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50589598-01

2020-10
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Ranger™

OVER-THE-WIRE

Paclitaxel-Coated PTA Balloon Catheter

TABLE OF CONTENTS

℞ ONLY

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

1. WARNING

A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel-coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. See Section 8.1 for further information.

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For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

2. DEVICE DESCRIPTION

The Ranger Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter (Ranger Drug-Coated Balloon) is an Over-the-Wire (OTW) PTA balloon catheter with a semi-compliant balloon coated with a formulation of paclitaxel (drug) and an excipient. The Ranger Drug-Coated Balloon (DCB) is designed to provide mechanical dilatation and inhibit restenosis by delivering drug to diseased arterial tissue.

The Ranger DCB has a coaxial shaft design. The outer lumen is used for inflation of the balloon, and the wire lumen permits the use of guidewires 0.014 in or 0.018 in (0.36 mm or 0.46 mm) to facilitate advancement of the catheter. The balloon is designed to provide an inflatable segment of known diameter and length at recommended pressures. The catheter includes a tapered tip to facilitate advancement to and through the stenosis.

The Ranger DCB has two 1.3 mm radiopaque marker bands (one proximal and one distal) which, in conjunction with fluoroscopy, aid in the placement of the balloon. The proximal shaft marks define the length to the distal end of the catheter.

The working lengths of the Ranger DCBs are 80 cm, 90 cm, 135 cm, and 150 cm. The 80 cm and 90 cm working length catheters have one mark at 50 cm and two marks at 60 cm. The 135 cm and 150 cm working length catheters have one mark at 90 cm and two marks at 100 cm.

The proximal portion of the Ranger DCB includes one female Luer-lock port connected to the inflation lumen, and one female Luer-lock port for the guidewire lumen. In addition, the Ranger DCB is equipped with a removable loading tool to help protect the drug coating prior to sheath insertion. Images of the Ranger Paclitaxel-Coated PTA Balloon Catheter are below (**Figure 1** and **Figure 2**).

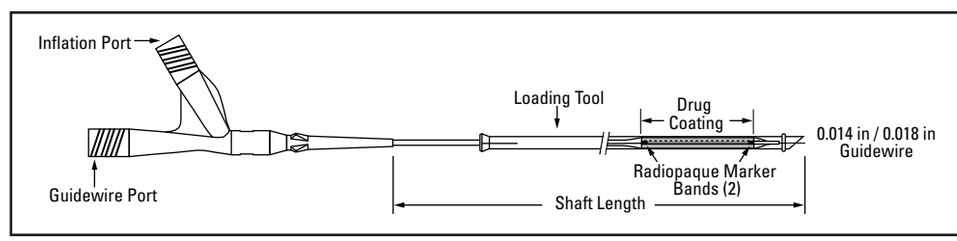


Figure 1: Ranger Paclitaxel-Coated PTA Balloon Catheter with Loading Tool

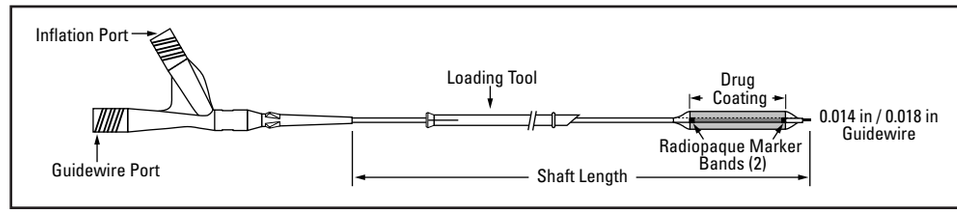


Figure 2: Ranger Paclitaxel-Coated PTA Balloon Catheter with Balloon Inflated and Loading Tool

Table 1: Recommended Introducer Sheath and Maximum Crossing Profile

Balloon Diameter (all lengths)	Recommended Introducer Sheath	Maximum Crossing Profile
4.0 mm and 5.0 mm	≥ 5F (1.7 mm)	≤ 5.3F (1.78 mm)
6.0 mm	≥ 5F (1.7 mm)	≤ 5.6F (1.88 mm)
7.0 mm	≥ 6F (2.0 mm)	≤ 6.6F (2.20 mm)

2.1. Drug Component Description

The Ranger™ Drug-Coated Balloon has a drug coating formulation consisting of paclitaxel (the active pharmaceutical ingredient) and an excipient (the inactive ingredient).

2.1.1. Paclitaxel

The active pharmaceutical ingredient in the balloon coating is paclitaxel (PTx). The dose density of paclitaxel is 2.0 µg per mm^2 of the balloon surface. The principal mechanism by which PTx inhibits neointimal growth is through the stabilization of microtubules by preventing depolymerization during the final G2/M phase of cell division. PTx is a semi-synthetic paclitaxel synthesized from precursor compounds, isolated from a spectrum of Taxus species and hybrids.

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

Table 2: Paclitaxel Dose per Balloon

		Balloon Length (mm)							
		30	40	60	80	100	120	150	200
Balloon Diameter (mm)	4	782 µg	1043 µg	1564 µg	2086 µg	2607 µg	3100 µg	3878 µg	5165 µg
	5	975 µg	1301 µg	1951 µg	2601 µg	3251 µg	3978 µg	4942 µg	6592 µg
	6	1100 µg	1467 µg	2200 µg	3108 µg	3889 µg	4809 µg	5975 µg	7966 µg
	7	1283 µg	1711 µg	2714 µg	3626 µg	4538 µg	5564 µg	6958 µg	9266 µg

2.1.2. Acetyl Tributyl Citrate

The coating utilizes the inactive ingredient Acetyl Tributyl Citrate (ATBC) as an excipient to facilitate the release and transfer of paclitaxel into the arterial wall. ATBC is a carboxylic acid ester with a molecular weight of 402.48 g/mol.

2.2. User Information

The Ranger Paclitaxel-Coated PTA Balloon Catheter is non-pyrogenic.

Only physicians who are familiar with the principles, clinical applications, complications, side effects, and hazards commonly associated with native superficial femoral or popliteal artery interventional procedures should use this device.

2.3. Contents

Quantity	Material
1	Ranger Drug-Coated Balloon (DCB)

3. INTENDED USE / INDICATIONS FOR USE

The Ranger Drug-Coated Balloon (DCB) 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 mm to 7 mm.

4. CONTRAINDICATIONS

Use of the Ranger DCB is contraindicated 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 men intending to father children.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.
- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries.

5. WARNINGS

- Never use air or any gaseous medium to inflate the balloon (a 50:50 mixture of contrast medium and sterile saline is recommended).
- When the balloon catheter is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation.
- Do not advance or retract the catheter unless the balloon is fully deflated under vacuum.
- If unusual resistance is felt during manipulation, determine the cause of the resistance before proceeding. If the source of resistance cannot be determined, it is recommended to extract the entire system with the guiding sheath.
- If difficulty is experienced during balloon inflation, do not continue. Deflate the balloon and remove the catheter.
- To reduce the potential for vessel damage, the inflated diameter of the balloon should approximate the diameter of the vessel segment to be treated. The inflated length of the balloon (shoulder to shoulder) may exceed the length of the lesion/stenosis by approximately 10 mm on either side within the targeted artery.
- Do not exceed the balloon rated burst pressure. Use of an inflation device is recommended to prevent over-pressurization.
- The safety of using multiple Ranger DCBs with a total drug dosage exceeding 9266 µg of Paclitaxel in a patient has not been studied.
- Using a drug-eluting stent in conjunction with Ranger DCB at the same treatment site has not been studied.

6. PRECAUTIONS

- The balloon catheter should be used only by physicians trained in the performance of percutaneous transluminal angioplasty.
- Use the balloon catheter prior to the "Use By" date specified on the package.
- The balloon catheter should be used with caution for procedures involving calcified lesions due to the abrasive nature of these lesions.
- The balloon catheter is not intended for injection of contrast medium.
- Full arterial wall apposition of the Ranger DCB is necessary for proper drug transfer to the vessel.
- Carefully inspect the balloon catheter prior to use to verify that it has not been damaged during shipment and that its size, shape and condition are suitable for the procedure for which it is to be used.
- If unusual resistance is felt during positioning of the loading tool, do not use the balloon catheter. Replace with a new Ranger DCB.
- If unusual resistance is felt during catheter advancement through the valve, do not use the balloon catheter. Replace with a new Ranger DCB.
- Do not touch, wipe, bend, or squeeze the balloon. Do not allow it to contact any liquids including organic solvents such as alcohol or detergents prior to insertion. Damage to the balloon coating or premature release of the drug may occur.
- To minimize the possible introduction of air into the system, it is imperative that prior to proceeding, careful attention is paid to the maintenance of tight catheter connections and thorough aspiration and flushing of the system.
- If using a Tuohy-Borst type adapter, take care not to over-tighten the hemostasis valve around the catheter shaft as lumen constriction may occur, affecting inflation/deflation of the balloon or damaging the drug coating.
- Never advance the balloon catheter without the guidewire extending from the distal tip.
- When using a sheath, do not insert the loading tool more than 20 mm into the sheath valve.
- This product should not be used in patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy.
- If loading tool tip will not enter the guide / introducer sheath valve, forcing the loading tool can cause catheter shaft kinking and damage to drug coating when advancing the catheter. Consider replacing introducer sheath.
- If treating a long lesion (longer than the maximum balloon length available), each individual segment should be treated only once with a drug-coated balloon. Treat each segment with a new balloon and minimize overlapping of treated segments.

6.1. Pregnancy / Lactation

This product has not been tested in pregnant or breastfeeding women or in men intending to father children; effects on the developing fetus have not been studied and the risks and reproductive effects remain unknown.

It is not recommended that the Ranger DCB be used in women attempting to conceive, or who are pregnant.

Prior to use, careful consideration should be given to the continuation of breastfeeding, taking into account the importance of the procedure to the mother. It is not known whether paclitaxel is distributed in human milk. In lactating rats, milk concentrations appeared to be higher than maternal plasma levels and declined in parallel with the maternal levels. Mothers should be advised of the potential for serious adverse reactions to paclitaxel in nursing infants.

6.2. Drug Information

The mechanism of action by which paclitaxel reduces or reverses neointima formation and proliferation, leading to restenosis, as demonstrated in clinical studies has not been established. It is known that paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

6.3. Drug Interaction

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated. Drug interactions of systemic chemotherapeutic levels of paclitaxel with possible concomitant medications are outlined in the labeling for finished pharmaceuticals containing paclitaxel, such as TAXOL™.

6.4. Carcinogenicity, Genotoxicity, and Reproductive Toxicology

No long-term studies in animals have been published in peer reviewed literature to evaluate the carcinogenic potential of paclitaxel. Paclitaxel interacts with microtubules; this is the major mechanism by which it inhibits cell growth. One consequence is the loss of whole chromosomes via interactions with spindle microtubules during cell division. As such, paclitaxel is defined as an aneugen (agent causing an alteration in chromosome number). This indirect action is consistent with positive responses in *in vitro* and *in vivo* micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT. Paclitaxel administered via IV prior to and during mating produced impairment of fertility in male and female rats at doses > 1 mg/kg. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day caused embryo- and fetotoxicity. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day; teratogenic potential

could not be assessed at higher doses due to extensive fetal mortality. For comparison, the worst-case dose of paclitaxel delivered by the Ranger™ DCB (assuming maximum size and number of balloons used in a lesion) is 9266 µg, which is approximately 6 and 19 times less than the dose that saw effects in rats and rabbits, respectively, when normalizing to body weight.

6.5. Pre and Post Procedure Antiplatelet Therapy

It is strongly advised that the treating physician follow the Inter-Society Consensus (TASC II) Guidelines recommendations (or other applicable country guidelines) for antiplatelet therapy pre- and post-procedure.

7. ADVERSE EVENTS

Potential adverse events include, but are not limited to, the following:

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

Potential adverse events not captured above that may be unique to the paclitaxel drug coating:

- 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.

There may be other potential adverse events that are unforeseen at this time.

8. CLINICAL STUDIES

8.1. Late Mortality Signal for Paclitaxel-Coated Devices

A meta-analysis of randomized controlled trials published in December 2018 by Katsanos et. al. identified an increased risk of late mortality at 2 years and beyond for paclitaxel-coated balloons and paclitaxel-eluting stents used to treat femoropopliteal arterial disease. In response to these data, FDA performed a patient-level meta-analysis of long-term follow-up data from the pivotal premarket randomized trials of paclitaxel-coated devices used to treat femoropopliteal disease using available clinical data through May 2019. The meta-analysis also showed a late mortality signal in study subjects treated with paclitaxel-coated devices compared to patients treated with uncoated devices. Specifically, in the 3 randomized trials with a total of 1090 patients and available 5-year data, the crude mortality rate was 19.8% (range 15.9% - 23.4%) in patients treated with paclitaxel-coated devices compared to 12.7% (range 11.2% - 14.0%) in subjects treated with uncoated devices. The relative risk for increased mortality at 5 years was 1.57 (95% confidence interval 1.16 - 2.13), which corresponds to a 57% relative increase in mortality in patients treated with paclitaxel-coated devices. As presented at the June 2019 FDA Advisory Committee Meeting, an independent meta-analysis of similar patient-level data provided by VIVA Physicians, a vascular medicine organization, reported similar findings with a hazard ratio of 1.38 (95% confidence interval 1.06 - 1.80). Additional analyses have been conducted and are underway that are specifically designed to assess the relationship of mortality to paclitaxel-coated devices.

The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

Paclitaxel-coated balloons and stents improve blood flow to the legs and decrease the likelihood of repeat procedures to reopen blocked blood vessels compared to uncoated devices. The benefits of paclitaxel-coated devices (e.g., reduced reinterventions) should be considered in individual patients along with potential risks (e.g., late mortality).

In the RANGER II SFA Trial, long term follow-up has not been completed beyond one year; follow-up through five years is ongoing. In the RANGER II SFA Trial, the Kaplan Meier mortality estimate at 1 year is 1.8% (95% CI: 0.8%, 4.4%) for the Ranger DCB treatment device and 2.1% (95% CI: 0.5%, 8.0%) for the standard PTA control device. Additional information regarding outcomes can be found in Section 8.2.

8.2. The RANGER II SFA Trial

The clinical evidence supporting the safety and effectiveness of the Ranger Paclitaxel Coated PTA Balloon Catheter for the treatment of symptomatic de novo or restenotic lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery (PPA) with reference vessel diameters (RVD) ranging from 4.0 mm - 7.0 mm is from the RANGER II SFA Trial.

A study titled "A 3:1 Randomized Trial Comparing the Boston Scientific RANGER Paclitaxel Coated Balloon vs Standard Balloon Angioplasty for the Treatment of Superficial Femoral Arteries (SFA) and Proximal Popliteal Arteries (PPA)" (RANGER II SFA) was conducted. The RANGER II SFA Trial is a global, prospective, multicenter, 3:1 randomized (Ranger DCB vs standard PTA balloon), controlled, single-blind, superiority trial (RCT). It also includes a concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) substudy.

8.2.1. Primary Objective

The primary objective of the study was to determine whether the Ranger Paclitaxel Coated PTA Balloon Catheter showed acceptable performance in long-term (12-month) safety rates and vessel patency when treating femoropopliteal lesions.

8.2.2. Study Design

A total of 388 subjects were enrolled in the RANGER II SFA Trial, including 376 subjects in the RCT, 12 subjects in the PK substudy. Subjects were enrolled at 67 centers located in the United States, Canada, Japan, New Zealand and Europe. Subject follow-up is ongoing and will extend for 5 years post index procedure.

Eligible subjects were 20 years or older and consented to participate in the study. These subjects had documented peripheral artery disease defined as Rutherford categories 2, 3, or 4 and evidence of a stenotic, restenotic or occlusive lesion(s) located in the native SFA or PPA with a degree of stenosis ≥ 70% by visual angiographic assessment. The vessel diameter was ≥ 4 mm and ≤ 8 mm and total lesion length (or series of lesions) was ≤ 180 mm. Of the total lesion length allowable of ≤ 180 mm, the total occlusion lesion length allowed was ≤ 100 mm. Lesions were located in the SFA and PPA down to the P1 segment. Subject follow-up is occurring at 1 month, 6 months, 12 months, 2 years, 3 years, 4 years and 5 years after the index procedure for the RCT and PK substudy.

Data collected through November 19, 2019 on the full RCT cohort is included below.

The primary study endpoints were as follows:

- 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.

The secondary study endpoints were as follows:

- 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 months, 12 months, 24 months, 36 months, 48 months and 60 months.
- TVR rates at 6 months, 12 months, 24 months, 36 months, 48 months and 60 months.
- TLR rates at 6 months, 12 months, 24 months, 36 months, 48 months and 60 months.
- Rate of Primary and Secondary sustained clinical improvement as assessed by changes in Rutherford Classification from baseline at 1 month, 6 months, 12 months, 24 months and 36 months post-procedure.
- Rate of Hemodynamic Improvement as assessed by changes in Ankle-Brachial Index (ABI) from baseline at 1 month, 6 months, 12 months, 24 months and 36 months post-procedure.
- Duplex-defined binary restenosis (PSVR > 2.4) of the target lesion at 1 month, 6 months, 12 months, 24 months 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 month, 6 months, 12 months, 24 months 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.

The RANGER II SFA Trial employed independent duplex ultrasound, angiographic and PK core laboratories to review and analyze key study variables. An independent data reviewer was used to review study data on an ongoing basis and identify any potential safety trends. Adjudication of any potential major adverse events was conducted by an independent Clinical Events Committee (CEC).

8.2.3. Patient Population

Table 3 provides a review of baseline demographics and medical history of the 376 subjects enrolled into the RANGER II SFA Randomized Controlled Trial (RCT).

Table 3: 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)
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)

Subject Characteristic	Ranger™ DCB (N=278 Subjects)	Standard PTA (N=98 Subjects)
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 (276) (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)

8.2.4. Lesion Characteristics

Table 4 presents the baseline lesion characteristics, procedural characteristics, and post-procedure measurements for the RCT.

Table 4: Baseline, Procedural 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)
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.

8.2.5. Study Results

Primary Effectiveness and Safety Results - RCT

Table 5 presents the primary effectiveness and safety results for the full RCT cohort. Ranger DCB will be concluded to be superior to standard PTA for primary effectiveness endpoint if the one-sided lower 97.5% confidence bound on the difference between treatment groups (Ranger DCB vs. standard PTA) in 12-month primary patency is greater than zero. Based on the intent-to-treat (ITT) population, the 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 Per-Protocol (PP) population which consisted of randomized subjects who met the eligibility criteria and received the assigned treatment, and had similar results to the ITT population. Therefore, the primary effectiveness endpoint was met and Ranger DCB is concluded to be superior to standard PTA for the primary effectiveness endpoint. Kaplan-Meier plot of primary patency through 13 months is presented in **Figure 3**.

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%). Based on the 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 PP population and had similar results. Therefore, the primary safety endpoint was met and Ranger DCB is concluded to be non-inferior to standard PTA for the primary safety endpoint. Kaplan-Meier plot of freedom from MAE through 365 days is presented in **Figure 4**.

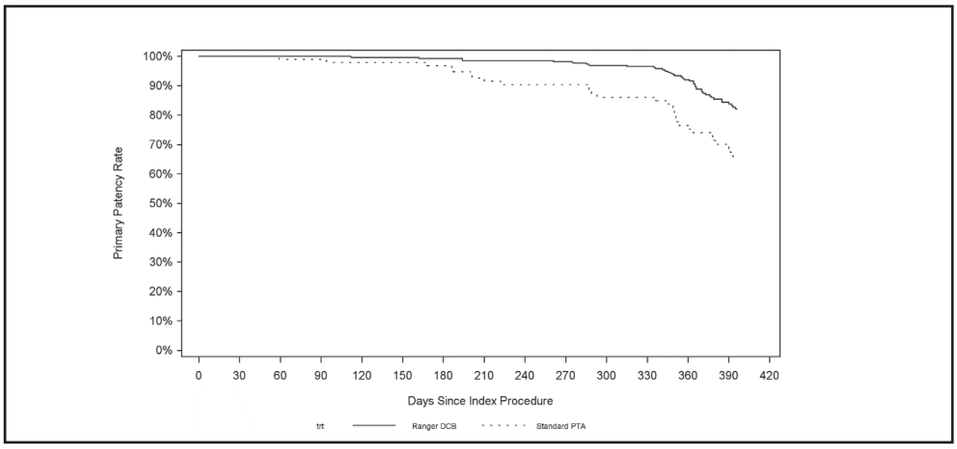
Table 5: Primary Effectiveness & Safety Endpoints - Full Cohort RCT, Intent-to-Treat (N=376 Subjects), Per Protocol (N=370 Subjects)

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
Intent-To-Treat (N=376)	**Ranger DCB (N=278 Subjects)**	**Standard PTA (N=98 Subjects)**	**Difference [95% CI]**	**One-sided 97.5% Lower CI**	**Non-Inferiority P-value[3]**
12-Month MAE-Free[2]	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**
12-Month Primary Patency[1]	83.1% (192/231)	66.7% (56/84)	16.5% [5.3%, 27.6%]	5.27%	0.0020
Per-Protocol (N=370)	**Ranger DCB (N=274 Subjects)**	**Standard PTA (N=96 Subjects)**	**Difference [95% CI]**	**One-sided 97.5% Lower CI**	**Non-Inferiority P-value[3]**
12-Month MAE[2]-Free	94.8% (239/252)	84.3% (75/89)	10.6% [2.5%, 18.6%]	2.53%	<.0001

[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.

[2] 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.
[3] 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.

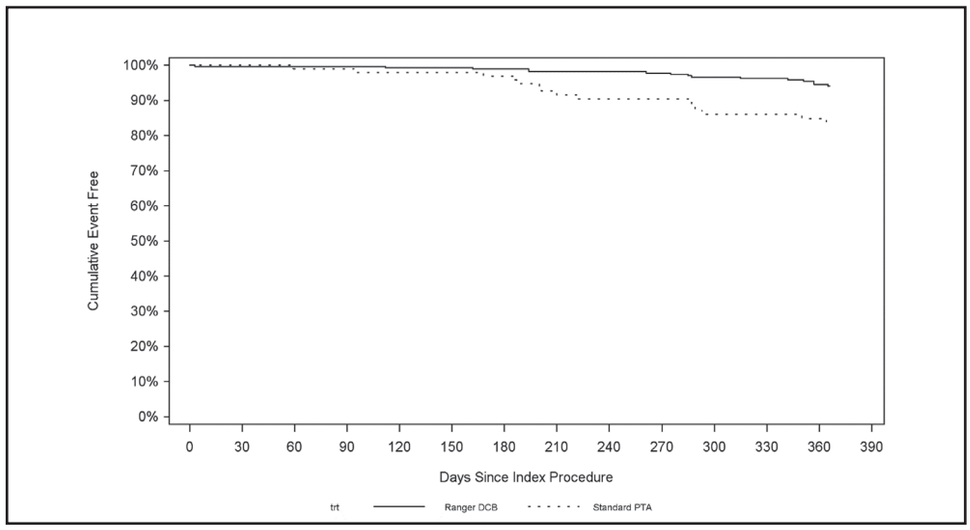
Figure 3: Kaplan-Meier Plot – Primary Patency Through 13 Months - Full Cohort RCT, Intent-to-Treat (N=376 Subjects)



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



	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.

Table 6 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.

Table 6: 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% (0/91)	

[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.

Secondary Endpoints

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 months and 12 months assessed by change in Six Minute Hall Walk (6 MHW) 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 7** displays hemodynamic improvement was achieved in 88.8% (230/259) in the Ranger DCB group and 75.9% (66/87) 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 8** displays primary sustained clinical improvement at 12 months was achieved in the Ranger DCB group at 87.6% (220/251) and standard PTA group at 75.8% (69/91).

Table 7: 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)
1 Month		
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 8: 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)
For discrete variables, the Chi-square test is used by default. The p-value is denoted with an asterisk "*" in the case where the Fisher's exact test is used.		

Walking improvement was observed throughout the study as well, with observed improvement in distance walked as measured by the 6 Minute Walk Test (6MWT) in **Table 9**, and in walking impairment as assessed by the Walking Impairment Questionnaire (WIQ) in **Table 10** and an observed increase in the EQ-5D™ Index Value as measured by the EQ-5D Questionnaire in **Table 11**.

Table 9: 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 10: 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 11: 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.		

8.2.6. Summary of Adverse Events - RCT

Table 12 displays the rates of site-reported Serious Adverse Events (SAEs) reported by MedDRA System Organ Class (SOC) and preferred term for the RCT. An SAE was defined as an adverse event that:

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

Table 12: Frequency of Site-Reported Serious Adverse Events to 12 Months – RCT, Intent-to-Treat (N=376)

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)
	Peripheral ischaemia	3	1.1% (3/278)	0	0.0% (0/98)
	Haematoma	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)
	Ischaemic 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)
	Anaemia postoperative	1	0.4% (1/278)	0	0.0% (0/98)
	Contusion	1	0.4% (1/278)	0	0.0% (0/98)
	Extradural haematoma	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 haematoma	1	0.4% (1/278)	0	0.0% (0/98)
	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)

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
	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 haematoma	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)
	Dyspnoea	1	0.4% (1/278)	0	0.0% (0/98)
	Haemothorax	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 disorders	Total	9	3.2% (9/278)	5	4.1% (4/98)
	Constipation	1	0.4% (1/278)	1	1.0% (1/98)
	Abdominal pain upper	1	0.4% (1/278)	0	0.0% (0/98)
	Diarrhoea	1	0.4% (1/278)	0	0.0% (0/98)
	Enteritis	1	0.4% (1/278)	0	0.0% (0/98)
	Gastrointestinal haemorrhage	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 haemorrhage	1	0.4% (1/278)	0	0.0% (0/98)
	Retroperitoneal haematoma	1	0.4% (1/278)	0	0.0% (0/98)
	Upper gastrointestinal haemorrhage	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)

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
	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)
	ntervertebral 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 lung	1	0.4% (1/278)	0	0.0% (0/98)
	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)
	Anaemia	2	0.7% (2/278)	1	1.0% (1/98)
	Iron deficiency anaemia	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)
	Hyperglycaemia	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)
	Haemoglobin decreased	0	0.0% (0/278)	1	1.0% (1/98)

"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.

8.2.7. Subgroup Analyses

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 13**), Primary Patency at 12 Months (**Table 14**), and Clinically-driven Target Lesion Revascularization at 12 Months (**Table 15**) 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 13: 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 14: 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 15: 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)
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. 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 16: Primary Safety and Primary Effectiveness Endpoints by Gender, Full Cohort 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.

8.2.8. Pharmacokinetic Substudy

Human pharmacokinetics was investigated as a sub-study of the RANGER II SFA Trial. This sub-study was a prospective, multicenter, non-randomized study arm (Ranger DCB) conducted at multiple prespecified U.S. investigational sites, designed to evaluate the levels of paclitaxel in the systemic circulation of subjects at multiple time points. Pharmacokinetic parameters were determined for a total of 12 subjects (4 male and 8 female).

The average lesion length for the PK sub-study was 154.2 mm (+/- 92.8 mm). At one hour following use of Ranger DCB, 11 of 12 patients had no measurable level of paclitaxel in the blood stream. All patients had no measureable level at the next time point (3 hours). The PTx limit of quantification is < 1 ng/mL.

A summary of the pharmacokinetic parameters is presented in **Table 17.** The pharmacokinetic sub-study demonstrated low systemic exposure with rapid clearance of paclitaxel.

Table 17: 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} (h) C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	The timepoint where C_{max} is reached Maximum plasma concentration Area under the blood concentration versus time curve from time zero up to the time of the last quantifiable concentration, calculated by trapezoidal methods	

9. HOW SUPPLIED

Sterile.

Do not use if package is opened or damaged.

Do not use if labeling is incomplete or illegible.

9.1. Handling and Storage

Store at 25 °C (77 °F); excursions permitted to 15 °C - 30 °C (59 °F - 86 °F).

10. OPERATIONAL INSTRUCTIONS

10.1. Recommended Materials

One or more of each of the following materials are recommended for PTA with the Ranger Drug-Coated Balloon:

- Guidewire(s) of appropriate size for advancement of balloon catheter
- Contrast medium
- Sterile saline solution
- Inflation device with manometer
- 10 ml, 12 ml, or 20 ml luer-lock inflation device
- Hemostasis valve
- Three-way stopcock

10.2. Ranger Drug-Coated Balloon Selection

Select an appropriately sized balloon catheter for the diameter of the targeted artery. The nominal length of the balloon may exceed the length of the lesion/stenosis by approximately 10 mm on either side. Select an appropriate catheter shaft length considering the distance between the arterial access point and the location of the targeted lesion.

Caution: If treating a long lesion (longer than the maximum balloon length available), each individual segment should be treated only once with a drug-coated balloon. Treat each segment with a new balloon and minimize overlapping of treated segments.

Warning: The safety of using multiple Ranger™ DCBs with a total drug dosage exceeding 9266 µg of Paclitaxel in a patient has not been studied.

Warning: Using a drug-eluting stent in conjunction with Ranger DCB at the same treatment site has not been studied.

10.3. Inspection Prior to Use

Carefully examine all equipment to be used during the procedure, including the balloon catheter, to verify proper function. Verify that the balloon catheter and sterile packaging have not been damaged. Do not use if sterile package is damaged. Verify that the catheter size is suitable for the specific procedure for which it is intended.

Caution: Do not touch, wipe, bend, or squeeze the balloon. Do not allow it to contact any liquids including organic solvents such as alcohol or detergents prior to insertion. Damage to the balloon coating or premature release of the drug may occur.

Note: Do not use the balloon catheter if damage occurs or sterility is compromised.

10.4. Inflation Device Preparation

1. Prepare the inflation device according to the manufacturer's instructions.
2. Purge the system of air.

10.5. Ranger Drug-Coated Balloon Preparation

1. Remove the balloon catheter from the protective coil. Use care when removing the balloon catheter to avoid damage (e.g., shaft kink).
2. Prepare the balloon catheter for purging. Fill a 10 ml, 12 ml or 20 ml luer-lock inflation device with appropriate balloon catheter inflation medium.

   Warning: Never use air or any gaseous medium to inflate the balloon (a 50:50 mixture of contrast medium and sterile saline is recommended).
3. Connect a three-way stopcock to the inflation port fitting on the balloon catheter. Close the stopcock to the balloon catheter and flush through the stopcock. Use care when connecting the balloon catheter to avoid damage (e.g., shaft kink).
4. Connect the inflation device to the stopcock. Assure luer connections are properly aligned to avoid stripping the luer thread and causing subsequent leakage.
5. Open the stopcock to the balloon catheter. Hold the inflation device with the nozzle pointing downward and aspirate for 15 seconds to 20 seconds. Release the plunger or open the stopcock to air.
6. Remove the inflation device and evacuate all air from the barrel.
7. To prevent the possibility of air embolization, reconnect the inflation device and aspirate for 15 seconds to 20 seconds until bubbles no longer appear. If bubbles persist, check the luer connections. Discard and replace the balloon catheter if the problem cannot be resolved.
8. Disconnect the inflation device used in preparation. To remove any air lodged in the distal luer fitting of the inflation device, purge approximately 1 ml of contrast medium while pointing the inflation device upwards.
9. Verify that contrast medium is evident in both the inflation port and the inflation device connection to ensure a fluid-to-fluid connection. Adding a drop of inflation medium to the port may be necessary. Securely couple the inflation device to the inflation port.
10. Open the stopcock to the balloon catheter and maintain neutral pressure.
11. Move the loading tool proximally until only the distal tip of the balloon catheter is visible. If unusual resistance is encountered, first move the loading tool slightly distal (no more than 1 cm).
12. With the tip of the catheter pointed down, flush the guidewire lumen of the balloon catheter with sterile saline. Check for bends, kinks and other damage. Do not use if any defects are noted.

10.6. Delivery Procedure

Note: It is recommended to always use a smaller diameter balloon dilatation catheter to pre-dilate the stenosis to facilitate passage of the drug-coated balloon catheter.

1. Catheter Advancement
   a) Access and cross the stenosis with a guidewire using standard practice and/or device(s) manufacturer's instructions.
   b) Thoroughly aspirate and flush the introducer sheath in preparation for introduction of the balloon catheter.
   c) Backload the distal tip of the balloon catheter onto the guidewire ensuring that the guidewire exits the wire port of the catheter manifold.

      Note: To avoid kinking, advance the catheter slowly, in small increments, until the proximal end of the guidewire emerges from the catheter.

   d) Holding the loading tool with the balloon catheter, carefully advance the balloon catheter to the guide or introducer sheath (refer to **Figure 5**).

      Caution: If loading tool tip will not enter the guide/introducer sheath valve, forcing the loading tool can cause catheter shaft kinking and damage to drug coating when advancing the catheter. Consider replacing introducer sheath.

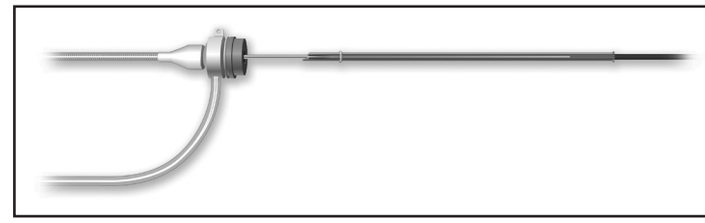


Figure 5: Inserting the Balloon Catheter with the Loading Tool

   e) With one hand grasp the distal end of the loading tool just proximal to the bump located near the distal end of the loading tool; with the other hand grasp the hemostasis valve on the guide/introducer sheath. Advance the loading tool into the hemostasis valve until the bump on the loading tool is in close proximity with the hemostasis valve.

      Caution: When using a sheath, do not insert the loading tool more than 20 mm into the sheath valve.

   f) While holding the proximal end of the loading tool in place, slowly advance the catheter through the introducer sheath by pushing the catheter shaft distally, without rotation, until the balloon is past the hemostasis valve. Ensure the distal end of the loading tool remains positioned in the hemostasis valve while advancing the balloon into the sheath.

      Caution: If unusual resistance is felt during catheter advancement through the valve, do not use the balloon catheter. Replace with a new Ranger DCB.

      Caution: If using a Tuohy-Borst type adapter, take care not to over-tighten the hemostasis valve around the catheter shaft as lumen constriction may occur, affecting inflation/deflation of the balloon or damaging the drug coating.

      Note: If additional working length is needed, the loading tool can be removed. Push the loading tool against the increasing diameter of the manifold strain until it splits, and then simultaneously peel the two sides away.

   g) Advance the balloon catheter over the guidewire under direct fluoroscopic visualization and position the balloon relative to the lesion to be treated. Use the radiopaque marker bands as a reference point. The outside edges of the marker bands indicate the balloon shoulders. Balloon inflation should not be undertaken if the balloon is not properly positioned within the stenosis.
2. Balloon Inflation
   a) Slowly inflate the balloon to the appropriate pressure (refer to **Table 18**). Fluoroscopic visualization during balloon expansion should be used to properly judge the optimum expanded balloon diameter as compared to the distal vessel diameter. The recommended balloon inflation time is three (3) minutes.

      Warning: Do not exceed the balloon rated burst pressure. Use of an inflation device is recommended to prevent over-pressurization.

      Warning: If difficulty is experienced during balloon inflation, do not continue. Deflate the balloon and remove the catheter.

   b) Apply negative pressure to fully deflate the balloon. Allow up to 60 seconds for full balloon deflation. Confirm that the balloon is fully deflated under fluoroscopy.
   c) Withdraw the balloon catheter until it is clear of the lesion. Maintain the guidewire across the stenosis.

      Warning: Do not advance or retract the catheter unless the balloon is fully deflated under vacuum.

      Caution: Full arterial wall apposition of the Ranger DCB is necessary for proper drug transfer to the vessel.
3. Catheter Removal
   a) Confirm with angiography that the lumen of the dilated vessel has not abruptly occluded. Also ensure the balloon is fully deflated.
   b) While maintaining negative pressure, withdraw the deflated balloon catheter and guidewire from the guiding sheath through the hemostasis valve.

      Warning: If unusual resistance is felt during manipulation, determine the cause of the resistance before proceeding. If the source of resistance cannot be determined, it is recommended to extract the entire system with the guiding sheath.

Table 18: Ranger™ Compliance

Pressure		Mean Balloon Diameter (Balloon Lengths)								
		4.0 mm	5.0 mm	5.0 mm	6.0 mm	6.0 mm	6.0 mm	7.0 mm	7.0 mm	7.0 mm
atm	kPa	all lengths	30 mm - 100 mm	120 mm - 200 mm	30 mm - 60 mm	80 mm - 100 mm	120 mm - 200 mm	30 mm - 40 mm	60 mm - 100 mm	120 mm - 200 mm
6	608	3.96	5.02	4.89	6.01	6.22	6.06	6.92	7.13	7.01
7	709	4.04	5.11	5.00	6.09	6.32	6.16	7.02	7.25	7.12
8	811	4.11	5.19	5.07	6.17	6.40	6.23	7.11	7.35	7.20
9	912	4.16	5.25	5.15	6.24	6.47	6.30	7.18	7.43	7.27
10	1013	4.22	5.31	5.21	6.29	6.53	6.36	7.25	7.49	7.34
11	1115	4.26	5.36	5.27	6.35	6.57	6.42	7.31	7.56	7.40
12	1216	4.30	5.41	5.32	6.39	6.62	6.46	7.36	7.61	7.46
13	1317	4.33	5.45	5.36	6.43	6.67	6.51	7.41	7.66	7.52
14	1419	4.37	5.49	5.41	6.48	6.72	6.56	7.46	7.73	7.58

11. WARRANTY

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EC REP **EU Authorized Representative**

Boston Scientific Limited
Ballybrit Business Park
Galway
IRELAND

AUS **Australian Sponsor Address**

Boston Scientific (Australia) Pty Ltd
PO Box 332
BOTANY
NSW 1455
Australia
Free Phone 1800 676 133
Free Fax 1800 836 666

ARG **Argentina Local Contact**

Para obtener información de contacto de Boston Scientific Argentina SA, por favor, acceda al link www.bostonscientific.com/arg

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Boston Scientific Corporation
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