stellarex™

0.035" OTW Drug-coated Angioplasty Balloon

Spectranetics®

INSTRUCTIONS FOR USE

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

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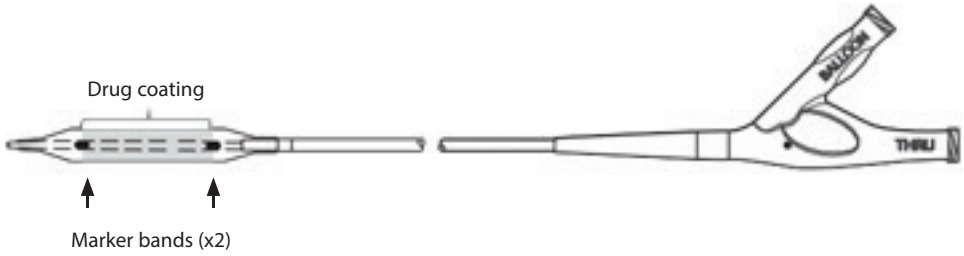
INSTRUCTIONS FOR USE

1. DEVICE DESCRIPTION

The Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon (Stellarex 035 DCB) is a sterile, single-use, over-the-wire (OTW) dual lumen catheter with a distally mounted semi-compliant inflatable balloon and an atraumatic tapered tip. The balloon is coated with a proprietary coating containing the drug paclitaxel.

The Stellarex 035 DCB primary mode of action is mechanical dilatation of de novo or restenotic lesions by means of PTA (percutaneous transluminal angioplasty) with a secondary action of inhibition of restenosis by means of the Paclitaxel transferred to the vessel wall. The Paclitaxel drug inhibits restenosis caused by the proliferative response from vessel injury due to PTA.



1.1 Percutaneous Transluminal Angioplasty (PTA) Catheter

The Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon (Stellarex balloon) consists of an over-the-wire (OTW) dual lumen catheter with a distally mounted semi-compliant inflatable balloon and an atraumatic tapered tip. The balloon is coated with a proprietary coating containing the drug paclitaxel.

The catheter is compatible with a 0.035" (0.89 mm) guide wire. Each device has a protective sheath over the drug-coated balloon portion of the catheter. A compliance chart is included on the product label for each device. The balloon has two radiopaque markers for positioning the balloon relative to the treatment area. The radiopaque marker bands indicate the working length of the balloon and facilitate fluoroscopic visualization during delivery and placement. The paclitaxel coating covers the working length of the balloon body.

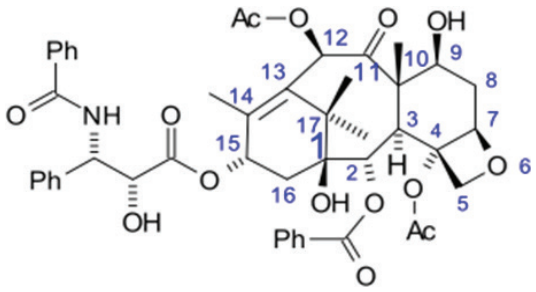
1.2 Drug Coating

The Stellarex 035 DCB is coated with EnduraCoat™ Technology a proprietary DCB coating with a nominal drug dose density of 2µg of paclitaxel per mm^2 of the expanded balloon surface blended with a hydrophilic polymer excipent (polyethylene glycol 8000), enabling adhesion and transfer of the active pharmaceutical ingredient (paclitaxel) from the balloon to the vessel wall when exposed to aqueous conditions. The EnduraCoat™ drug coating covers the working length of the balloon component of the catheter. The key functional characteristic of the drug coating is to allow for release of paclitaxel to the tissue of the vascular wall during balloon inflation.

Active Pharmaceutical Ingredient (API) – Paclitaxel

The API of the Stellarex 035 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 1 below.

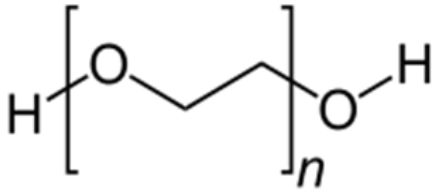
Figure 1. Paclitaxel Chemical Structure



Excipient – Polyethylene Glycol 8000

The hydrophilic polymer polyethylene glycol (PEG) 8000 is used as an excipient to promote the adhesion and transfer of the active pharmaceutical ingredient (paclitaxel) from the balloon to the vessel wall when exposed to aqueous conditions. The chemical structure of PEG is shown in Figure 2 below.

Figure 2. PEG Chemical Structure



1.3 Product Matrix and Paclitaxel Content

Available Balloon Diameters (mm) and Lengths (mm)

		Balloon Length (mm)				
		40	60	80	100	120
Balloon Diameter (mm)	4	X	X	X	X	X
	5	X	X	X	X	X
	6	X	X	X	X	X

Balloon Drug Coating (EnduraCoat ™)

Paclitaxel (Active Pharmaceutical Ingredient)
Polyethylene Glycol and Iodine (Excipient)

Catheter Design

Over-the-Wire (OTW)

Usable Catheter Lengths

80cm and 135cm

Balloon Inflation Pressure

Nominal Balloon Pressure

		Balloon Length (mm)				
		40	60	80	100	120
Balloon Diameter (mm)	4	10atm (1013 kPa)	10atm (1013 kPa)	10atm (1013 kPa)	10atm (1013 kPa)	10atm (1013 kPa)
	5	10atm (1013 kPa)	10atm (1013 kPa)	10atm (1013 kPa)	10atm (1013 kPa)	10atm (1013 kPa)
	6	8atm (811kPa)	8atm (811kPa)	8atm (811kPa)	8atm (811kPa)	8atm (811kPa)

Rated Burst Pressure

		Balloon Length (mm)				
		40	60	80	100	120
Balloon Diameter (mm)	4	20atm (2027 kPa)	20atm (2027 kPa)	20atm (2027 kPa)	20atm (2027 kPa)	20atm (2027 kPa)
	5	18atm (1824kPa)	18atm (1824kPa	18atm (1824kPa)	18atm (1824kPa)	16atm (1621 kPa)
	6	14atm (1419 kPa)	14atm (1419 kPa)	14atm (1419 kPa)	14atm (1419 kPa)	12atm (1216kPa)

Minimum Introducer Sheath Compatibility

Balloon Diameter	Maximum Crossing Profile	Introducer Sheath
4mm	5.94Fr (0.078in)	6Fr
5mm	Not Available	
6mm	6.17Fr(0.081in)	

Guide Wire Compatibility

The catheter is compatible with a guidewire diameter of 0.035 in (0.89 mm).

Product Codes and Paclitaxel Content

Product Code (80 cm Usable Catheter Length)	Product Code (135 cm Usable Catheter Length)	Nominal Balloon Diameter (mm)	Nominal Balloon Length (mm)	Nominal Paclitaxel Content (µg)
AB35SX040040080	AB35SX040040135	4	40	1124
AB35SX040060080	AB35SX040060135	4	60	1674
AB35SX040080080	AB35SX040080135	4	80	2211
AB35SX040100080	AB35SX040100135	4	100	2759
AB35SX040120080	AB35SX040120135	4	120	3307
AB35SX050040080	AB35SX050040135	5	40	1335
AB35SX050060080	AB35SX050060135	5	60	1998
AB35SX050080080	AB35SX050080135	5	80	2636
AB35SX050100080	AB35SX050100135	5	100	3245
AB35SX050120080	AB35SX050120135	5	120	3880
AB35SX060040080	AB35SX060040135	6	40	1619
AB35SX060060080	AB35SX060060135	6	60	2410
AB35SX060080080	AB35SX060080135	6	80	3174
AB35SX060100080	AB35SX060100135	6	100	3957
AB35SX060120080	AB35SX060120135	6	120	4721

2. INDICATIONS FOR USE

The Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon is indicated for percutaneous transluminal angioplasty (PTA), after appropriate vessel preparation of *de novo* or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6 mm.

3. CONTRAINDICATIONS

The Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon 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.

4. WARNINGS

- **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 11.1 for further information.**
- The Stellarex 035 DCB is supplied STERILE for single use only. Do not reprocess or re-sterilize. Reprocessing and re-sterilizing could increase the risk of patient infection and risk of compromised device performance.
- The Stellarex 035 DCB should not be inflated in excess of the rated burst pressure (RBP). Balloon rupture may occur if RBP is exceeded. Use of pressures higher than the RBP may result in a ruptured balloon with possible intimal damage and dissection.
- Do not use after the "Use By" date on the package.
- Never use air or any gaseous medium to inflate the Stellarex 035 DCB to avoid air emboli in case of balloon rupture.
- Do not manipulate the Stellarex 035 DCB in an inflated state. Manipulating the inflated device may cause damage to the device or patient's vessel.
- If resistance is encountered at any time during the insertion procedure, do not force passage. Resistance may cause damage to the device or lumen. Carefully withdraw the catheter.
- The safety of utilizing multiple Stellarex 035 DCBs with a total drug dose greater than 14,200 µg paclitaxel has not been clinically evaluated.

5. PRECAUTIONS

- The Stellarex 035 DCB should be used only by physicians who are experienced and knowledgeable of the clinical and technical aspects of percutaneous transluminal angioplasty.
- The outer foil pouch is not a sterile barrier. The inner Tyvek pouch is the product sterile barrier. Do not allow the Tyvek inner pouch to contact the sterile field.
- Allergic reactions to contrast medium, antiplatelet medications, or paclitaxel should be identified before PTA angioplasty.
- Precautions to prevent or reduce clotting should be considered. Physician experience and discretion will determine the appropriate anticoagulant/antiplatelet therapy for each patient.
- When the Stellarex balloon Stellarex 035 DCB is exposed to the vascular system, it should be manipulated under high quality fluoroscopic observation.
- Carefully inspect the Stellarex 035 DCB and package prior to use. Do not use the catheter if it is damaged or if the size, shape or condition is unsuitable for the intended procedure. Do not use if there is a breach in the sterile field.
- Do not immerse or wipe the balloon section of the Stellarex 035 DCB with any fluid as the integrity of the drug coating may be damaged or compromised. Replace any Stellarex 035 DCB where the balloon has come into contact with fluids prior to use.
- Use sterile gloves to handle the Stellarex 035 DCB prior to use. Care should be taken to minimize contact with the coated balloon portion of the device.
- Avoid saline solution contact with the Stellarex 035 DCB coating when flushing the guide wire lumen.
- Never inflate the Stellarex 035 DCB outside the body or prior to reaching the target lesion as it may disrupt the coating integrity.
- Do not attempt to pass the Stellarex 035 DCB through a smaller French size guide catheter or introducer sheath than indicated on the label. Refer to package label for guide catheter compatibility.
- This product is not intended for the expansion or delivery of a stent.
- Do not use the Stellarex 035 DCB for pre-dilatation or for post-dilatation.
- Treatment of the target lesion with the Stellarex 035 DCB should cover the entire area. Always manipulate the Stellarex 035 DCB under fluoroscopic observation when in the body.
- For proper drug delivery to the target lesion, maintain inflation of the Stellarex 035 DCB for a minimum of 60 seconds. In order to optimize lesion dilatation, longer inflation times may be performed at the discretion of the operator.
- Formal drug interaction studies have not been conducted with the Stellarex 035 DCB. In the clinical pharmacokinetic (PK) sub-study, systemic levels of paclitaxel following treatment with Stellarex 035 DCB were low and cleared rapidly, reducing possible impact of drug-drug interactions due to concomitant medications. Consideration for both systemic and local drug interactions should be given when deciding to use Stellarex 035 DCB in a patient who is taking a drug with known interactions to paclitaxel or when deciding to initiate therapy with such a drug in a patient who has recently been treated with Stellarex 035 DCB. Please refer to Drug Information (Section 8.0).
- Use of the Stellarex 035 DCB has not been studied in conjunction with other interventional techniques.
- After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.
- The use of this product carries the risks associated with percutaneous transluminal angioplasty, including thrombosis, vascular complications, and/or bleeding events.
- The extent of the patient's exposure to the drug coating is directly related to the number of balloons used. Refer to Using Multiple Stellarex 035 DCBs (Section 16.6) and Product Matrix and Paclitaxel Content (Section 1.3) for details regarding the use of multiple balloons and a product matrix containing the nominal paclitaxel content for each device size, respectively.

6. PRE-PROCEDURE AND POST-PROCEDURE MEDICATION REGIMEN

Dual antiplatelet therapy [clopidogrel and acetylsalicylic acid (ASA or aspirin)] is recommended to be administered prior to the procedure and following the procedure. Ticlopidine should be administered if the patient has a known allergy to clopidogrel. The optimal duration of antiplatelet therapy is at the discretion of the physician. The recommended pre-procedure and post-procedure medication regimen is described below.

Pre-Procedure

- Clopidogrel 75mg/day for 3 days prior to the angioplasty procedure or 300 mg as a loading dose on the day of the procedure.
- Acetylsalicylic acid (ASA) 81mg/day to 325mg/day on the day of the angioplasty procedure or prior at the discretion of the physician.

Post-Procedure

- Clopidogrel: 75mg/day for a minimum of 30 days following the angioplasty procedure or prolonged use at the discretion of the physician. The recommended dose of ticlopidine is 250mg twice a day.
- Acetylsalicylic acid (ASA): Minimum of 81mg/day for a minimum of 6 months following the angioplasty procedure.

In patients ≥ 75 years of age, prasugrel is generally not recommended because of the increased risk of fatal intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or history of prior myocardial infarction, where its effect appears to be greater and its use may be considered). The effectiveness and safety of the 5mg/day dose has not been prospectively studied. Always refer to the package insert of the medication for complete prescribing information.

7. USE IN SPECIAL POPULATIONS

Pregnancy - The Stellarex 035 DCB is contraindicated in women who are pregnant or breastfeeding. It is unknown whether paclitaxel will be excreted in human milk, and whether there is a potential for adverse reaction from paclitaxel exposure in nursing infants.

Gender- Gender was analyzed as a subgroup in the pivotal clinical study. The outcomes are shown in Primary Safety Composite and Primary Effectiveness by Gender (Table 8). The results of an interaction analysis indicate that the treatment differences between Stellarex 035 DCB and PTA groups are consistent between male and female subjects.

Ethnicity- Clinical studies of the Stellarex 035 DCB did not include a sufficient number of patients to assess for differences in safety or effectiveness due to ethnicity, regardless of assessment by individual ethnicity categories or assessment by Caucasian or non-Caucasian categories.

Pediatrics-The safety and effectiveness of the Stellarex 035 DCB has not been established in pediatric patients (< 18 years of age).

Geriatric- Clinical studies of the Stellarex 035 DCB did not have an upper age limit.

8. DRUG INFORMATION

8.1 Mechanism of Action

The Stellarex 035 DCB coating contains paclitaxel, an anti-proliferative pharmaceutical that specifically binds to and stabilizes microtubules. Paclitaxel inhibits smooth muscle cell and fibroblast proliferation/migration as well as secretion of extracellular matrix by blocking microtubule proliferation. The combination of these effects results in the inhibition of neointimal hyperplasia and therefore restenosis.

8.2 Metabolism

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Potential drug interactions may occur with any drug that affects these isoenzymes. In the absence of formal drug interaction studies, caution should be exercised when administering paclitaxel.

8.3 Carcinogenicity, Genotoxicity and Reproductive Toxicology

No long-term studies have been performed to evaluate the carcinogenic potential of the Stellarex 035 DCB. Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay; however, it has been shown to be clastogenic (causing chromosome aberrations) *in vitro* in human cells as well as *in vivo* in the mouse micronucleus assay. This effect is likely due to the mechanism of action of paclitaxel wherein it interferes with normal microtubule organization during cell division. Reproductive toxicity of paclitaxel has been evaluated in rats and rabbits. Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses ≥ 1 mg/kg/day and increased embryo- and fetotoxicity. 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 Stellarex 035 DCB (assuming maximum size and number of balloons used in a lesion) is 14.2 mg, which is approximately 4 and 14 times less than the dose that saw effects in rats and rabbits, respectively, when normalizing to body weight.

8.4 Pharmacokinetics

The pharmacokinetic (PK) profile of paclitaxel following treatment with the Stellarex 035 DCB was evaluated in 25 subjects receiving paclitaxel dosages ranging from 1.3 to 9.4 mg. This evaluation was conducted as part of the ILLUMENATE PK study, and is described in Summary of Clinical Studies (Section 11). Paclitaxel systemic exposure in the treated subjects was low and cleared rapidly with a biphasic decline. Paclitaxel concentrations after 24 hours were below the quantitation limit (<0.100ng/mL) for all but one subject. The C_{max} values ranged from 0.55 to 574.00 ng/mL and the AUC0-∞ values ranged from 0.55 to 296.00 hr*ng/mL. These data indicate that treatment with the Stellarex 035 DCB results in limited systemic exposure of paclitaxel.

9. POTENTIAL COMPLICATIONS / ADVERSE EVENTS

Potential complications which may be associated with a peripheral balloon dilation procedure include, but may not be limited to, the following:

- Abrupt Vessel Closure
- Allergic reaction to contrast medium, anti-platelet therapy, or catheter system components (drug, excipients, and materials)
- Amputation/Loss of limb
- Arrhythmias
- Arterial aneurysm
- Thrombosis
- Arterio-venous fistula (AVF)
- Bleeding
- Death
- Embolism/Device embolism
- Fever
- Hematoma
- Hemorrhage
- Hypertension/Hypotension
- Infection or pain at insertion site
- Inflammation
- Ischemia or infarction of tissue/organ
- Occlusion
- Pain or tenderness
- Perforation or rupture of the artery
- Peripheral edema
- Pseudoaneurysm
- Renal insufficiency or failure
- Restenosis
- Sepsis or systemic infection
- Shock
- Stroke/Cerebrovascular accident
- Vessel dissection, perforation, rupture, spasm, or recoil
- Vessel trauma which requires surgical repair

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

- Balloon rupture
- Detachment of a component of the balloon and/or catheter system
- Failure of the balloon to perform as intended
- Failure to cross the lesion

These complications may result in adverse events.

Potential complications which may be associated with the addition of paclitaxel to a PTA balloon catheter include, but may not be limited to, the following:

- Allergic/Immunologic reaction to paclitaxel
- Alopecia
- Anemia
- Gastrointestinal symptoms (diarrhea, nausea, pain, vomiting)
- Hematologic dyscrasia (including neutropenia, leucopenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall including inflammation, cellular damage, or necrosis
- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

Refer to the Physician's Desk Reference for more information on the potential adverse events observed with paclitaxel. There may be other potential adverse events that are unforeseen at this time. For the specific adverse events that occurred in the clinical study, please see Table 9 in the Clinical Studies section below.

10. PATIENT COUNSELING INFORMATION

Physicians should advise patients on the following:

- Risks associated with a PTA procedure
- Risks associated with the Stellarex 035 DCB
- Risks and benefits of the treatment specific to the patient
- Discuss short-term and long-term changes to patient lifestyle
- Pre- and post-procedure care including antiplatelet therapy and risks of early discontinuation of antiplatelet therapy

11. SUMMARY OF CLINICAL STUDIES

The safety and effectiveness of the Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon is supported with data from the ILLUMENATE Pivotal Study. Additional data from the pharmacokinetic (PK), European Union-Randomized Controlled Trial (EU-RCT), Global, and First In Human (FIH) studies are provided as supporting information but are not considered part of the primary data set.

11.1 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 ILLUMENATE Pivotal Study, Kaplan Meier mortality estimates at 2 and 3 years are 6.8% (95% confidence interval 4.0 - 11.4%), and 9.0% (95% confidence interval 5.7 - 14.1%), respectively, for the Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon treatment device, and 7.2% (95% confidence interval 3.5 - 14.5%), and 10.4% (95% confidence interval 5.7 - 18.5%), respectively, for the EverCross™ Balloon Catheter control device. Additional information regarding long-term outcomes can be found in Section 11.5.

11.2 ILLUMENATE Pivotal Study

11.2.1 Objective

The purpose of the ILLUMENATE Pivotal Study is to demonstrate safety and effectiveness of the Stellarex 035 DCB compared to a control PTA balloon catheter for the treatment of de novo or post-PTA restenotic (except for in-stent) superficial femoral (SFA) and/or popliteal arteries.

11.2.2 Study Design

The ILLUMENATE Pivotal study is a prospective, randomized, multi-center, single-blind study comparing the Stellarex 035 DCB to standard balloon angioplasty (PTA) for treatment of femoropopliteal arteries in a single limb. Subjects were randomized to the Stellarex 035 DCB or the control PTA device in a 2:1 ratio. Each subject will be followed for 5 years (60 months) after treatment. Subjects with a target lesion length of ≥3 cm and ≤18 cm and target reference vessel diameter of ≥4 mm and ≤6 mm (by visual estimation) were considered for enrollment.

All subjects are required to complete follow-up office visits at 6, 12, 24, and 36 months. During these follow-up office visits, subjects are assessed for:

- Duplex ultrasound (DUS)
- Limb assessment [Ankle-brachial Index (ABI) and Rutherford-Becker Clinical Category (RCC)]
- 6 minute walk test (6MWT)
- Walking impairment questionnaire (WIQ)
- Quality of life (EQ-5D)
- Laboratory assessment (at 6 and 12 month follow-up only)

A follow-up telephone contact or optional office visits occur at 1, 48 and 60 months to review medication compliance and adverse events.

The primary endpoints for the ILLUMENATE Pivotal Study are listed below:

Non-inferior safety: The primary safety endpoint was defined as freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 12 months post-procedure. The primary analysis of safety event rates employed multiple imputation analysis. Non-inferior safety of treatment compared to control was evaluated by testing the following hypothesis, where π is the population proportion for the corresponding treatment group:

$$H_0: \pi_{DCB} \leq \pi_{PTA} - 0.05$$
$$H_1: \pi_{DCB} > \pi_{PTA} - 0.05$$

In the event the primary non-inferiority analysis was successful, a superiority analysis of the primary safety endpoint would be conducted.

Superior primary effectiveness: The primary effectiveness endpoint was defined as patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by DUS peak systolic velocity ratio (PSVR) ≤ 2.5 and freedom from CD-TLR. The primary analysis of the primary effectiveness endpoint was performed using multiple imputation analysis. Superior effectiveness of treatment compared to control was evaluated by testing the following hypothesis:

$$H_0: \pi_{DCB} \leq \pi_{PTA}$$
$$H_1: \pi_{DCB} > \pi_{PTA}$$

The primary analysis set was Intention-to-Treat (ITT). The ITT set was comprised of all subjects who were enrolled and randomized to receive either the Stellarex 035 DCB or the PTA control device. Per protocol (PP) analyses were also conducted.

The secondary endpoints for the ILLUMENATE Pivotal study are listed below.

- Major adverse event (MAE) rate in the hospital and at 1, 6, 12, 24, 36, 48 and 60 months post-procedure, defined as a composite rate of cardiovascular death, target limb major amputation and clinically-driven target lesion revascularization (CD-TLR).
- Rate of vascular access and bleeding complications in the hospital and at 1, 6, 12 and 24 months.
- Rate of clinically-driven target lesion revascularization at 6, 12, 24, 36, 48 and 60 months.
- Rate of target lesion revascularization at 6, 12, 24, 36, 48 and 60 months.
- Rate of clinically-driven target vessel revascularization at 6, 12, 24 and 36 months.
- Rate of target limb major amputation at 1, 6, 12, 24, 36, 48 and 60 months.
- Mortality rate at 6, 12, 24, 36, 48 and 60 months.
- Rate of occurrence of arterial thrombosis of the treated segment at 1, 6, 12, 24, 36, 48 and 60 months.
- Rate of ipsilateral embolic events of the target limb.
- Patency rate defined as the absence of target lesion restenosis as determined by duplex ultrasound (PSVR ≤ 2.5) and freedom from clinically-driven TLR at 6, 24 and 36 months.
- Lesion success, defined as achievement of a final in-lesion residual diameter stenosis of ≤50% (as determined by the angiographic core lab), using any device after wire passage through the lesion.
- Technical success, defined as achievement of a final in-lesion residual diameter stenosis of ≤50% (as determined by the angiographic core lab), using the Stellarex 035 DCB or PTA control device without a device malfunction after guide wire passage through the lesion.
- Clinical success (per subject) defined as technical success without the occurrence of major adverse events during the procedure.
- Procedural success (per subject) defined as lesion success without the occurrence of major adverse events during the procedure.
- Change in ankle-brachial index (ABI) from pre-procedure to 6, 12, 24 and 36 months.
- Change in walking impairment questionnaire (WIQ) from pre-procedure to 6, 12, 24 and 36 months.
- Change in walking distance from pre-procedure to 6, 12, 24 and 36 months.
- Change in Rutherford-Becker classification of chronic limb ischemia from pre-procedure to 6, 12, 24 and 36 months.
- Change in EQ-5D from pre-procedure to 6, 12, 24 and 36 months.

11.2.3 Patient Population

A total of 300 subjects were randomized 2:1 to the Stellarex 035 DCB test device (n=200) and PTA control device (n=100) at 41 sites in the United States and 2 sites in Austria. Baseline demographics, medical history, and risk factors were similar between the DCB and PTA groups. Data for the ILLUMENATE Pivotal Study are summarized in Table 1.

Table 1. Baseline Demographics and Medical History

Characteristic	Stellarex 035 DCB (N=200)	PTA (N=100)	p-value[a]
Clinical Characteristics			
Age (years)	68.3 ± 10.3 (200) 67.2 (42.6, 93.8)	69.8 ± 9.8 (100) 68.7 (43.7, 92.7)	0.225
Male	56.0% (112/200)	64.0% (64/100)	0.185
Body Mass Index (BMI)	29.0 ± 6.1 (200) 27.9 (15.6, 54.9)	28.8 ± 5.6 (100) 27.9 (16.5, 52.5)	0.812
Hispanic or Latino	15.1% (27/179)	12.5% (11/88)	0.570
Race			0.670
American Indian or Alaska Native	1.1% (2/190)	0.0% (0/96)	
Asian	1.1% (2/190)	1.0% (1/96)	
Black or African American	18.4% (35/190)	19.8% (19/96)	
White	74.7% (142/190)	70.8% (68/96)	
Other	4.7% (9/190)	8.3% (8/96)	
Baseline Ankle Brachial Index			
Ankle Brachial Index	0.75 ± 0.21 (193) 0.75 (0.00, 1.27)	0.76 ± 0.20 (100) 0.76 (0.00, 1.28)	0.508
Non-compressible[1]	3.0% (6/199)	0.0% (0/100)	0.184
Baseline Rutherford-Becker Clinical Category			0.735
2	31.5% (63/200)	35.0% (35/100)	
3	64.5% (129/200)	60.0% (60/100)	
4	4.0% (8/200)	5.0% (5/100)	
Medical History / Risk Factors			
Hypertension	93.5% (187/200)	94.0% (94/100)	0.867
Hyperlipidemia	88.0% (176/200)	90.0% (90/100)	0.606
Coronary Heart Disease			
Myocardial Infarction (MI)	21.0% (42/200)	22.0% (22/100)	0.842
Angina Pectoris	15.0% (30/200)	20.0% (20/100)	0.273
Congestive Heart Failure (CHF)	11.5% (23/200)	8.0% (8/100)	0.348
Previous Percutaneous or Surgical Coronary Revascularization	45.0% (90/200)	48.0% (48/100)	0.623
Renal Insufficiency	18.0% (36/200)	16.0% (16/100)	0.666
Cerebrovascular Disease	23.5% (47/200)	20.0% (20/100)	0.493
Chronic Obstructive Pulmonary Disease (COPD)	16.0% (32/200)	21.0% (21/100)	0.284
Diabetes	49.5% (99/200)	52.0% (52/100)	0.683
Type I	4.0% (8/200)	3.0% (3/100)	0.757
Type II	45.5% (91/200)	49.0% (49/100)	0.567
Smoker			
Never Smoked	16.0% (32/200)	25.0% (25/100)	
Previous or Current Smoker	84.0% (168/200)	75.0% (75/100)	
Previous Intervention of the Lower Limb	43.5% (87/200)	41.0% (41/100)	0.680
Previous Intervention of the Study Limb	24.0% (48/200)	23.0% (23/100)	0.848

Continuous data are presented as Mean ± SD (N), Median (Min, Max). Categorical data are presented as % (n/N).
[a]p-value is from a t-test for continuous variables, a chi-square test or Fisher's exact test as appropriate for nominal categorical variables, or a Cochran-Mantel-Haenszel test for a difference in mean rank scores for ordinal variables.
[1]Non-compressible arteries includes those reported on the CRF and those with ABIs (manual or automatic) reported as >=1.3.

Baseline lesion characteristics were similar between the DCB and PTA groups. The total target lesion length treated was similar between treatment groups (DCB 79.7 cm, PTA 88.8 cm; p= 0.105). Reference vessel diameter was smaller in the Stellarex 035 DCB group compared to the PTA group (4.86 to 5.15; p=0.017). Pre-dilatation using a PTA catheter was performed as part of the clinical study to prepare the vessel and occurred in 100% of DCB subjects.

The Baseline lesion characteristics are summarized in Table 2.
Angiographic core laboratory data is presented unless indicated otherwise.

Table 2: Baseline Lesion Characteristics

Angiographic Lesion Characteristic[1]	Stellarex 035 DCB (N=200)	PTA (N=100)	p-value[a]
Lesion Type			0.035
De novo	90.5% (181/200)	82.0% (82/100)	
Restenotic	9.5% (19/200)	18.0% (18/100)	
Lesion Location (Most Proximal)			0.611
Proximal SFA	11.0% (22/200)	9.0% (9/100)	
Mid SFA	50.5% (101/200)	49.0% (49/100)	
Distal SFA	34.0% (68/200)	33.0% (33/100)	
Proximal Popliteal	3.5% (7/200)	7.0% (7/100)	
Mid Popliteal	1.0% (2/200)	2.0% (2/100)	
Lesion Length (mm)	79.7 ± 45.3 (199)	88.8 ± 46.0 (100)	0.105
Reference Vessel Diameter (RVD) (mm)	4.86 ± 0.92 (200)	5.15 ± 1.05 (100)	0.017
Minimum Lumen Diameter (MLD) (mm)	1.27 ± 0.88 (200)	1.32 ± 0.96 (100)	0.660
Diameter Stenosis (%)	73.9 ± 16.9 (200)	74.8 ± 17.0 (100)	0.673
Total Occlusion (100% Stenosis)	19.0% (38/200)	18.0% (18/100)	0.834
Calcification[2]			0.804
None/Mild	34.3% (68/198)	32.0% (32/100)	
Moderate	21.7% (43/198)	25.0% (25/100)	
Severe	43.9% (87/198)	43.0% (43/100)	
TASC II Lesion Classification			0.298
Type A	61.3% (122/199)	53.0% (53/100)	
Type B	29.1% (58/199)	38.0% (38/100)	
Type C	9.5% (19/199)	9.0% (9/100)	
At Least One Patent Run-off Vessel	94.9% (168/177)	98.9% (87/88)	0.172
Post-Procedure Minimum Lumen Diameter[3] (MLD) (mm)	3.63 ± 0.68 (199)	3.71 ± 0.71 (100)	0.347
Post-Procedure Diameter Stenosis (%)[3]	25.2 ± 11.7 (199)	27.4 ± 10.1 (100)	0.107
Procedural Characteristics			
Pre-Dilatation Performed[4]	100% (200/200)	100% (100/100)	N/A
Post-Dilatation Performed[4]	17.0% (34/200)	16.0% (16/100)	0.827
Bailout Stent[4]	6.0% (12/200)	6.0% (6/100)	1.000

Continuous data are presented as Mean ± SD (N). Categorical data are presented as % (n/N).
[a]p-value is from a t-test for continuous variables, a chi-square test or Fisher's exact test as appropriate for nominal categorical variables, or a Cochran-Mantel-Haenszel test for a difference in mean rank scores for ordinal variables.
[1]Angiographic core laboratory reported data except where indicated otherwise.
[2]Per Angiographic Core Lab Definitions; None/Mild: No radiopacities noted; Moderate: Radiopacities noted on one side of the arterial wall or less than one cm of length prior to contrast injection or digital subtraction; Severe: Radiopacities noted on both sides of the arterial wall and extending more than one cm of length prior to contrast injection or digital subtraction.
[3]Post-procedure results are determined from post-dilatation/post-additional treatment data for lesions with additional treatment after the study device and post-study device data otherwise.
[4] Site reported data.

Subject follow-up compliance at the 12-month follow-up visit is presented in Table 3. Follow-up compliance within the follow-up window was 89.5% for the Stellarex 035 DCB subjects and 90.9% for the PTA subjects.

Table 3: Subject Follow-Up Compliance at 12 Months

12 Month (365 Days ± 30 Days)	Stellarex 035 DCB (N = 200)	PTA (N=100)
Eligible Subjects[1]	190	99
Study Exits[2]	10	1
Death[2]	4	1
Withdrawn[2]	4	0
Lost-to-follow-up[2]	2	0
Clinical Follow-up		
Follow-up Visit in Window	170	90
Follow-up Compliance (%)[3]	89.5%	90.9%
Follow-up Visit Out of Window	11	4
Follow-up Visit Missed	9	5

[1]Eligible subjects are all subjects who have a follow-up visit form or are past due for their follow-up visit and have not exited the study prior to the upper limit of the visit window.
[2]Study exits are cumulative through the upper limit of the visit window. Exited subjects with a follow-up visit form are considered eligible and are not considered as a study exit until the next follow-up visit.
[3]Follow-up compliance is calculated as the number of subjects having an in-window follow-up visit out of the total number of subjects eligible for follow-up.

11.2.4 Primary Safety and Effectiveness Endpoints

The primary safety endpoint, a composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months post-procedure, was 92.1% in the DCB group and 83.2% in the PTA group. The DCB group met the pre-defined 5% non-inferiority margin and in a sequential testing procedure, the DCB showed superiority in safety against the PTA group (p=0.0246).

The primary effectiveness endpoint, primary patency at 12 months, was 76.3% in the DCB group and 57.6% for the PTA group. The DCB group showed statistical superiority to the PTA group (p=0.003).

The primary safety and effectiveness endpoint rates are presented in Table 4. Kaplan-Meier analysis of the primary safety endpoint is presented in Figure 3 and primary patency is presented in Figure 4.

Table 4: Primary Safety and Effectiveness Endpoints

Outcome	Stellarex 035 DCB (N = 200)[3]	PTA (N=100)[3]	Difference [95% CI][a]	p-value[a]
Primary Safety Endpoint[1]	92.1% (174/189)	83.2% (79/95)	8.3% [0.03%, 16.57%]	0.0246
Primary Effectiveness Endpoint-Patency at 12 Months[2]	76.3% (135/177)	57.6% (53/92)	16.9% [5.1%, 28.7%]	0.003

[1]Primary safety endpoint was defined as the composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 12 months post-procedure (410 days).
[2]The primary effectiveness endpoint was defined as patency at 12 months. Patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR) through 12 months (410 days). In the case where duplex data was not available angiographic core laboratory assessment of restenosis was utilized.
[3]Data are based on complete data without multiple imputation and presented as % (n/N).
[a]Estimate of the difference (DCB-PTA), 95% CI, and 1-sided p-value are based on the model based estimates resulting from multiple-imputation of missing data. For safety, the non-inferiority margin of 5% was met, therefore the results shown above are for superiority testing.

Figure 3: Kaplan-Meier Plot Freedom from Primary Safety Event

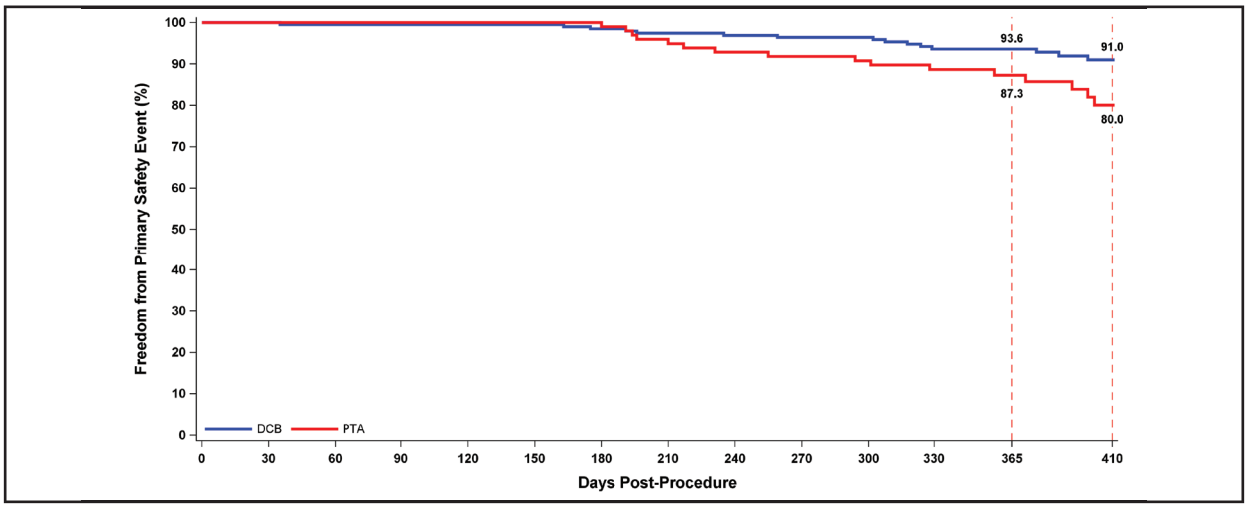


Table 5: Kaplan-Meier Data Freedom from Primary Safety Event

Days	Stellarex 035 DCB (N=200)				PTA (N=100)					
	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	Difference [95% CI][1]	Log-Rank p-value
0	200	0	100.0	--	100	0	100.0	--	0.0 [0.0, 0.0]	
30	200	0	100.0	--	100	0	100.0	--	0.0 [0.0, 0.0]	
180	191	3	98.5	[95.3, 99.5]	99	1	99.0	[93.0, 99.9]	-0.5 [-3.1, 2.1]	0.025
365	130	12	93.6	[89.0, 96.3]	59	12	87.3	[78.6, 92.6]	6.3 [-1.3, 14.0]	
410	83	15	91.0	[85.2, 94.6]	37	16	80.0	[68.8, 87.6]	10.9 [0.7, 21.2]	

Freedom from primary safety event was defined as freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 12 months post-procedure.
[1]The 95% CI of the difference was calculated assuming an asymptotic normal distribution of the difference in survival point estimates.

11.2.5 Summary of Serious Adverse Events

Serious adverse event (SAE) rates by MedDRA version 17.0 system organ class (SOC) and preferred term (PT) through 12 months (410 days) are shown in Table 6. A SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires medical/surgical intervention to prevent life-threatening illness or injury or to prevent permanent impairment of a body structure or function, or a congenital anomaly or birth defect.

Table 6: Summary of Serious Adverse Events through 12 Months through 410 Days

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
Not Yet Coded	1.0% (2/200)	0.0% (0/100)
Not Reported	0.5% (1/200)	0.0% (0/100)
SUSPICION OF WORSENING OF ALCOHOL ABUSE	0.5% (1/200)	0.0% (0/100)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2.5% (5/200)	1.0% (1/100)
ANAEMIA	1.5% (3/200)	1.0% (1/100)
HYPOCHROMIC ANAEMIA	0.5% (1/200)	0.0% (0/100)
LEUKOCYTOSIS	0.5% (1/200)	0.0% (0/100)
CARDIAC DISORDERS	11.0% (22/200)	6.0% (6/100)
ACUTE MYOCARDIAL INFARCTION	1.5% (3/200)	0.0% (0/100)
ANGINA PECTORIS	2.5% (5/200)	2.0% (2/100)
ANGINA UNSTABLE	1.0% (2/200)	1.0% (1/100)
ATRIAL FIBRILLATION	2.0% (4/200)	1.0% (1/100)
ATRIOVENTRICULAR BLOCK	0.5% (1/200)	0.0% (0/100)
CARDIAC ARREST	0.5% (1/200)	0.0% (0/100)
CARDIAC FAILURE	0.5% (1/200)	0.0% (0/100)
CARDIAC FAILURE CONGESTIVE	1.0% (2/200)	0.0% (0/100)
CORONARY ARTERY DISEASE	1.5% (3/200)	1.0% (1/100)
MITRAL VALVE INCOMPETENCE	0.5% (1/200)	0.0% (0/100)
MYOCARDIAL INFARCTION	1.5% (3/200)	0.0% (0/100)
SICK SINUS SYNDROME	0.0% (0/200)	2.0% (2/100)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0.0% (0/200)	1.0% (1/100)
HYDROCELE	0.0% (0/200)	1.0% (1/100)
ENDOCRINE DISORDERS	0.0% (0/200)	1.0% (1/100)
HYPOTHYROIDISM	0.0% (0/200)	1.0% (1/100)
EYE DISORDERS	0.5% (1/200)	2.0% (2/100)
BLINDNESS UNILATERAL	0.5% (1/200)	0.0% (0/100)
CATARACT	0.0% (0/200)	1.0% (1/100)
RETINAL ARTERY OCCLUSION	0.0% (0/200)	1.0% (1/100)
GASTROINTESTINAL DISORDERS	8.0% (16/200)	6.0% (6/100)
ABDOMINAL HERNIA	0.5% (1/200)	1.0% (1/100)
ABDOMINAL PAIN	0.5% (1/200)	0.0% (0/100)
ABDOMINAL PAIN UPPER	0.5% (1/200)	0.0% (0/100)
BARRETT'S OESOPHAGUS	0.5% (1/200)	0.0% (0/100)
COLITIS	0.5% (1/200)	1.0% (1/100)
DIARRHOEA	1.0% (2/200)	0.0% (0/100)
DIARRHOEA HAEMORRHAGIC	0.0% (0/200)	1.0% (1/100)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
DUODENAL ULCER	0.5% (1/200)	0.0% (0/100)
GASTROINTESTINAL ANGIODYSPLASIA	0.5% (1/200)	0.0% (0/100)
GASTROINTESTINAL ANGIODYSPLASIA HAEMORRHAGIC	0.5% (1/200)	0.0% (0/100)
GASTROINTESTINAL HAEMORRHAGE	1.5% (3/200)	0.0% (0/100)
INTESTINAL ISCHAEMIA	1.0% (2/200)	0.0% (0/100)
MELAENA	0.0% (0/200)	1.0% (1/100)
NAUSEA	0.5% (1/200)	0.0% (0/100)
RECTAL HAEMORRHAGE	0.5% (1/200)	1.0% (1/100)
SMALL INTESTINAL OBSTRUCTION	0.0% (0/200)	1.0% (1/100)
UPPER GASTROINTESTINAL HAEMORRHAGE	0.5% (1/200)	0.0% (0/100)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7.5% (15/200)	7.0% (7/100)
CATHETER SITE HAEMATOMA	0.5% (1/200)	0.0% (0/100)
CATHETER SITE HAEMORRHAGE	0.0% (0/200)	1.0% (1/100)
CHEST DISCOMFORT	0.5% (1/200)	0.0% (0/100)
CHEST PAIN	4.0% (8/200)	4.0% (4/100)
DEATH	0.0% (0/200)	2.0% (2/100)
DEVICE OCCLUSION	1.0% (2/200)	0.0% (0/100)
NON-CARDIAC CHEST PAIN	1.0% (2/200)	0.0% (0/100)
SUDDEN CARDIAC DEATH	0.5% (1/200)	0.0% (0/100)
VESSEL PUNCTURE SITE THROMBOSIS	0.5% (1/200)	0.0% (0/100)
HEPATOBILIARY DISORDERS	1.5% (3/200)	0.0% (0/100)
BILE DUCT STENOSIS	0.5% (1/200)	0.0% (0/100)
CHOLANGITIS	0.5% (1/200)	0.0% (0/100)
CHOLANGITIS ACUTE	0.5% (1/200)	0.0% (0/100)
CHOLECYSTITIS	0.5% (1/200)	0.0% (0/100)
CHOLELITHIASIS	0.5% (1/200)	0.0% (0/100)
IMMUNE SYSTEM DISORDERS	0.0% (0/200)	1.0% (1/100)
HYPERSENSITIVITY	0.0% (0/200)	1.0% (1/100)
INFECTIONS AND INFESTATIONS	9.0% (18/200)	6.0% (6/100)
APPENDICITIS PERFORATED	0.5% (1/200)	0.0% (0/100)
BACTERAEMIA	1.0% (2/200)	0.0% (0/100)
BRONCHITIS	1.0% (2/200)	0.0% (0/100)
BRONCHOPNEUMONIA	0.5% (1/200)	0.0% (0/100)
BURSITIS INFECTIVE	0.0% (0/200)	1.0% (1/100)
CELLULITIS	1.0% (2/200)	2.0% (2/100)
DIABETIC FOOT INFECTION	0.0% (0/200)	1.0% (1/100)
ENDOCARDITIS	0.5% (1/200)	0.0% (0/100)
ESCHERICHIA SEPSIS	0.5% (1/200)	0.0% (0/100)
FUNGAEMIA	0.5% (1/200)	0.0% (0/100)
GASTROENTERITIS	1.0% (2/200)	0.0% (0/100)
GASTROENTERITIS VIRAL	0.5% (1/200)	0.0% (0/100)
H1N1 INFLUENZA	0.5% (1/200)	0.0% (0/100)
PNEUMONIA	1.5% (3/200)	3.0% (3/100)
SEPSIS	1.0% (2/200)	0.0% (0/100)
STAPHYLOCOCCAL INFECTION	0.5% (1/200)	0.0% (0/100)
URINARY TRACT INFECTION	2.0% (4/200)	0.0% (0/100)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	12.5% (25/200)	12.0% (12/100)
ACCIDENTAL OVERDOSE	0.5% (1/200)	0.0% (0/100)
ANAEMIA POSTOPERATIVE	0.5% (1/200)	0.0% (0/100)
CONCUSSION	0.5% (1/200)	1.0% (1/100)
FALL	0.5% (1/200)	1.0% (1/100)
FEMUR FRACTURE	0.5% (1/200)	0.0% (0/100)
HIP FRACTURE	0.5% (1/200)	0.0% (0/100)
MULTIPLE FRACTURES	0.0% (0/200)	1.0% (1/100)
PERIPHERAL ARTERIAL REOCCLUSION	0.5% (1/200)	0.0% (0/100)
PERIPHERAL ARTERY RESTENOSIS	4.0% (8/200)	7.0% (7/100)
POST PROCEDURAL HAEMATOMA	1.0% (2/200)	1.0% (1/100)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
SPINAL COMPRESSION FRACTURE	0.5% (1/200)	0.0% (0/100)
TOXICITY TO VARIOUS AGENTS	0.0% (0/200)	1.0% (1/100)
UPPER LIMB FRACTURE	0.5% (1/200)	0.0% (0/100)
VASCULAR GRAFT OCCLUSION	1.0% (2/200)	0.0% (0/100)
VASCULAR PSEUDOANEURYSM	2.0% (4/200)	1.0% (1/100)
WRIST FRACTURE	1.0% (2/200)	0.0% (0/100)
METABOLISM AND NUTRITION DISORDERS	3.0% (6/200)	0.0% (0/100)
HYPERGLYCAEMIA	0.5% (1/200)	0.0% (0/100)
HYPERKALAEMIA	1.0% (2/200)	0.0% (0/100)
HYPOGLYCAEMIA	0.5% (1/200)	0.0% (0/100)
HYPOKALAEMIA	1.5% (3/200)	0.0% (0/100)
HYPONATRAEMIA	0.5% (1/200)	0.0% (0/100)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6.5% (13/200)	5.0% (5/100)
ARTHRALGIA	1.0% (2/200)	0.0% (0/100)
BACK PAIN	0.5% (1/200)	0.0% (0/100)
CERVICAL SPINAL STENOSIS	0.0% (0/200)	1.0% (1/100)
DUPUYTREN'S CONTRACTURE	0.5% (1/200)	0.0% (0/100)
INTERVERTEBRAL DISC PROTRUSION	0.0% (0/200)	1.0% (1/100)
MUSCULOSKELETAL PAIN	1.5% (3/200)	0.0% (0/100)
OSTEOARTHRITIS	0.5% (1/200)	1.0% (1/100)
PAIN IN EXTREMITY	3.0% (6/200)	2.0% (2/100)
SYNOVIAL CYST	0.0% (0/200)	1.0% (1/100)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2.5% (5/200)	2.0% (2/100)
BASAL CELL CARCINOMA	0.5% (1/200)	0.0% (0/100)
BLADDER CANCER	0.5% (1/200)	0.0% (0/100)
LYMPHOMA	0.5% (1/200)	0.0% (0/100)
MALIGNANT MELANOMA	0.5% (1/200)	1.0% (1/100)
NEOPLASM PROSTATE	0.5% (1/200)	0.0% (0/100)
SALIVARY GLAND NEOPLASM	0.0% (0/200)	1.0% (1/100)
SQUAMOUS CELL CARCINOMA	0.5% (1/200)	0.0% (0/100)
NERVOUS SYSTEM DISORDERS	1.0% (2/200)	7.0% (7/100)
CAROTID ARTERY STENOSIS	0.5% (1/200)	2.0% (2/100)
HEADACHE	0.0% (0/200)	1.0% (1/100)
HYDROCEPHALUS	0.5% (1/200)	0.0% (0/100)
PARAESTHESIA	0.0% (0/200)	1.0% (1/100)
SYNCOPE	0.5% (1/200)	2.0% (2/100)
TRANSIENT ISCHAEMIC ATTACK	0.0% (0/200)	1.0% (1/100)
PSYCHIATRIC DISORDERS	0.0% (0/200)	2.0% (2/100)
DEPRESSION	0.0% (0/200)	1.0% (1/100)
MENTAL STATUS CHANGES	0.0% (0/200)	1.0% (1/100)
RENAL AND URINARY DISORDERS	5.5% (11/200)	2.0% (2/100)
HAEMATURIA	0.5% (1/200)	0.0% (0/100)
NEPHROLITHIASIS	0.0% (0/200)	1.0% (1/100)
RENAL ARTERY STENOSIS	0.5% (1/200)	1.0% (1/100)
RENAL FAILURE	1.5% (3/200)	0.0% (0/100)
RENAL FAILURE ACUTE	3.0% (6/200)	0.0% (0/100)
RENAL FAILURE CHRONIC	0.5% (1/200)	0.0% (0/100)
URINARY RETENTION	0.5% (1/200)	0.0% (0/100)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0.5% (1/200)	2.0% (2/100)
BENIGN PROSTATIC HYPERPLASIA	0.0% (0/200)	1.0% (1/100)
OVARIAN CYST	0.5% (1/200)	1.0% (1/100)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2.5% (5/200)	1.0% (1/100)
BRONCHOSPASM	0.5% (1/200)	0.0% (0/100)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0.5% (1/200)	0.0% (0/100)
DYSPNOEA	0.5% (1/200)	0.0% (0/100)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
EPISTAXIS	0.5% (1/200)	0.0% (0/100)
HAEMOPTYSIS	0.5% (1/200)	0.0% (0/100)
RESPIRATORY FAILURE	0.0% (0/200)	1.0% (1/100)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2.0% (4/200)	0.0% (0/100)
DERMATITIS CONTACT	0.5% (1/200)	0.0% (0/100)
RASH MACULO-PAPULAR	0.5% (1/200)	0.0% (0/100)
SKIN ULCER	0.5% (1/200)	0.0% (0/100)
URTICARIA	0.5% (1/200)	0.0% (0/100)
SURGICAL AND MEDICAL PROCEDURES	2.0% (4/200)	1.0% (1/100)
KNEE ARTHROPLASTY	0.5% (1/200)	0.0% (0/100)
OBESITY SURGERY	0.5% (1/200)	0.0% (0/100)
PERIPHERAL REVASCULARISATION	0.0% (0/200)	1.0% (1/100)
TOE AMPUTATION	0.5% (1/200)	0.0% (0/100)
WOUND DRAINAGE	0.5% (1/200)	0.0% (0/100)
VASCULAR DISORDERS	30.5% (61/200)	33.0% (33/100)
AORTIC ANEURYSM	0.5% (1/200)	1.0% (1/100)
AORTIC STENOSIS	0.5% (1/200)	0.0% (0/100)
DEEP VEIN THROMBOSIS	0.0% (0/200)	1.0% (1/100)
FEMORAL ARTERY DISSECTION	8.5% (17/200)	6.0% (6/100)
FEMORAL ARTERY OCCLUSION	0.5% (1/200)	0.0% (0/100)
HAEMORRHAGE	0.5% (1/200)	0.0% (0/100)
HYPERTENSION	1.0% (2/200)	0.0% (0/100)
HYPERTENSIVE CRISIS	0.5% (1/200)	0.0% (0/100)
HYPOTENSION	2.0% (4/200)	1.0% (1/100)
INTERMITTENT CLAUDICATION	8.0% (16/200)	6.0% (6/100)
ISCHAEMIA	0.5% (1/200)	0.0% (0/100)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	1.5% (3/200)	0.0% (0/100)
PERIPHERAL ARTERY DISSECTION	0.0% (0/200)	1.0% (1/100)
PERIPHERAL ARTERY STENOSIS	11.0% (22/200)	18.0% (18/100)
PERIPHERAL EMBOLISM	0.5% (1/200)	0.0% (0/100)
PERIPHERAL ISCHAEMIA	0.5% (1/200)	0.0% (0/100)
PERIPHERAL VASCULAR DISORDER	1.5% (3/200)	1.0% (1/100)
VENOUS INSUFFICIENCY	0.5% (1/200)	0.0% (0/100)
TOTAL	60.0% (120/200)	63.0% (63/100)

Includes all events reported through 410 days.

[1] Events are stratified by MedDRA system organ class (SOC) and preferred term (PT); bold rows indicate the SOC summarized. Subjects may experience multiple event types, thus the sum of the subjects by PT need not equal the total number of subjects in the summary for each SOC. In cases where the event verbatim term was updated by the CEC, the MedDRA coding was based on the event verbatim term provided by the CEC. Otherwise, the MedDRA coding was based on the site-reported event verbatim term.

[2] Numbers are % (n/N) where the numerator is the number of subjects with at least one event, the denominator is the total number of subjects enrolled.

Figure 4: Kaplan-Meier Plot Freedom from Loss of Patency through 12 Months

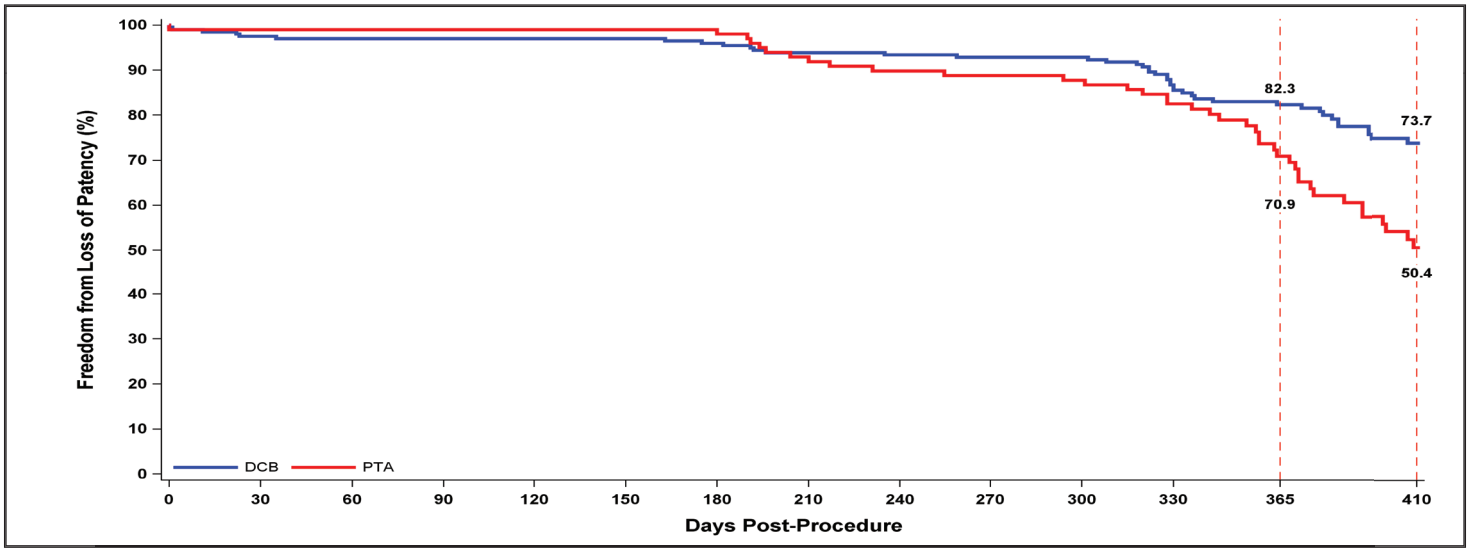


Table 7: Kaplan-Meier Data Freedom from Loss of Patency through 12 Months

Days	Stellarex 035 DCB (N=200)				PTA (N=100)					
	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	Difference [95% CI][1]	Log-Rank p-value
0	200	1	99.5	[96.5, 99.9]	100	1	99.0	[93.1, 99.9]	0.5 [-1.7, 2.7]	0.002
30	195	5	97.5	[94.1, 99.0]	99	1	99.0	[93.1, 99.9]	-1.5 [-4.4, 1.4]	
180	186	8	96.0	[92.1, 98.0]	98	2	98.0	[92.2, 99.5]	-2.0 [-5.9, 1.9]	
365	118	32	82.3	[75.8, 87.2]	51	26	70.9	[60.0, 79.3]	11.4 [0.3, 22.5]	
410	69	42	73.7	[65.8, 80.1]	28	39	50.4	[38.2, 61.4]	23.3 [9.6, 37.0]	

Freedom from loss of patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR).
In the case where duplex ultrasound data was not available, angiographic results assessed by the angiographic core laboratory were utilized.
Lesions with follow-up within or past the 12 month visit window who were free from CD-TLR but without an evaluable assessment of target lesion restenosis were censored at their time of last contact.
[1]The 95% CI of the difference is calculated assuming an asymptotic normal distribution of the difference in survival point estimates.

11.2.6 Summary of Secondary Endpoints

Secondary endpoints were analyzed, and no hypothesis testing was planned. The 12-month major adverse event rate was 9.4% in the DCB group versus 17.7% in the PTA group. The rate of clinically-driven target lesion revascularization was lower in the DCB group versus the PTA group (9.5% and 17.9%, respectively). All-cause mortality and acute success were similar between the DCB group and PTA group. Select secondary endpoints are summarized in Table 8.

Table 8: Secondary Endpoint Results

Major Adverse Events	Stellarex 035 DCB (N=200)[1]	PTA (N=100)[1]	Difference
Major Adverse Event at 12 Months	9.4% (18/191)	17.7% (17/96)	-8.3%
Cardiovascular Death	1.6% (3/191)	2.1% (2/96)	-0.5%
Target Limb Major Amputation	0.0% (0/189)	0.0% (0/95)	--
Clinically-Driven TLR	7.9% (15/189)	16.8% (16/95)	8.9%
Target Lesion Revascularization			
12 Months	9.5% (18/189)	17.9% (17/95)	-8.4%
Clinically Driven Target Vessel Revascularization			
12 Months	7.9% (15/189)	16.8% (16/95)	-8.9%
Arterial Thrombosis of Treated Segment			
12 Months	1.1% (2/189)	0.0% (0/95)	1.1%
Death - All Cause			
12 Months	2.6% (5/192)	2.1% (2/96)	0.5%
Acute Success			
Lesion Success	98.5% (196/199)	98.0% (98/100)	0.5%
Technical Success	98.5% (196/199)	98.0% (98/100)	0.5%
Clinical Success	98.5% (196/199)	98.0% (98/100)	0.5%
Procedural Success	98.5% (196/199)	98.0% (98/100)	0.5%

[1]Numbers are % (n/N). The numerator is the number of subjects with an event prior to the close of the visit window. The denominator includes subjects with an event or those without an event having follow-up on or past the opening of the visit window.

11.2.7 Gender Analysis

Subgroup analyses were conducted to examine the influence of gender on the primary safety and effectiveness endpoints. Table 8 summarizes the results by gender (male vs. female).

There were 176 males and 124 females enrolled in the ILLUMENATE Pivotal Study. Based on gender subgroup analyses, there is no evidence of a difference in treatment effect by gender for the primary safety or primary effectiveness endpoints.

Table 9: Gender Analyses of the Primary Safety and Effectiveness Endpoint

Females			
Outcome	**Stellarex 035 DCB (N=88 Subjects)**	**PTA (N=36 Subjects)**	**Odds Ratio [2]**
Primary Safety[1]	89.3% (75/84)	78.8% (26/33)	2.244
Primary Effectiveness[3]	77.6% (59/76)	58.1% (18/31)	2.507
Males			
Outcome	**Stellarex 035 DCB (N=112 Subjects)**	**PTA (N=64 Subjects)**	**Odds Ratio [2]**
Primary Safety[1]	94.3% (99/105)	85.5% (53/62)	2.802
Primary Effectiveness[3]	75.2% (76/101)	57.4% (35/61)	2.258

[1]Primary safety endpoint was defined as the composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 12 months post-procedure (410 days).
Analysis was based on non-missing data; Imputation of missing outcome status or subgroup data was not applied.
[2]Odds ratio for DCB vs. PTA.
[3]Primary effectiveness endpoint was defined as patency at 12 months. Patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR) through 12 months (410 days).

11.2.8 Pharmacokinetic Sub-Study

The ILLUMENATE PK Study is a prospective, non-randomized, single-arm, multi-center, pharmacokinetic study that was designed to determine the pharmacokinetics profile of paclitaxel in plasma following treatment with the Stellarex 035 DCB. Twenty-five (25) subjects were enrolled at 2 sites in New Zealand. Each enrolled subject will be followed for 2 years (24 months) after treatment. Determination of circulating plasma paclitaxel concentration occurred immediately after the last Stellarex 035 DCB deployment, at 1, 4, and 24 hours, and at 7, 14, 30, 60 and 180 days (as applicable) post-procedure. All subjects were required to have a follow-up telephone contact at 1 month. Follow-up office visits are required at 6, 12, and 24 months. Table 10 summarizes the pharmacokinetic parameters including maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve ($AUC_{0\text{-}24h}$) and terminal elimination half-life ($T_{1/2}$).

Table 10: Summary of Pharmacokinetic Parameters

Parameter	**N**	**Mean**	**Standard Deviation**	**CV (%)**	**Range (Min, Max)**
$AUC^{0\text{-}24h}$ (ng*hours/mL)	25	37.2	59.18	159.1	(0.55, 296.00)
C_{max} (ng/mL)	25	54.4	116.85	214.9	(0.55, 574.00)
T_{max} (hours)	25	0.0167	0.0000	0.0	(0.0167, 0.0167)
$T_{1/2}$ (hours)[1]	9	10.0	1.56	15.6	(8.20, 12.40)

[1]Half-life not able to be calculated for 8 subjects due to R-Squared < 0.850. An additional 8 subjects had insufficient volume after T_{max} for regression.

11.3 Summary of Supplemental Clinical Information

11.3.1 ILLUMENATE European Union Randomized Controlled Trial

The ILLUMENATE EU RCT study is a prospective, randomized, multi-center, single-blind study to evaluate the Stellarex 035 DCB test device compared to the PTA control device in the treatment of de novo or restenotic lesions in the superficial femoral and/or popliteal arteries. A total of 294 subjects were randomized in a 3:1 randomization ratio (222 DCB subjects: 72 PTA subjects) at 18 sites in Austria and Germany. An additional 33 subjects were enrolled in the stent cohort and received post-dilatation with the DCB after stent implantation for >70% residual stenosis following pre-dilatation. Follow-up visits will occur at 1 month, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months.

The primary safety and effectiveness results are represented in Table 11 and Table 12.

Table 11: EU RCT Study Primary Safety Endpoint

Safety Endpoint	**Stellarex 035 DCB (N Subjects=219)[2]**	**PTA (N Subjects=68)[2]**	**Difference**	**Endpoint**
Primary Safety Endpoint[1]	94.1% (193/205)	83.3% (50/60)	10.8%	Met

[1]Primary safety endpoint was defined as the composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through the end of the 12-month visit window (395 days).
[2]Data are presented per subject as % (n/N)

Table 12: EU RCT Study Primary Efficacy Endpoint

Efficacy Endpoint	Stellarex 035 DCB (N Subjects=222) (N Lesions=254)[2]	PTA (N Subjects=72) (N Lesions=79) [2]	Difference
Primary Efficacy Endpoint[1]	83.9%	60.6%	23.3%

[1]Primary efficacy endpoint was defined as patency at 12 months. Patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR) through 395 days. In the case where duplex ultrasound data are not available, angiographic results assessed by the angiographic core laboratory are utilized.
[2]Data are presented) as the within-group patency success rate.

11.3.2 ILLUMENATE Global Study

The ILLUMENATE Global study is a prospective, international, multi-center, single-arm study to assess the safety and performance of the Stellarex 035 DCB in the treatment of de novo or restenotic lesions in the superficial femoral (SFA) and/or popliteal arteries. At the end of enrollment, 371 subjects were enrolled at 37 sites. Follow-up visits are required at 1 month, 6 months, 12 months, 24 months, 36 months, and 48 months. Phone contacts (or optional office visits) will occur at 48 and 60 months.

The primary safety and effectiveness results are presented in Table 13 and Table 14.

Table 13: Global Study Primary Safety Endpoint

Safety Endpoint	At Risk	Number With Event	Event Free (%)
Primary Safety Endpoint[1]	204	19	94.8

[1]Primary safety endpoint was defined as the composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD TLR) through 12 months post-procedure.

Table 14: Global Study Primary Efficacy Endpoint

Efficacy Endpoint	Stellarex 035 DCB (N Subjects=371) (N Lesions=417)[2]
Primary Efficacy Endpoint[1]	77.2% (285/369)

[1]Efficacy endpoint was defined as primary patency at 12 months. Primary patency is defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR) through 395 days. In the case where duplex ultrasound data were not available, angiographic results assessed by the angiographic core laboratory were utilized.
[2]Data are presented per lesion as % (n/N).

11.3.3 ILLUMENATE First-In-Human Trial

The ILLUMENATE FIH Study was a non-randomized, multi-center, single-arm clinical study conducted in subjects requiring treatment of lesions in the SFA/popliteal artery due to occlusion/restenosis. Eighty subjects were enrolled at 3 sites. The first 50 subjects were enrolled in Cohort 1, pre-dilatation before treatment with DCB. The last 30 subjects were enrolled in Cohort 2, direct DCB without pre-dilatation. After treatment, follow-up visits occurred prior to hospital discharge and at 1 month, 6 months, 12 months and 24 months post-procedure.

The primary endpoint was angiographic late lumen loss (LLL) at 6 months post-procedure, defined as the difference between minimum lumen diameter (MLD) after intervention and follow up, with comparison to an objective performance criterion (OPC). The primary endpoint of mean late lumen loss at 6 months for the Cohort 1 intent-to-treat (ITT) analysis set was 0.54±0.97mm. This was significantly less than the objective performance criterion (OPC=1.1mm) and the primary endpoint was met. The late lumen less for Cohort 2 was 0.10±0.76mm, demonstrating the effectiveness of the study device in the direct DCB application as well as following pre-dilatation.

The major secondary safety endpoint was Major Adverse Event (MAE) at 6-months post procedure, defined as composite rate of cardiovascular death, index limb amputation, and ischemia driven target lesion revascularization. The major secondary safety endpoint of Major Adverse Events (MAEs) at 6 months for the Cohort 1 was 4.0%, lower than the objective performance criterion of 30%. The endpoint was met. The MAE rate at 6 months was 6.7% for the Cohort 2 ITT analysis set.

11.4 Summary of Rare Adverse Events

Rare adverse events (RAEs) were evaluated in more than 900 subjects from the ILLUMENATE clinical program (ILLUMENATE Pivotal, ILLUMENATE PK, ILLUMEATE EURCT, ILLUMENATE Global, and ILLUMENATE FIH). Rare Adverse Events were adjudicated by the independent Clinical Events Committee (CEC) and included the following device-related adverse events within 365 days: arterial thrombosis of the treated segment, ipsilateral embolic events of the target limb, neutropenia, and drug hypersensitivity/reactions.

No neutropenia or drug-hypersensitivity/reaction device-related adverse events occurred in any of the subjects treated with the DCB. Of the 928 Stellarex balloon subjects, 15 (1.6%) had an ipsilateral embolic event of the target limb and 8 (0.9%) had an arterial thrombosis of the treated segment within 365 days. There was no indication these events were related to the paclitaxel drug coating**.**

11.5 ILLUMENATE Post-Approval Study

11.5.1 Study Objective

The purpose of the ILLUMENATE Post-Approval Study is to evaluate the long-term safety and effectiveness of the Stellarex 035 DCB in 300 subjects from the premarket ILLUMENATE Pivotal Study discussed in Section 11.2, ILLUMENATE Pivotal Study.

11.5.2 Study Design

The ILLUMENATE Post-Approval Study is a continued follow-up study of the ILLUMENATE Pivotal Study, which was designed as a prospective, randomized, multi-center, single-blind study comparing the Stellarex 035 DCB to standard balloon angioplasty (PTA) for treatment of femoropopliteal arteries in a single limb. Subjects were randomized to the Stellarex 035 DCB or the control PTA device in a 2:1 ratio.

11.5.3 Patient Population

The 261 subjects assessed for the ILLUMENATE Post-Approval Study at 24 months were originally enrolled in the ILLUMENATE Pivotal Study. Information on the study population is provided in Section 11.2.3, Patient Population.

11.5.4 Study Endpoints

Primary Safety Endpoint

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

Primary Effectiveness Endpoint

The primary effectiveness endpoint is patency of the target lesion at 24 months post-procedure. Patency is defined as the absence of target lesion restenosis as determined by DUS (PSVR ≤ 2.5) and freedom from-CD-TLR.

Secondary Endpoints

The secondary endpoints for the ILLUMENATE Post-Approval Study are listed below.

- Major adverse event (MAE) rate at 24, 36, 48 and 60 months post-procedure, defined as a composite rate of cardiovascular death, target limb major amputation and clinically-driven target lesion revascularization (TLR).
- Rate of clinically-driven target lesion revascularization at 24, 36, 48 and 60 months.
- Rate of target lesion revascularization at 24, 36, 48 and 60 months.
- Rate of clinically-driven target vessel revascularization at 24 and 36 months.
- Rate of target limb major amputation at 24, 36, 48 and 60 months.
- Mortality rate at 24, 36, 48 and 60 months.
- Rate of occurrence of arterial thrombosis of the treated segment at 24, 36, 48 and 60 months.

11.5.5 Total Number of Enrolled Study Sites and Subjects, Follow-up Rate

A total of 300 subjects were randomized 2:1 to the Stellarex 035 DCB test device (n=200) and PTA control device (n=100) in the ILLUMENATE Pivotal Study at 43 sites. The 261 subjects evaluated for the ILLUMENATE Post-Approval Study at 24 months were originally enrolled in the ILLUMENATE Pivotal Study. Follow-up compliance through 24 months is presented in Table 15.

Table 15: Follow-Up Compliance through 24 Months

24 Month (730 Days ± 45 Days)	Stellarex 035 DCB (N = 200)	PTA (N=100)
Eligible Subjects[1]	172	89
Study Exits[2]	28	11
Death[2]	13	6
Withdrawn[2]	12	2
Lost-to-follow-up[2]	3	3
Clinical Follow-up		
Follow-up Visit in Window	170	90
Follow-up Compliance (%)[3]	89.5%	90.9%
Follow-up Visit Out of Window	11	4
Follow-up Visit Missed	9	5
Duplex Ultrasound Follow-up		
Duplex Ultrasound in Window	128	76
Diagnostic Duplex Ultrasound in Window[4]	123 (71.5%)	72 (80.9%)
Duplex Ultrasound Out of Window	14	6

[1]Eligible subjects are all subjects who have a follow-up visit form or are past due for their follow-up visit and have not exited the study prior to the upper limit of the visit window.

[2]Study exits are cumulative through the upper limit of the visit window. Exited subjects with a follow-up visit form are considered eligible and are not considered as a study exit until the next follow-up visit.

[3]Follow-up compliance is calculated as the number of subjects having an in-window follow-up visit out of the total number of subjects eligible for follow-up.

[4]Diagnostic duplex ultrasound percentage is calculated as the number of subjects having an in-window, diagnostic ultrasound of the total number of subjects eligible for follow-up. Ultrasounds reported as diagnostic but the target lesion was not measured are not considered diagnostic.

11.5.6 Summary of Primary Safety and Effectiveness Endpoints

The primary safety endpoint, a composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 24 months post-procedure, was 83.0% in the DCB group and 79.3% in the PTA group.

The primary effectiveness endpoint, primary patency at 24 months, was 60.3% in the DCB group and 51.7% for the PTA group.

The primary safety and effectiveness endpoint rates are presented in Table 16. Kaplan-Meier analysis of the primary safety endpoint is presented in Figure 5 and the primary patency endpoint is presented in Figure 6.

Table 16: Primary Safety and Effectiveness Endpoints at 24 months

Outcome	Stellarex 035 DCB (N = 200)[2]	PTA (N=100)[2]	Difference [95% CI][a]	p-value[a]
Primary Safety Endpoint[1] at 775 days	83.0% (142/171)	79.3% (73/92)	3.5% [-5.91%, 13.01%]	0.002
Primary Effectiveness Endpoint[2] at 775 days	60.3% (88/146)	51.7% (45/87)	8.9% [-4.3%, 22.0%]	0.093

[1]Primary safety endpoint was defined as the composite of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 24 months post-procedure (775 days).

[2]The primary effectiveness endpoint was defined as patency at 24 months. Patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR) through 24 months (775 days). In the case where duplex data was not available angiographic core laboratory assessment of restenosis was utilized.

[3]Data are based on complete data without multiple imputation and presented as % (n/N).

[a]Estimate of the difference (DCB-PTA), 95% CI, and 1-sided p-value are based on the model based estimates resulting from multiple-imputation of missing data. For safety, the non-inferiority margin of 5% was met, therefore the results shown above are for superiority testing.

Figure 5: Kaplan-Meier Plot Freedom from Primary Safety Event

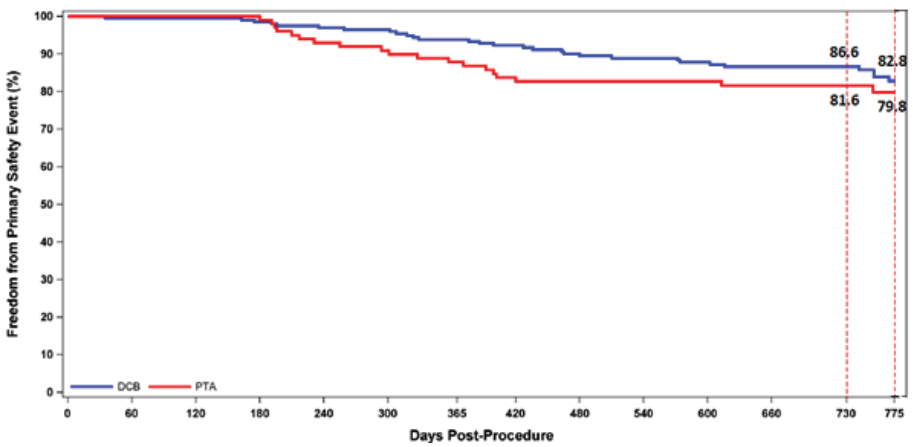


Table 17: Kaplan-Meier Data Freedom from Primary Safety Event through 24 Months

	DCB (N=200)				PTA (N=100)					
Days	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	Difference [95% CI][1]	Log-Rank p-value
0	200	0	100.0	--	100	0	100.0	--	0.0 [0.0, 0.0]	0.322
30	200	0	100.0	--	100	0	100.0	--	0.0 [0.0, 0.0]	
180	192	3	98.5	[95.4, 99.5]	100	1	99.0	[93.1, 99.9]	-0.5 [-3.1, 2.1]	
365	179	12	93.8	[89.4, 96.4]	85	12	87.8	[79.5, 92.9]	6.0 [-1.3, 13.3]	
540	155	21	88.9	[83.4, 92.6]	77	17	82.6	[73.6, 88.8]	6.2 [-2.5, 15.0]	
730	116	25	86.6	[80.8, 90.7]	52	18	81.6	[72.3, 88.0]	5.0 [-4.1, 14.2]	
775	76	29	82.8	[75.9, 87.9]	42	19	79.8	[69.9, 86.7]	3.0 [-7.1, 13.2]	

Freedom from primary safety event was defined as freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) through 24 months post-procedure.

[1]The 95% CI of the difference was calculated assuming an asymptotic normal distribution in survival point estimates.

Figure 6: Kaplan-Meier Plot Freedom from Loss of Patency through 24 Months

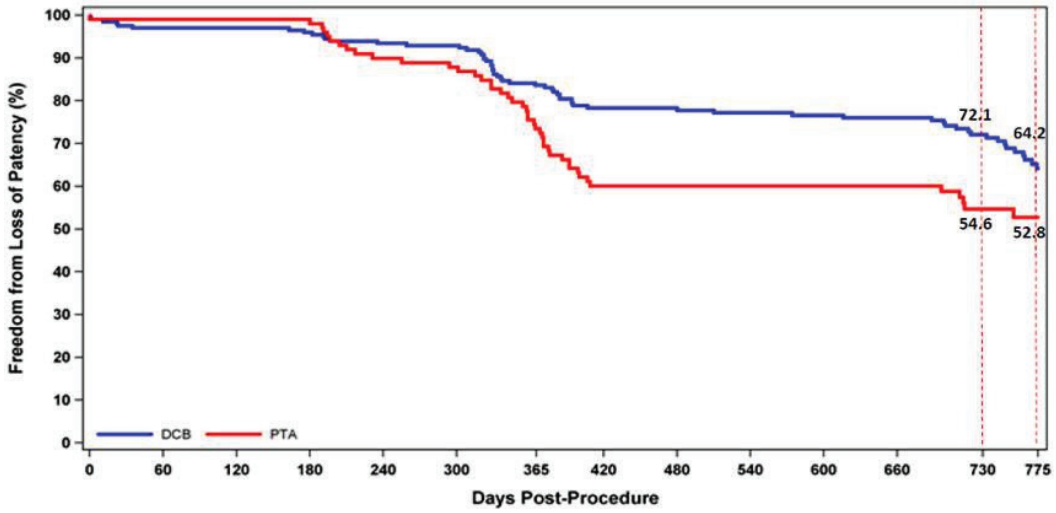


Table 18: Kaplan Meier Data Freedom from Loss of Patency through 24 Months

	DCB (N=200)				PTA (N=100)					
Days	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	Difference [95% CI][1]	Log-Rank p-value
0	200	1	99.5	[96.5, 99.9]	100	1	99.0	[93.1, 99.9]	0.5 [-1.7, 2.7]	0.015
30	195	5	97.5	[94.1, 99.0]	99	1	99.0	[93.1, 99.9]	-1.5 [-4.4, 1.4]	
180	187	8	96.0	[92.1, 98.0]	99	2	98.0	[92.2, 99.5]	-2.0 [-5.9, 1.8]	
365	160	32	83.6	[77.6, 88.1]	71	26	73.5	[63.6, 81.1]	10.1 [-0.1, 20.3]	
540	134	44	77.2	[70.6, 82.5]	56	39	60.0	[49.6, 69.0]	17.1 [5.7, 28.5]	
730	100	52	72.1	[65.0, 78.0]	32	43	54.6	[43.9, 64.2]	17.4 [5.3, 29.6]	
775	63	61	64.2	[56.0, 71.2]	27	44	52.8	[41.8, 62.6]	11.4 [-1.6, 24.4]	

Freedom from loss of patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR).

In the case where duplex ultrasound data was not available, angiographic results assessed by the angiographic core laboratory were utilized.

Lesions with follow-up within or past the 24 month visit window (775 days) who were free from CD-TLR but without an evaluable assessment of target lesion restenosis were censored at their time of last contract.

[1]The 95% CI of the difference is calculated assuming an asymptotic normal distribution of the difference in survival point estimates.

11.5.7 Summary of Serious Adverse Events

Serious adverse event (SAE) rates by MedDRA system organ class (SOC) and preferred term (PT) through 24 months (775 days) are shown in Table 19. A SAE is identified as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires medical/surgical intervention to prevent life-threatening illness or injury or to prevent permanent impairment of a body structure or function, or a congenital anomaly or birth defect .

Table 19: Summary of Serious Adverse Events through 24 Months

Event[1]	DCB (N=200)[2]	PTA (N=100)[2]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4.0% (8/200)	2.0% (2/100)
ANAEMIA	3.0% (6/200)	2.0% (2/100)
HYPOCHROMIC ANAEMIA	0.5% (1/200)	0.0% (0/100)
LEUKOCYTOSIS	0.5% (1/200)	0.0% (0/100)
CARDIAC DISORDERS	18.0% (36/200)	12.0% (12/100)
ACUTE MYOCARDIAL INFARCTION	2.0% (4/200)	1.0% (1/100)
ANGINA PECTORIS	4.0% (8/200)	2.0% (2/100)
ANGINA UNSTABLE	1.5% (3/200)	2.0% (2/100)
AORTIC VALVE STENOSIS	0.5% (1/200)	0.0% (0/100)
ATRIAL FIBRILLATION	2.5% (5/200)	2.0% (2/100)
ATRIOVENTRICULAR BLOCK	0.5% (1/200)	0.0% (0/100)
ATRIOVENTRICULAR BLOCK SECOND DEGREE	0.5% (1/200)	1.0% (1/100)
CARDIAC ARREST	0.5% (1/200)	0.0% (0/100)
CARDIAC FAILURE	1.0% (2/200)	1.0% (1/100)
CARDIAC FAILURE CONGESTIVE	3.0% (6/200)	1.0% (1/100)
CORONARY ARTERY DISEASE	3.5% (7/200)	3.0% (3/100)
CORONARY ARTERY STENOSIS	0.5% (1/200)	0.0% (0/100)
MITRAL VALVE INCOMPETENCE	0.5% (1/200)	0.0% (0/100)
MYOCARDIAL INFARCTION	1.5% (3/200)	0.0% (0/100)
SICK SINUS SYNDROME	0.0% (0/200)	2.0% (2/100)
SINUS BRADYCARDIA	0.5% (1/200)	0.0% (0/100)
TACHYCARDIA	0.0% (0/200)	1.0% (1/100)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0.0% (0/200)	1.0% (1/100)
HYDROCELE	0.0% (0/200)	1.0% (1/100)
ENDOCRINE DISORDERS	0.0% (0/200)	1.0% (1/100)
HYPOTHYROIDISM	0.0% (0/200)	1.0% (1/100)
EYE DISORDERS	1.0% (2/200)	2.0% (2/100)
BLINDNESS UNILATERAL	0.5% (1/200)	0.0% (0/100)
CATARACT	0.0% (0/200)	1.0% (1/100)
MACULAR FIBROSIS	0.5% (1/200)	0.0% (0/100)
RETINAL ARTERY OCCLUSION	0.0% (0/200)	1.0% (1/100)
GASTROINTESTINAL DISORDERS	12.0% (24/200)	9.0% (9/100)
ABDOMINAL DISCOMFORT	0.5% (1/200)	0.0% (0/100)
ABDOMINAL HERNIA	0.5% (1/200)	1.0% (1/100)
ABDOMINAL PAIN	0.5% (1/200)	0.0% (0/100)
ABDOMINAL PAIN LOWER	0.0% (0/200)	1.0% (1/100)
ABDOMINAL PAIN UPPER	1.5% (3/200)	0.0% (0/100
BARRETT'S OESOPHAGUS	0.5% (1/200)	0.0% (0/100
COLITIS	0.5% (1/200)	1.0% (1/100)
DIARRHOEA	1.0% (2/200)	0.0% (0/100)
DIARRHOEA HAEMORRHAGIC	0.0% (0/200)	1.0% (1/100)
DUODENAL ULCER	0.5% (1/200)	0.0% (0/100)
GASTRIC ULCER	0.5% (1/200)	0.0% (0/100)
GASTRITIS	0.5% (1/200)	1.0% (1/100)
GASTROINTESTINAL ANGIODYSPLASIA	0.5% (1/200)	0.0% (0/100)
GASTROINTESTINAL ANGIODYSPLASIA HAEMORRHAGIC	0.5% (1/200)	0.0% (0/100)
GASTROINTESTINAL HAEMORRHAGE	2.5% (5/200)	1.0% (1/100)
INTESTINAL ISCHAEMIA	1.0% (2/200)	0.0% (0/100)
LARGE INTESTINE POLYP	0.5% (1/200)	0.0% (0/100)
MELAENA	0.0% (0/200)	1.0% (1/100)
NAUSEA	0.5% (1/200)	0.0% (0/100)
RECTAL HAEMORRHAGE	0.5% (1/200)	1.0% (1/100)
SMALL INTESTINAL OBSTRUCTION	0.0% (0/200)	1.0% (1/100)

Event[1]	DCB (N=200)[2]	PTA (N=100)[2]
UMBILICAL HERNIA	0.5% (1/200)	0.0% (0/100)
UPPER GASTROINTESTINAL HAEMORRHAGE	0.5% (1/200)	0.0% (0/100)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	10.5% (21/200)	8.0% (8/100)
CATHETER SITE HAEMATOMA	0.5% (1/200)	0.0% (0/100)
CATHETER SITE HAEMORRHAGE	0.0% (0/200)	1.0% (1/100)
CHEST DISCOMFORT	0.5% (1/200)	0.0% (0/100)
CHEST PAIN	5.0% (10/200)	4.0% (4/100)
DEATH	0.0% (0/200)	2.0% (2/100)
DEVICE DEPLOYMENT ISSUE	0.5% (1/200)	0.0% (0/100)
DEVICE OCCLUSION	2.0% (4/200)	0.0% (0/100)
MULTI-ORGAN FAILURE	0.0% (0/200)	1.0% (1/100)
NON-CARDIAC CHEST PAIN	1.5% (3/200)	0.0% (0/100)
OEDEMA PERIPHERAL	0.5% (1/200)	0.0% (0/100)
SUDDEN CARDIAC DEATH	0.5% (1/200)	0.0% (0/100)
THROMBOSIS IN DEVICE	0.5% (1/200)	0.0% (0/100)
VESSEL PUNCTURE SITE THROMBOSIS	0.5% (1/200)	0.0% (0/100)
HEPATOBILIARY DISORDERS	2.0% (4/200)	1.0% (1/100)
BILE DUCT STENOSIS	0.5% (1/200)	0.0% (0/100)
CHOLANGITIS	0.5% (1/200)	0.0% (0/100)
CHOLANGITIS ACUTE	0.5% (1/200)	0.0% (0/100)
CHOLECYSTITIS	1.0% (2/200)	0.0% (0/100)
CHOLELITHIASIS	0.5% (1/200)	0.0% (0/100)
HEPATORENAL FAILURE	0.0% (0/200)	1.0% (1/100)
IMMUNE SYSTEM DISORDERS	0.0% (0/200)	1.0% (1/100)
HYPERSENSITIVITY	0.0% (0/200)	1.0% (1/100)
INFECTIONS AND INFESTATIONS	13.0% (26/200)	9.0% (9/100)
APPENDICITIS PERFORATED	0.5% (1/200)	0.0% (0/100)
BACTERAEMIA	1.0% (2/200)	0.0% (0/100)
BRONCHITIS	1.5% (3/200)	0.0% (0/100)
BRONCHOPNEUMONIA	0.5% (1/200)	0.0% (0/100)
BURSITIS INFECTIVE	0.0% (0/200)	1.0% (1/100)
CELLULITIS	1.5% (3/200)	2.0% (2/100)
DIABETIC FOOT INFECTION	0.0% (0/200)	1.0% (1/100)
ENDOCARDITIS	0.5% (1/200)	0.0% (0/100)
ESCHERICHIA SEPSIS	0.5% (1/200)	0.0% (0/100)
FUNGAEMIA	0.5% (1/200)	0.0% (0/100)
GASTROENTERITIS	1.0% (2/200)	0.0% (0/100)
GASTROENTERITIS VIRAL	0.5% (1/200)	0.0% (0/100)
H1N1 INFLUENZA	0.5% (1/200)	0.0% (0/100)
PASTEURELLA INFECTION	0.5% (1/200)	0.0% (0/100)
PNEUMONIA	3.5% (7/200)	5.0% (5/100)
SEPSIS	1.0% (2/200)	0.0% (0/100
STAPHYLOCOCCAL INFECTION	1.0% (2/200)	0.0% (0/100
URINARY TRACT INFECTION	3.0% (6/200)	1.0% (1/100)
UROSEPSIS	0.5% (1/200)	0.0% (0/100)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	19.0% (38/200)	17.0% (17/100)
ACCIDENT	0.5% (1/200)	0.0% (0/100)
ACCIDENTAL OVERDOSE	0.5% (1/200)	0.0% (0/100)
ANAEMIA POSTOPERATIVE	0.5% (1/200)	0.0% (0/100)
CONCUSSION	0.5% (1/200)	1.0% (1/100)
CORONARY BYPASS THROMBOSIS	**0.5% (1/200)**	0.0% (0/100)
FALL	0.5% (1/200)	2.0% (2/100)
FEMUR FRACTURE	0.5% (1/200)	1.0% (1/100)
HIP FRACTURE	0.5% (1/200)	0.0% (0/100)
MULTIPLE FRACTURES	0.0% (0/200)	1.0% (1/100)
PERIPHERAL ARTERIAL REOCCLUSION	0.5% (1/200)	0.0% (0/100)
PERIPHERAL ARTERY RESTENOSIS	9.5% (19/200)	10.0% (10/100)

Event[1]	DCB (N=200)[2]	PTA (N=100)[2]
POST PROCEDURAL HAEMATOMA	1.0% (2/200)	1.0% (1/100)
POST PROCEDURAL HAEMORRHAGE	0.5% (1/200)	0.0% (0/100)
SPINAL COMPRESSION FRACTURE	0.5% (1/200)	0.0% (0/100)
SUBDURAL HAEMATOMA	0.5% (1/200)	0.0% (0/100)
TOXICITY TO VARIOUS AGENTS	0.0% (0/200)	1.0% (1/100)
UPPER LIMB FRACTURE	0.5% (1/200)	0.0% (0/100)
VASCULAR GRAFT OCCLUSION	1.0% (2/200)	0.0% (0/100)
VASCULAR PSEUDOANEURYSM	2.5% (5/200)	1.0% (1/100)
WRIST FRACTURE	1.0% (2/200)	0.0% (0/100)
INVESTIGATIONS	1.0% (2/200)	1.0% (1/100)
BLOOD GLUCOSE INCREASED	0.0% (0/200)	1.0% (1/100)
BLOOD PRESSURE INCREASED	0.5% (1/200)	0.0% (0/100)
HAEMOGLOBIN DECREASED	0.5% (1/200)	0.0% (0/100)
METABOLISM AND NUTRITION DISORDERS	4.0% (8/200)	1.0% (1/100)
DIABETIC COMPLICATION	0.5% (1/200)	0.0% (0/100)
FLUID OVERLOAD	0.0% (0/200)	1.0% (1/100)
HYPERGLYCAEMIA	0.5% (1/200)	0.0% (0/100)
HYPERKALAEMIA	1.0% (2/200)	0.0% (0/100)
HYPOCALCAEMIA	0.5% (1/200)	0.0% (0/100)
HYPOGLYCAEMIA	0.5% (1/200)	0.0% (0/100)
HYPOKALAEMIA	1.5% (3/200)	0.0% (0/100)
HYPONATRAEMIA	0.5% (1/200)	0.0% (0/100)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8.0% (16/200)	9.0% (9/100)
ARTHRALGIA	1.5% (3/200)	1.0% (1/100)
BACK PAIN	0.5% (1/200)	0.0% (0/100)
CERVICAL SPINAL STENOSIS	0.0% (0/200)	1.0% (1/100)
DUPUYTREN'S CONTRACTURE	0.5% (1/200)	0.0% (0/100)
INTERVERTEBRAL DISC PROTRUSION	0.5% (1/200)	1.0% (1/100)
MUSCLE SPASMS	0.5% (1/200)	0.0% (0/100)
MUSCULOSKELETAL PAIN	1.5% (3/200)	0.0% (0/100)
OSTEOARTHRITIS	0.5% (1/200)	2.0% (2/100)
OSTEONECROSIS	0.0% (0/200)	1.0% (1/100)
PAIN IN EXTREMITY	4.0% (8/200)	2.0% (2/100)
SPINAL COLUMN STENOSIS	0.0% (0/200)	1.0% (1/100)
SYNOVIAL CYST	0.0% (0/200)	1.0% (1/100)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4.5% (9/200)	5.0% (5/100)
BASAL CELL CARCINOMA	0.5% (1/200)	0.0% (0/100)
BLADDER CANCER	0.5% (1/200)	0.0% (0/100)
BREAST CANCER	0.5% (1/200)	0.0% (0/100)
COLON ADENOMA	0.0% (0/200)	1.0% (1/100)
LUNG CANCER METASTATIC	0.5% (1/200)	0.0% (0/100)
LUNG NEOPLASM MALIGNANT	0.0% (0/200)	1.0% (1/100)
LYMPHOMA	0.5% (1/200)	0.0% (0/100)
MALIGNANT MELANOMA	0.5% (1/200)	1.0% (1/100)
METASTATIC MALIGNANT MELANOMA	0.0% (0/200)	1.0% (1/100)
NEOPLASM PROSTATE	0.5% (1/200)	0.0% (0/100)
PANCREATIC CARCINOMA	0.5% (1/200)	0.0% (0/100)
PROSTATE CANCER	0.5% (1/200)	0.0% (0/100)
SALIVARY GLAND NEOPLASM	0.0% (0/200)	1.0% (1/100)
SMALL CELL LUNG CANCER	0.5% (1/200)	0.0% (0/100)
SQUAMOUS CELL CARCINOMA	0.5% (1/200)	0.0% (0/100)
NERVOUS SYSTEM DISORDERS	5.5% (11/200)	11.0% (11/100)
CAROTID ARTERY OCCLUSION	0.0% (0/200)	1.0% (1/100)
CAROTID ARTERY STENOSIS	1.5% (3/200)	2.0% (2/100)
CEREBRAL INFARCTION	0.5% (1/200)	0.0% (0/100)
CEREBROVASCULAR ACCIDENT	1.5% (3/200)	0.0% (0/100)

Event[1]	DCB (N=200)[2]	PTA (N=100)[2]
CEREBROVASCULAR DISORDER	0.5% (1/200)	0.0% (0/100)
CONVULSION	0.0% (0/200)	2.0% (2/100)
DYSARTHRIA	0.5% (1/200)	0.0% (0/100)
ENCEPHALOPATHY	0.0% (0/200)	1.0% (1/100)
HEADACHE	0.0% (0/200)	1.0% (1/100)
HYDROCEPHALUS	0.5% (1/200)	0.0% (0/100)
PARAESTHESIA	0.0% (0/200)	1.0% (1/100)
RADICULOPATHY	0.0% (0/200)	1.0% (1/100)
SYNCOPE	1.0% (2/200)	2.0% (2/100)
TRANSIENT ISCHAEMIC ATTACK	1.0% (2/200)	1.0% (1/100)
UNRESPONSIVE TO STIMULI	0.0% (0/200)	1.0% (1/100)
PSYCHIATRIC DISORDERS	0.5% (1/200)	2.0% (2/100)
ALCOHOL ABUSE	0.5% (1/200)	0.0% (0/100)
DEPENDENCE	0.5% (1/200)	0.0% (0/100)
DEPRESSION	0.0% (0/200)	1.0% (1/100)
MENTAL STATUS CHANGES	0.0% (0/200)	1.0% (1/100)
RENAL AND URINARY DISORDERS	8.0% (16/200)	3.0% (3/100)
HAEMATURIA	0.5% (1/200)	0.0% (0/100)
NEPHROLITHIASIS	0.5% (1/200)	1.0% (1/100)
RENAL ARTERY STENOSIS	0.5% (1/200)	1.0% (1/100)
RENAL FAILURE	1.5% (3/200)	0.0% (0/100)
RENAL FAILURE ACUTE	4.0% (8/200)	1.0% (1/100)
RENAL FAILURE CHRONIC	1.0% (2/200)	1.0% (1/100)
URINARY RETENTION	1.0% (2/200)	0.0% (0/100)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0.5% (1/200)	2.0% (2/100)
BENIGN PROSTATIC HYPERPLASIA	0.0% (0/200)	1.0% (1/100)
OVARIAN CYST	0.5% (1/200)	1.0% (1/100)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6.0% (12/200)	5.0% (5/100)
ACUTE RESPIRATORY FAILURE	0.5% (1/200)	0.0% (0/100)
BRONCHOSPASM	0.5% (1/200)	0.0% (0/100)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1.0% (2/200)	1.0% (1/100)
DYSPNOEA	1.5% (3/200)	1.0% (1/100)
EPISTAXIS	1.0% (2/200)	0.0% (0/100)
HAEMOPTYSIS	0.5% (1/200)	0.0% (0/100)
PLEURAL EFFUSION	1.0% (2/200)	0.0% (0/100)
PULMONARY EMBOLISM	0.0% (0/200)	1.0% (1/100)
PULMONARY HYPERTENSION	0.0% (0/200)	1.0% (1/100)
PULMONARY OEDEMA	0.0% (0/200)	1.0% (1/100)
RESPIRATORY FAILURE	0.0% (0/200)	3.0% (3/100)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2.0% (4/200)	1.0% (1/100)
DECUBITUS ULCER	0.0% (0/200)	1.0% (1/100)
DERMATITIS CONTACT	0.5% (1/200)	0.0% (0/100)
RASH MACULO-PAPULAR	0.5% (1/200)	0.0% (0/100)
SKIN ULCER	0.5% (1/200)	1.0% (1/100)
URTICARIA	0.5% (1/200)	0.0% (0/100)
SURGICAL AND MEDICAL PROCEDURES	2.5% (5/200)	1.0% (1/100)
CATARACT OPERATION	0.5% (1/200)	0.0% (0/100)
KNEE ARTHROPLASTY	0.5% (1/200)	0.0% (0/100)
OBESITY SURGERY	0.5% (1/200)	0.0% (0/100)
PERIPHERAL REVASCULARISATION	0.0% (0/200)	1.0% (1/100)
TOE AMPUTATION	0.5% (1/200)	0.0% (0/100)
WOUND DRAINAGE	0.5% (1/200)	0.0% (0/100)
VASCULAR DISORDERS	41.0% (82/200)	36.0% (36/100)
AORTIC ANEURYSM	0.5% (1/200)	1.0% (1/100)
AORTIC STENOSIS	1.0% (2/200)	0.0% (0/100)
ARTERIAL STENOSIS	0.0% (0/200)	1.0% (1/100)
DEEP VEIN THROMBOSIS	1.0% (2/200)	1.0% (1/100)

Event[1]	DCB (N=200)[2]	PTA (N=100)[2]
FEMORAL ARTERY DISSECTION	8.5% (17/200)	6.0% (6/100)
FEMORAL ARTERY OCCLUSION	1.5% (3/200)	1.0% (1/100)
HAEMORRHAGE	0.5% (1/200)	0.0% (0/100)
HYPERTENSION	1.5% (3/200)	1.0% (1/100)
HYPERTENSIVE CRISIS	0.5% (1/200)	0.0% (0/100)
HYPOTENSION	2.0% (4/200)	1.0% (1/100)
INTERMITTENT CLAUDICATION	13.5% (27/200)	8.0% (8/100)
ISCHAEMIA	0.5% (1/200)	0.0% (0/100)
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	3.0% (6/200)	1.0% (1/100)
PERIPHERAL ARTERY DISSECTION	0.0% (0/200)	1.0% (1/100)
PERIPHERAL ARTERY STENOSIS	17.5% (35/200)	20.0% (20/100)
PERIPHERAL EMBOLISM	0.5% (1/200)	0.0% (0/100)
PERIPHERAL ISCHAEMIA	1.0% (2/200)	0.0% (0/100)
PERIPHERAL VASCULAR DISORDER	1.5% (3/200)	1.0% (1/100)
VARICOSE VEIN	0.0% (0/200)	1.0% (1/100)
VENOUS INSUFFICIENCY	0.5% (1/200)	0.0% (0/100)
TOTAL	**72.5% (145/200)**	**73.0% (73/100)**

Includes all events reported through 775 days.
[1] Events are stratified by MedDRA system organ class (SOC) and preferred term (PT); bold rows indicate the SOC summarized. Subjects may experience multiple event types, thus the sum of the subjects by PT need not equal the total number of subjects in the summary for each SOC. In cases where the event verbatim term was updated by the CEC, the MedDRA coding was based on the event verbatim term provided by the CEC. Otherwise, the MedDRA coding was based on the site-reported event verbatim term.
[2] Numbers are % (n/N) where the numerator is the number of subjects with at least one event, and the denominator is the total number of subjects enrolled.

11.5.8 Summary of Secondary Endpoints

Secondary endpoints were analyzed, and no hypothesis testing was planned. The 24-month major adverse event rate was 18.9% in the DCB group versus 23.4% in the PTA group. Select secondary endpoints are summarized in Table 19.

Table 20: Secondary Endpoint Results

Major Adverse Events	Stellarex 035 DCB (N=200)[1]	PTA (N=100)[1]	Difference
Major Adverse Event	18.9% (33/175)	23.4% (22/94)	-4.5%
Target Lesion Revascularization	18.6% (32/172)	21.7% (20/92)	-3.1%
Clinically Driven Target Vessel Revascularization	0.6% (1/161)	1.2% (1/83)	-0.6%
Target Limb Major Amputation	0.0% (0/170)	0.0% (0/90)	--
Arterial Thrombosis of Treated Segment	1.8% (3/170)	0.0% (0/90)	1.8%
Death - All Cause	7.1% (13/182)	7.4% (7/95)	-0.2%

Sum of the components may not add up to the overall rate as some subjects may experience more than one event type.
[1]Numbers are % (n/N). The numerator is the number of subjects with an event prior to the close of the visit window. The denominator includes subjects with an event or those without an event having follow-up on or past the opening of the visit window.

12. HOW SUPPLIED

The Stellarex 035 DCB is supplied STERILE for single use only (ethylene oxide sterilization). The Stellarex 035 DCB is contained within an inner Tyvek pouch within an outer foil pouch. The pouches are contained within a single unit box.

WARNING: The outer foil pouch is not a sterile barrier. The inner Tyvek pouch is the product sterile barrier. Do not allow the Tyvek inner pouch to contact the sterile field.

WARNING: The Stellarex 035 DCB is supplied STERILE for single use only. Do not reprocess or resterilize. Reprocessing and resterilizing could increase the risk of patient infection and risk of compromised device performance.

13. STORAGE

The Stellarex 035 DCB should be stored at room temperature in a dry location in its original packaging. The device should be used prior to the "Use By" date printed on the device packaging.

14. COMPATIBILITY

Prepare the following items using sterile technique:

- 10 cc syringe filled with sterile heparinized saline
- Three-way stopcock
- Contrast media - the standard inflation medium is a 1:1 mixture of contrast medium and sterile saline.
  CAUTION: *Do not use contrast media that is contraindicated for intravascular use.*
- 0.035" guidewire (refer to product labeling)
- Appropriately sized hemostatic introducer sheath (refer to product labeling)
- Inflation device with manometer
- Vessel preparation device

15. INSPECTION PROCEDURES

Inspect the Stellarex 035 DCB and packaging. Do not use if packaging or product damage is evident.

PRECAUTION: After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.

Inspect the Stellarex 035 DCB "Use By" date on the package. Use before the "Use By" date.

CAUTION: *Carefully inspect the Stellarex 035 DCB prior to use. Do not use the catheter if it is damaged or if the size, shape or condition is unsuitable for the intended procedure.*

16. DIRECTIONS FOR USE

16.1 Balloon Catheter Size Selection

Select the appropriate size Stellarex 035 DCB for the procedure.

The nominal balloon diameter should match the diameter of the vessel distal to the lesion. The balloon length must exceed the lesion length by at least 5mm beyond both the proximal and distal edges.

If the lesion is longer than the longest available Stellarex 035 DCB, use multiple Stellarex 035 DCBs to treat the lesion, using the recommended overlap, as described in Use of Multiple Stellarex 035 DCBs (Section 16.6).

16.2 Recommendations for Optimal Treatment

WARNING: The outer foil pouch is not a sterile barrier. The inner Tyvek pouch is the product sterile barrier. Do not allow the Tyvek inner pouch to contact the sterile field.

CAUTION: *Use sterile gloves to handle the Stellarex 035 DCB prior to use. Care should be taken to minimize contact with the coated balloon portion of the device.*

1. Appropriate vessel preparation is required prior to the use of the Stellarex 035 DCB. NOTE: Vessel preparation using only pre-dilatation was studied in the clinical study. Other methods of vessel preparation, such as atherectomy, have not been studied clinically with Stellarex 035 DCB.
2. Select the appropriate size balloon for the procedure.
3. Outside of the sterile field, remove inner Tyvek pouch from the outer foil pouch and carton.
4. Remove the catheter sterile hoop from the Tyvek inner pouch.
5. Carefully remove the catheter from the hoop.
6. Remove the protective sheath on the balloon. Discard protective sheath. Flush the guidewire lumen with heparinized saline solution through the guide wire lumen marked "THRU."

   CAUTION: *Avoid saline solution contact with the Stellarex 035 DCB coating when flushing the wire lumen.*
7. Fill a 10 cc syringe with approximately 4 cc of equal volume (1:1) of contrast media and saline.
8. Evacuate air from the balloon and balloon lumen:
   a. Attach the syringe to the balloon lumen, marked "BALLOON."
   b. Apply negative pressure and aspirate for 15 seconds. Slowly release the pressure to neutral, allowing contrast media to fill the shaft of the catheter.
   c. Disconnect the syringe from the "BALLOON" port of the catheter.
   d. Remove all air from the syringe. Reconnect the syringe to the "BALLOON" port.
   e. Apply negative pressure on the balloon until air no longer returns to the device.
   f. Slowly release the device pressure to neutral.
   g. Repeat as necessary to remove all air from the balloon and lumen.
9. Replace the syringe with an inflation device with manometer, taking care not to introduce air into the catheter.

CAUTION: *Do not immerse or wipe the balloon section of the Stellarex 035 DCB with any fluid as the integrity of the drug coating may be damaged or compromised. Replace any Stellarex 035 DCB where the balloon has come into contact with fluids prior to use.*

16.3 Stellarex 035 DCB Insertion and Dilatation

The Stellarex 035 DCB can be introduced percutaneously through an appropriate sized introducer sheath.

CAUTION: *Do not attempt to pass the Stellarex 035 DCB through a smaller French size guide catheter or introducer sheath than indicated on the label. Refer to package label for guide catheter compatibility.*

1. Apply negative pressure to the balloon.
2. Place the prepared catheter over a pre-positioned guidewire, which has been placed through the lesion, and introduce the catheter percutaneously. Negative pressure should be maintained during advancement over the guidewire.
3. Advance the catheter tip to the treatment location. A suitable length guidewire should be used at all times to maintain control and position of the guidewire.

   CAUTION: *Use fluoroscopic guidance to manipulate the Stellarex 035 DCB during the procedure.*

WARNING: If resistance is encountered at any time during the insertion procedure, do not force passage. Resistance may cause damage to the device or lumen. Carefully withdraw the catheter.

4. Position the catheter in the treatment location. The radiopaque marker bands indicate the working length of the balloon. The position of the balloon catheter may only be changed with the guidewire in place.
5. Inflate the balloon to dilate the target area according to the compliance chart printed on the device packaging. Inflation should be maintained for sixty (60) seconds.

   WARNING: The Stellarex 035 DCB should not be inflated in excess of the rated burst pressure (RBP). Balloon rupture may occur if RBP is exceeded.

   CAUTION: *Treatment of the target lesion with the Stellarex 035 DCB should cover the entire area. Always manipulate the Stellarex 035 DCB under fluoroscopic observation when in the body.*
6. For proper drug delivery to the target lesion, maintain inflation of the Stellarex 035 DCB for a minimum of 60 seconds. In order to optimize lesion dilatation, longer inflation times may be performed at the discretion of the operator.
7. Deflate the balloon and apply negative pressure.
8. With the guidewire in place and with negative pressure in the balloon, withdraw the catheter. Do not retract the catheter unless the balloon is free and fully deflated.
9. Results should be verified by angiography.
10. If a Stellarex 035 DCB has entered the vasculature and cannot be deployed, the balloon CANNOT be re-inserted for deployment.

16.4 Post-Treatment Dilatation or Stenting

If required, post-treatment balloon dilatation is allowed with a standard PTA catheter.

CAUTION: *If provisional (bail out) stenting is required, a bare metal stent indicated for treatment of the femoropopliteal arteries should be used.*

16.5 Disposal

CAUTION: *After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.*

16.6 Use of Multiple Stellarex 035 DCBs

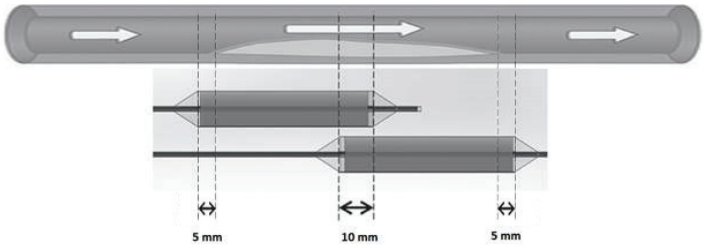
WARNING: *The safety of utilizing multiple Stellarex 035 DCBs with a total drug dose greater than 14,200 µg paclitaxel has not been evaluated.*

Table 21: Nominal Paclitaxel Dose

Balloon Diameter (mm)	Total Nominal Paclitaxel Dose per Balloon Size (µg)				
	Balloon Length (mm)				
	40	60	80	100	120
4.0	1124	1674	2211	2759	3307
5.0	1335	1998	2636	3245	3880
6.0	1619	2410	3174	3957	4721

If multiple Stellarex 035 DCBs are required to treat a lesion, the sequentially used Stellarex 035 DCBs should be angiographically positioned so that the marker bands of consecutively placed balloons overlap a minimum of 10 mm and the most proximal and most distal balloons extend 5 mm beyond the predilated segment. The use of an arterial land marking system (eg. radiopaque ruler) must be used to ensure appropriate placement of the Stellarex 035 DCBs.

Figure 7: Multiple Stellarex 035 DCB



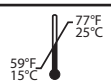
17. WARRANTY

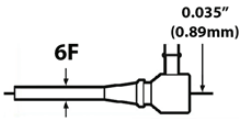
Although this product has been manufactured under carefully controlled conditions, Spectranetics® has no control over the conditions under which this product is used. Spectranetics® therefore disclaims all warranties, both express and implied, with respect to the product including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Spectranetics® shall not be liable to any person or entity for any medical expenses or any direct, incidental or consequential damages caused by any use, defect, failure or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort or otherwise. No person has any authority to bind Spectranetics® to any representation or warranty with respect to the product. Descriptions or specifications in Spectranetics printed and electronic materials, including this publication, are meant solely to generally describe the products at the time of manufacture and do not constitute any express warranties.

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

Spectranetics assumes no liability with respect to instruments reused, reprocessed, or resterilized.

18. EXPLANATION OF SYMBOLS ON PACKAGE LABELING

Standard Symbols (ISO 15223-1 2016)	
Symbol	**Description of Symbol**
	Consult instructions for use
 www.spnc.com	Electronic IFU indicator
	Sterilized using ethylene oxide
	Authorized representative in the European Community
	Do not use if package is damaged
	Use by date
	Do not reuse
	Keep dry
	Batch code
	Catalog number
	Keep away from sunlight
	Manufacturer
	Temperature limit
	Caution, consult the instructions for use for accompanying information

Non-Standard Symbols	
Symbol	**Description of Symbol**
Rx ONLY	For prescription use only
	Guidewire and Introducer Sheath Compatibility
QTY	Package Quantity
	Peel here
	The outer foil pouch is not a sterile barrier
	Shaft length
	Balloon length
	Balloon diameter
NOM	Nominal pressure
RBP	Rated burst pressure

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