-procedure when comparing Late Lumen Loss (LLL). The study population consisted of subjects with clinically significant symptomatic leg ischemia requiring treatment (Rutherford clinical category of 2-4). The index lesion was required to be a clinically and hemodynamically significant stenotic or restenotic lesion located in the native non-stented, non-atherectomy treated superficial femoral artery or proximal popliteal artery, with angiographic stenosis ≥ 70% by visual assessment and lesion length ≥ 20 mm and ≤ 150 mm. Eligible subjects were randomly assigned (2:1) to treatment with the Ranger DCB or a non-drug-coated PTA balloon. Follow-up visits scheduled at 6 and 12 months post-procedure included hemodynamic and clinical outcome assessments; angiography at 6 months was used to determine the primary endpoint of in-segment LLL. Health-related quality of life was assessed at 36 months via mail-administered EQ5D and SF-12 questionnaires. Non-serious, non-device-related adverse events were reported up to the 6-month follow-up. Serious (SAE), major, unanticipated and/or device-related adverse events were reported up to the 36-month follow-up. A Clinical Events Committee reviewed all reported SAEs and deaths.

A total of 105 subjects received study treatment at 10 centers located in Germany, France and Austria. Demographic and clinical characteristics of the Ranger DCB (N=71) and control (N=34) groups were similar, with mean age (±SD) 68 ± 8 years, 75% men, and 39% with diabetes in the Ranger DCB group, and age 67 ± 9 years, 68% men, and 35% with diabetes in the control group. Patients treated with Ranger DCB had a mean lesion length of 68 ± 46 mm, 34% had occlusions, and 35% had severe calcification; patients in the control group had a mean lesion length of 60 ± 48 mm, 34% had occlusions, and 22% had severe calcification. The primary efficacy endpoint of in-segment late lumen loss at 6 months was significantly less in the Ranger DCB group than in the control group (-0.16 ± 0.99 mm vs. 0.76 ±1.4 mm; p=0.0017), therefore the primary endpoint was met. The primary patency rate, defined as the percentage of lesions that reach endpoint without a hemodynamically significant stenosis on duplex ultrasound (PSVR > 2.4) and without target lesion revascularization (TLR) or bypass of the target lesion, was observed to be greater at 12 months for subjects treated with the Ranger DCB (86% vs 52%). Clinical outcomes up to 12 months, including Rutherford classification, ankle-brachial index, Walking Impairment Questionnaire (WIQ) scores, and quality of life assessments were generally similar between the control and Ranger DCB groups.

The Ranger DCB demonstrated a good safety profile in the RANGER SFA study, with AE (83% vs 76%) and SAE (69% vs 68%) rates through 36 months for subjects treated with Ranger DCB similar to those treated with a non-drug- coated balloon. No target limb amputations or deaths related to the study device were reported. The observed TLR rate for subjects treated with Ranger DCB was less than that of subjects in the control group

(8.5% vs 29%) at 12 months, and this trend was maintained through 36 months with the Ranger DCB group showing a TLR rate of one-half that of the control group (17% vs 32%). No unanticipated serious adverse device effects were reported.

Twelve deaths occurred through the 36 month follow up, 9 in the Ranger DCB group and 3 in the control group; none were reported to be related to the study procedure or device.

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 RANGER II SFA study was not included in these analyses, though the RANGER SFA-FIM study was considered in the initial meta-analysis published by Katsanos et. al in 2018[2]. The magnitude and mechanism for the increased risk in mortality is currently unclear.

Because there is limited follow-up data at 2 and 3 years from the RANGER II SFA pivotal study, in order to demonstrate that the Ranger DCB does not represent an unacceptable risk of late mortality compared to the currently marketed devices, 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 provided by the sponsor. Data availability included the following:

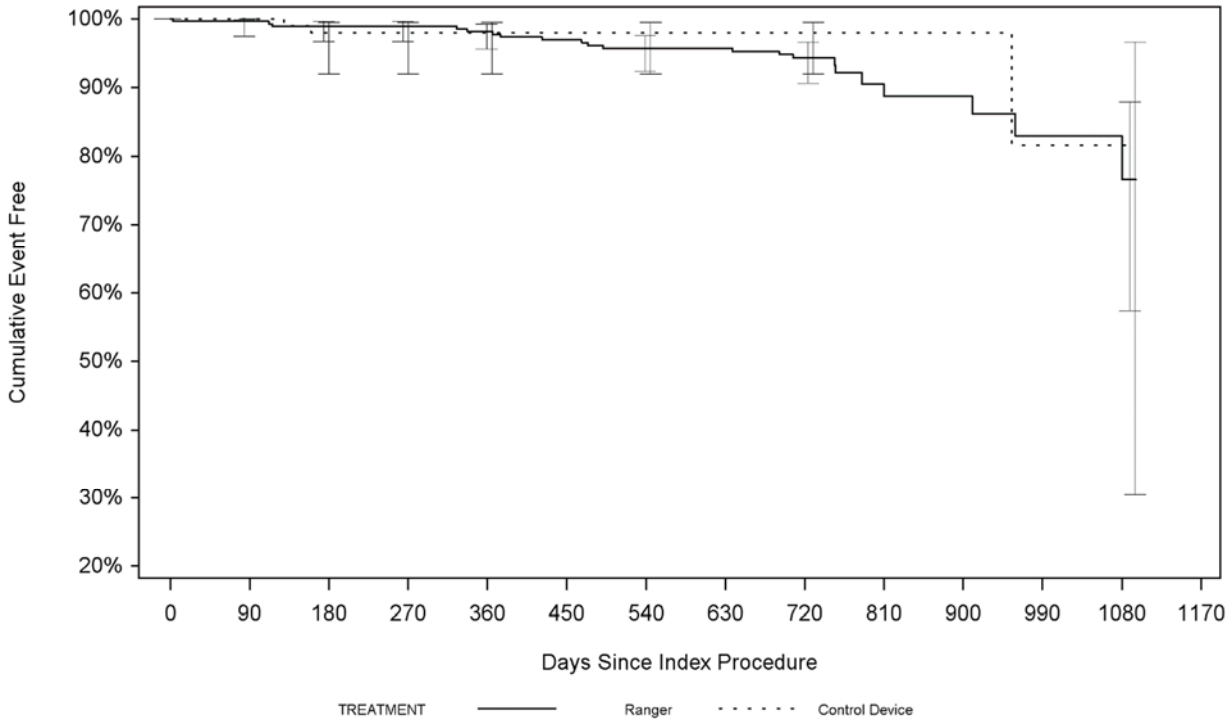
- RANGER II SFA pivotal study:
  - Data cutoff date: Jun 15, 2020
  - 2-year mortality data[a]: 229 Ranger DCB subjects, 81 PTA subjects
  - 3-year mortality data[a]: 40 Ranger DCB subjects, 8 PTA subjects
- RANGER SFA-FIM Study
  - Data cutoff date: March 11, 2019
  - 2-year mortality data[b]: 69 Ranger DCB subjects, 31 PTA subjects
  - 3-year mortality data[b]: 65 Ranger DCB subjects, 28 PTA subjects
- COMPARE I Study
  - Ranger vs. IN.PACT DCB; data cutoff date: Jun 15, 2020
  - 2-year mortality data[a]: 170 Ranger DCB subjects
  - 3-year mortality data[a]: 44 Ranger DCB subjects

a: Includes subjects with death, and subjects without death but have follow-up at least 700/1065 days for the 2 and 3 year mortality data, respectively.

b: Includes subjects with death, and subjects without death but have follow-up at least 366/731 days for the 2 and 3 year mortality data, respectively

Below is a summary of the results of the 3-year mortality analyses for the Ranger DCB:

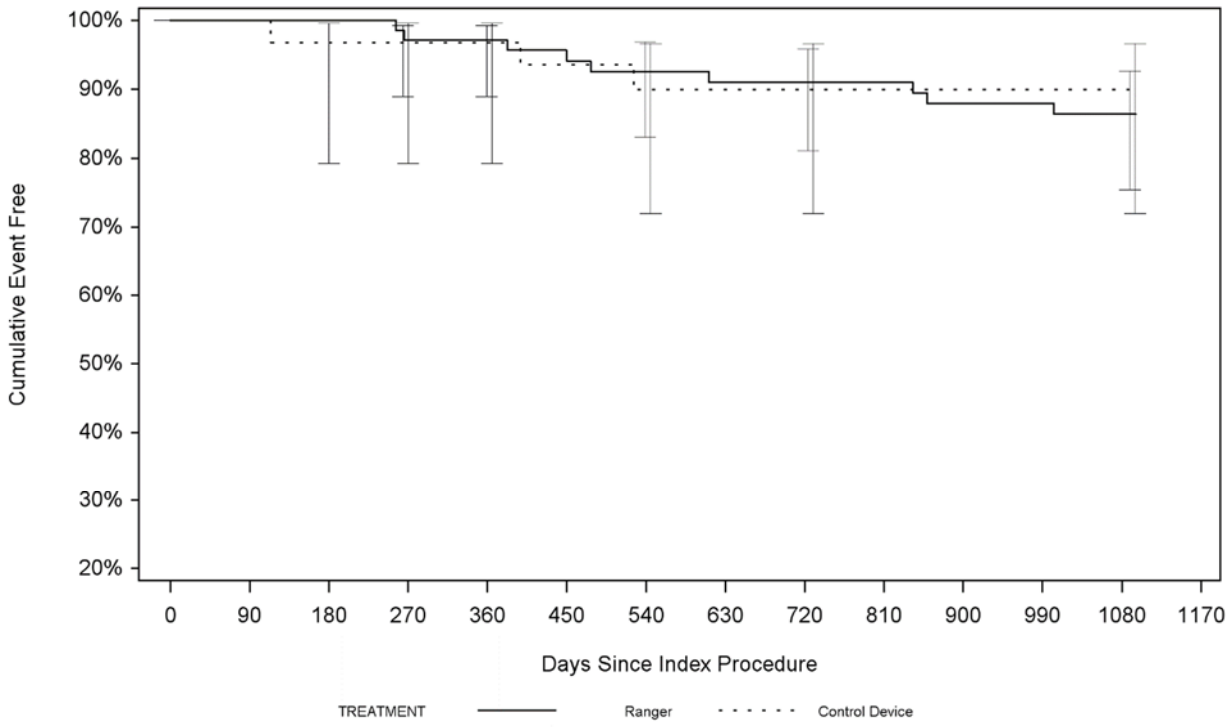
Kaplan Meier Analysis:



	Time from Index Procedure (Days)							
Number of Subjects with Ranger Device	**0**	**1-90**	**91-180**	**181-270**	**271-365**	**366-545**	**546-730**	**731-1095**
Entered	278	277	274	271	263	249	224	147
Censored	1	2	1	8	12	19	74	135
Events	0	1	2	0	2	6	3	7
Event Rate	0%	0.4%	1.1%	1.1%	1.8%	4.3%	5.7%	23.4%
Event Free	100%	99.6%	98.9%	98.9%	98.2%	95.7%	94.3%	76.6%
Std Error	0%	0.4%	0.6%	0.6%	0.8%	1.3%	1.5%	7.6%
Number of Subjects with Control Device	**0**	**1-90**	**91-180**	**181-270**	**271-365**	**366-545**	**546-730**	**731-1095**
Entered	98	98	98	95	93	89	80	50
Censored	0	0	1	2	4	9	30	48
Events	0	0	2	0	0	0	0	1
Event Rate	0%	0%	2.1%	2.1%	2.1%	2.1%	2.1%	18.4%
Event Free	100%	100%	97.9%	97.9%	97.9%	97.9%	97.9%	81.6%
Std Error	0%	0%	1.4%	1.4%	1.4%	1.4%	1.4%	14.9%

Subjects event-free at 1095 days or later are censored at greater than 1095 days.
Event rate and standard error estimates are for interval end. Standard errors by Greenwood formula.
The computation of the 95% CI is based on a log-log transformation.
Additional post-hoc analysis requested by FDA. The reported 95% CIs are without multiplicity adjustment and need to be interpreted with caution.

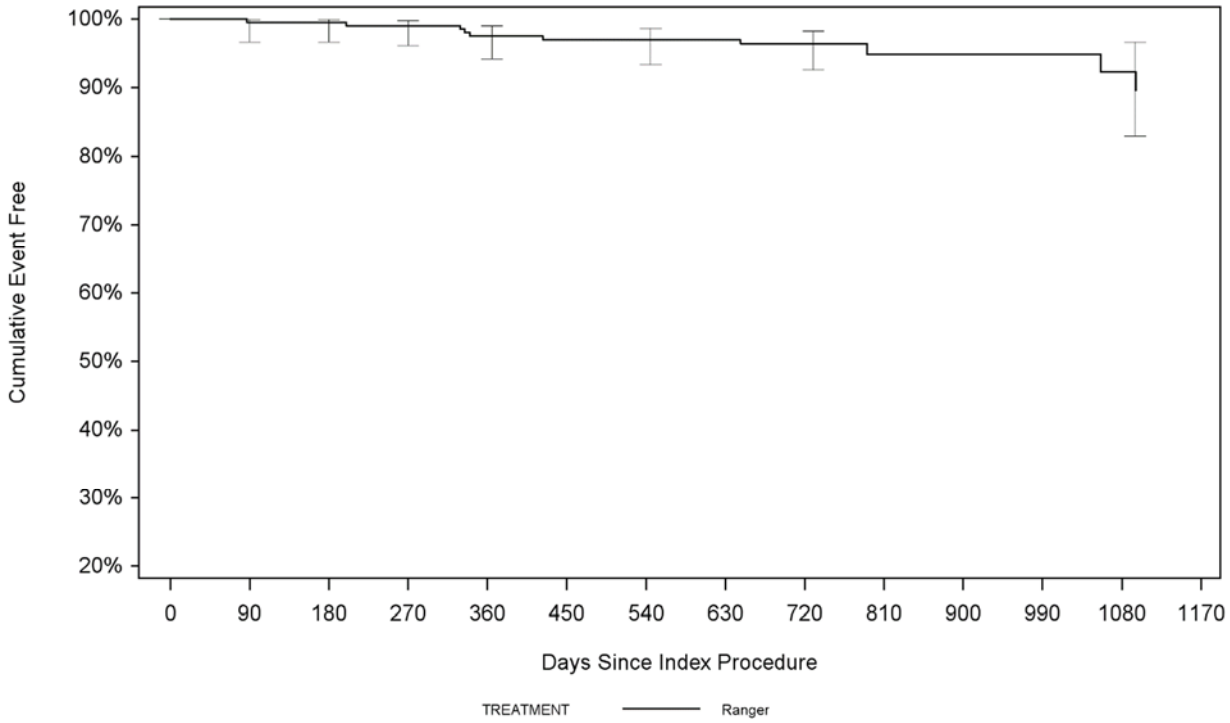
Figure 6: Kaplan-Meier Survival Through 36 Months - RANGER II SFA Study



	Time from Index Procedure (Days)							
Number of Subjects with Ranger Device	**0**	**1-90**	**91-180**	**181-270**	**271-365**	**366-545**	**546-730**	**731-1095**
Entered	71	71	70	70	67	67	60	59
Censored	0	1	0	1	0	4	0	25
Events	0	0	0	2	0	3	1	3
Event Rate	0%	0%	0%	2.9%	2.9%	7.4%	9.0%	13.6%
Event Free	100%	100%	100%	97.1%	97.1%	92.6%	91.0%	86.4%
Std Error	0%	0%	0%	2.0%	2.0%	3.2%	3.5%	4.2%
Number of Subjects with Control Device	**0**	**1-90**	**91-180**	**181-270**	**271-365**	**366-545**	**546-730**	**731-1095**
Entered	34	32	31	30	30	30	25	25
Censored	2	1	0	0	0	3	0	13
Events	0	0	1	0	0	2	0	0
Event Rate	0%	0%	3.2%	3.2%	3.2%	10.0%	10.0%	10.0%
Event Free	100%	100%	96.8%	96.8%	96.8%	90.0%	90.0%	90.0%
Std Error	0%	0%	3.2%	3.2%	3.2%	5.5%	5.5%	5.5%

Subjects event-free at 1095 days or later are censored at greater than 1095 days.
Event rate and standard error estimates are for interval end. Standard errors by Greenwood formula.
The computation of the 95% CI is based on a log-log transformation.
Additional post-hoc analysis requested by FDA. The reported 95% CIs are without multiplicity adjustment and need to be interpreted with caution.

Figure 7: Kaplan-Meier Survival Through 36 Months – RANGER SFA-FIM Study



	Time from Index Procedure (Days)							
Number of Subjects with Ranger Device	**0**	**1-90**	**91-180**	**181-270**	**271-365**	**366-545**	**546-730**	**731-1095**
Entered	207	207	204	204	201	189	169	111
Censored	0	2	0	2	9	19	57	75
Events	0	1	0	1	3	1	1	2
Event Rate	0%	0.5%	0.5%	1.0%	2.5%	3.0%	3.6%	7.7%
Event Free	100%	99.5%	99.5%	99.0%	97.5%	97.0%	96.4%	92.3%
Std Error	0%	0.5%	0.5%	0.7%	1.1%	1.2%	1.3%	3.2%

Subjects event-free at 1095 days or later are censored at greater than 1095 days.
Event rate and standard error estimates are for interval end. Standard errors by Greenwood formula
The computation of the 95% CI is based on a log-log transformation.
Additional post-hoc analysis requested by FDA. The reported 95% CIs are without multiplicity adjustment and need to be interpreted with caution.

Figure 8: Kaplan-Meier Survival Through 36 Months - Ranger COMPARE I Study

Bayesian Predictive Modeling:

Bayesian predictive modeling was used to estimate the 3-year mortality rate for the Ranger DCB with priors generated from RANGER SFA-FIM (FIM) and COMPARE studies with specific weights. The upper limit of "one-sided" 95% Bayesian credible interval (BCI) of 3-year mortality rate was compared to a performance goal (PG) of 12.9%. This performance goal was determined based on the upper limit of the 95% CI of mortality rates obtained using a random-effects meta-analysis model, combining the 3-year mortality rates of the currently US marketed paclitaxel coated devices[1]. Analyses were performed with

various choices of weights for the FIM and COMPARE studies, and in all cases, the upper limit of "one-sided" 95% BCI of 3-year mortality rate did not exceed the PG.

Based on the totality of the data provided, the Ranger DCB does not appear to present an unacceptable mortality risk compared to currently marketed paclitaxel-coated devices.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The RANGER II SFA clinical study is a prospective, randomized, multi-center, single-blind study comparing the Ranger Paclitaxel-Coated PTA Balloon Catheter (Ranger DCB) to standard balloon angioplasty (PTA) for treatment of femoropopliteal arteries in a single limb. The RANGER II SFA clinical study met its primary effectiveness endpoint for primary patency at 12 months, demonstrating superiority in the Ranger DCB test group compared to the PTA control group. As a result, the primary patency at 12 months for the full RCT cohort was 82.9% in the Ranger DCB group and 66.3% in the Standard PTA group respectively, with the one-sided lower 97.5% confidence bound on the difference to be 5.53% (p-value=0.0017).

Therefore, the primary effectiveness endpoint was met and Ranger DCB is concluded to be superior to Standard PTA for the primary effectiveness endpoint. Secondary effectiveness endpoints showed favorable results for the Ranger DCB group.

These results support the effectiveness of the Ranger DCB for the treatment of symptomatic vascular disease of the superficial femoral and popliteal arteries.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in the clinical studies conducted to support PMA approval, as described above. The RANGER II SFA study met its primary safety endpoint. Ranger DCB will be concluded to be non-inferior to Standard PTA for the primary safety endpoint if the one-sided lower (97.5%) confidence bound on the difference between treatment groups (Ranger DCB vs. Standard PTA) in 12-month MAE-free rate is greater than -0.1 (or -10%). As a result, the MAE-free rate at 12 months in the full RCT cohort was 94.1% in the Ranger DCB group and 83.5% in the Standard PTA group respectively, with the one-sided lower 97.5% confidence bound on the difference to be 2.48% (non-inferiority p-value <.0001). Therefore, the primary safety endpoint was met and Ranger DCB is concluded to be non-inferior to Standard PTA for the primary safety endpoint. Further, available longer-term mortality data suggests

that the risk for mortality with the Ranger DCB is similar to that of similar, approved products. These results support the safety of the Ranger DCB for the treatment of symptomatic vascular disease of the superficial femoral and popliteal arteries.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval, as well as additional analyses, as described above. The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit of the Ranger DCB improving patients' symptoms and quality of life outweigh the probable risks associated with use of the device. Additional factors to be considered in determining probable risks and benefits for the Ranger DCB include:

1. The clinical study provided adequate follow-up (12 months) to evaluate safety and effectiveness, with measures taken to assess the impact of missing data. Additional longer-term follow-up data was provided throughout the review.
2. The device is intended for use in subjects with peripheral vascular disease of the superficial femoral and popliteal arteries. The results adequately support general use in the identified population.
3. There are alternative treatments available for this disease, such as percutaneous transluminal angioplasty (PTA) alone, but this treatment has been shown to be superior to PTA alone with regard to effectiveness. Other drug coated balloons are also available. This product has shown similar safety and effectiveness results to these approved products.
4. Patient risk is minimized by limiting the use to operators who have the necessary training to use the device safely and effectively. Adherence to the recommended periprocedural medication regimens is also stressed.
5. The frequency and types of the adverse events reported throughout the pivotal clinical study are in alignment with what might be expected in the studied patient population and therapeutic area. No unanticipated adverse device effects were reported in the study.
6. In consideration of the mortality signal observed in patients after 2 years post-treatment with paclitaxel-coated devices used to treat femoropopliteal atherosclerotic disease, long-term Ranger DCB mortality data was evaluated to demonstrate the Ranger DCB does not represent an unacceptable risk of late mortality compared to marketed devices.

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, the data support that for the percutaneous transluminal angioplasty 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 of the RANGER II SFA study show the Ranger DCB is non-inferior to PTA in safety and superior in effectiveness based on the totality of the Ranger II SFA data, and confirm the Ranger DCB is appropriate for the treatment of SFA and PPA lesions when used in accordance with the labeling and Directions for Use (DFU).

XIV. CDRH DECISION

CDRH issued an approval order on October 30, 2020.

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

1. *RANGER II SFA Continued Follow-Up Study:* This study will evaluate the long-term safety and effectiveness of the Ranger DCB in 376 subjects from the premarket study (RANGER II SFA trial). The RANGER II SFA trial was designed as a global, single-blind, multicenter, randomized (3:1 Ranger DCB to PTA) trial. Subjects will be followed annually through 5 years post-procedure with no more than 15% attrition.

   The primary effectiveness endpoint is primary patency of the target lesion at 24 months.

   The primary safety endpoint is a composite of freedom from device- and procedure-related death at 30 days and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) at 24 months.

   The endpoints to be assessed through 5 years post-procedure are rate of: (1) major adverse events (MAE), (2) clinically-driven target lesion revascularization (CD-TLR), (3) all TLR, (4) clinically-driven target vessel revascularization (CD-TVR), (5) target limb major amputation, (6) arterial thrombosis and (7) mortality status. The endpoints to be assessed at 2 and 3 years post-procedure are: (1) patency, (2) change in ankle-brachial index (ABI), (3) change in walking impairment questionnaire (WIQ), (4) change in walking distance, (5) change in Rutherford classification, and (6) change in quality of life assessment by EQ-5D questionnaire.

   Robust independent adjudication of events (i.e., Clinical Events Committee) will be maintained throughout the PAS study, unmodified from the pivotal portion of the study. In addition, COVID-19 testing and adjudication of COVID-19 related events will be included. RANGER II SFA updates will be provided semi-annually for 2 years and annually thereafter until all subjects have completed the 5 year follow-up visit, are discontinued prior to the 5 year follow-up visit, have died, or the 5 year follow-up window has closed.

2. Ranger Long Balloon, Ranger China, and COMPARE I Follow-up Studies: These studies will provide additional safety and effectiveness data for the Ranger DCB. Updates will be provided on the following ongoing clinical studies:

Ranger Long Balloon Substudy: The Ranger Long Balloon Substudy is a non-blinded, non-randomized, single-arm Long Balloon (LB) Sub Study to fulfill the post-market clinical follow-up requirement by DEKRA in Europe and New Zealand regions following enrolled patients for one year. Semi-annual updates, including mortality status, will be provided for the Ranger Long Balloon Sub study until all subjects have completed the 12 month follow-up visit, are discontinued prior to the 12 month follow-up visit, have died, or the 12 month follow-up window has closed.

Ranger China Study: The Ranger China study, is a prospective, non-randomized, multi-center, premarket clinical study to demonstrate acceptable safety and performance of Ranger DCB used for angioplasty of femoropopliteal artery lesions. This study will enroll 123 subjects at up to 15 sites in China that will follow patients through 12 months. Annual updates, including mortality status, will be provided.

COMPARE I Study: the COMPARE I Study (NCT02701543), an investigator sponsored, prospective, multi-center, 1:1 randomized trial comparing Ranger and IN.PACT™ DCBs in the treatment of high grade stenotic or occluded lesions in the SFA and/or PPA in PAD patient with Rutherford class 2-4 This European post-market study enrolled 414 subjects (approximately 207 Ranger DCB) at up to 18 sites with a follow-up period 24 months to assess patency by duplex ultrasound (DUS) and major adverse events (MAEs). Annual updates, including mortality status up to 5 years, will be provided.

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.