SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Coated Balloon (DCB) Percutaneous Transluminal Angioplasty Catheter
Device Trade Name:	Stellarex™ 0.035" OTW Drug-Coated Angioplasty Balloon
Device Procode:	ONU
Applicant's Name and Address:	The Spectranetics Corporation (SPNC) 6531 Dumbarton Circle Fremont, CA 94555 USA
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160049
Date of FDA Notice of Approval:	July 26, 2017

II. 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.

III. 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 anti-platelet and/or anti-coagulation therapy.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children.
- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Stellarex 0.035" OTW Drug-coated Angioplasty Balloon labeling.

V. DEVICE DESCRIPTION

The Stellarex 0.035" OTW Drug-coated Angioplasty Balloon (Stellarex 035 DCB) (**Figure 1**) is a sterile, single-use, over-the-wire (OTW) device/drug combination product comprised of two regulated components:

- **Base PTA Catheter:** Percutaneous transluminal angioplasty balloon catheter uses mechanical force of balloon expansion across a lesion to establish patency
- **Drug Coating:** A formulation of the active pharmaceutical ingredient paclitaxel incorporated in an excipient, to serve as an adjunct to the mechanical action of balloon angioplasty and assist in maintaining long term vessel patency post-procedure

Figure 1: Schematic of the Stellarex 035 DCB

PTA Catheter Component

The Stellarex 035 DCB is available in balloon lengths ranging from 40 mm to 120 mm, balloon diameters ranging from 4.0 mm to 6.0 mm, and is offered in catheter working lengths of 80 cm and 135 cm. Note that all device sizes provided in **Table 1** below were included in the clinical trials. The Stellarex 035 DCB is compatible with 0.035" guidewires and with 6F introducer sheaths.

Table 1: Stellarex 035 DCB Product Matrix

Diameter (mm)	Balloon Length (mm)			
	40	**60**	**80**	**120**
4.0	X	X	X	X
5.0	X	X	X	X
6.0	X	X	X	X

Drug Component

The Stellarex 035 DCB EnduraCoat™ Technology is a proprietary DCB coating with a nominal drug dose density of 2 μg of paclitaxel per mm^2 of the expanded balloon surface blended with a hydrophilic polymer excipient (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™ coating solution contains an azeotropic mixture of ethanol and acetonitrile which evaporate off the balloon surface after the coating is applied.

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

Table 2: Nominal Paclitaxel Content by Balloon Size

Diameter (mm)	Balloon Length (mm)			
	40	**60**	**80**	**120**
4.0	1124 µg	1674 µg	2211 µg	3307 µg
5.0	1335 µg	1998 µg	2636 µg	3880 µg
6.0	1619 µg	2410 µg	3174 µg	4721 µg

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 2**.

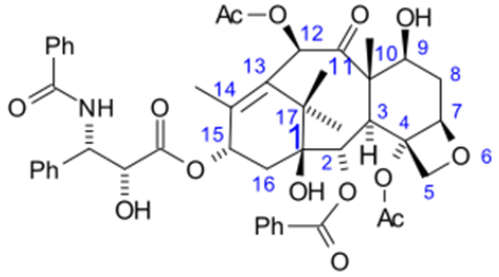


Figure 2: Paclitaxel Chemical Structure

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 3** below.

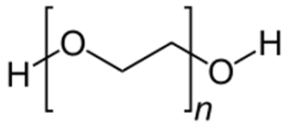


Figure 3: PEG Chemical Structure

Mechanism of Action

The primary mode of action for Stellarex 035 DCB is mechanical dilatation of de novo or restenotic lesions by means of percutaneous transluminal angioplasty, with a secondary action of inhibition of restenosis (caused by the proliferative response to the PTA)

through the application of paclitaxel to the vessel wall. The paclitaxel drug inhibits restenosis caused by the proliferative response from vessel injury due to PTA.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

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

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

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

VII. MARKETING HISTORY

The Stellarex 035 DCB has been available for distribution in the European Union (EU) since receiving CE mark on December 31, 2014. The Stellarex 035 DCB has not been withdrawn from marketing for any reason related to safety or effectiveness. As of October 2016, over 9,000 Stellarex 035 DCB units have been sold. The Stellarex 035 DCB is available for commercial distribution in 43 countries listed in **Table 3**.

Table 3: Commercial Availability of the Stellarex 035 DCB

Austria	Finland	Lebanon	Portugal
Belgium	France	Liechtenstein	Romania
Brunei	Germany	Lithuania	Saudi Arabia
Bulgaria	Greece	Luxembourg	Slovakia
Cambodia	Haiti	Macao	Slovenia
Chile	Hong Kong	Malaysia	Spain
Croatia	Hungary	Malta	Sweden
Cyprus	Iceland	Myanmar	Switzerland
Czech Republic	Ireland	Netherlands	Turkey
Denmark	Italy	Norway	United Kingdom
Estonia	Latvia	Poland	

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Abrupt Vessel Closure
- Allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (drug, excipients, and materials)
- Amputation/ Loss of limb
- Arrhythmias
- Arterial Aneurysm
- 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
- 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:

- 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

Potential complications which may be associated with the use of paclitaxel include, but are not limited to:

- 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 13** in the Clinical Studies section below.

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies were performed with the Stellarex 035 DCB. These evaluations included biocompatibility studies, *in vitro* bench testing, Good Laboratory Practice (GLP) animal studies, analytical testing, stability and shelf life, and sterilization. A summary for each of the evaluations is provided below.

A. Biocompatibility Studies

Biocompatibility testing for the Stellarex 035 DCB was conducted separately on the balloon with the drug coating and the remainder of the balloon catheter. In addition, chemical characterization was conducted *in vitro* while thrombogenicity was conducted *in vivo* on the entire balloon catheter including the drug coating, in order to support the overall biocompatibility of the drug-coated balloon. For the purposes of this testing, the balloon with the drug coating was categorized as an implant device with permanent blood contact (>30 days), and the remainder of the balloon catheter was categorized as an externally communicating device with limited contact duration (<24 hours) with circulating blood. A summary of the biocompatibility testing and results can be found in **Table 4**.

Table 4: Summary of Biocompatibility Testing

Test Name	Test Description	Coated Balloon	Catheter Body	Results
Cytotoxicity	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	X	X	Non-toxic response for catheter body; acceptable response for the coated balloon*
Sensitization	ISO Guinea Pig Maximization	X	X	Non-sensitizing
Irritation	ISO Intracutaneous Reactivity	X	X	Non-irritating
Acute Systemic Toxicity	ISO Systemic Toxicity	X	X	Non-toxic
Pyrogenicity	USP Material Mediated Pyrogenicity	X	X	Non-pyrogenic
Hemocompatibility	ASTM Hemolysis (Direct and Indirect Contact)	X	X	Non-hemolytic for the catheter body; slightly hemolytic for the coated balloon
	Complement Activation Assay (C3a and SC5b-9)	X	X	Not a complement activator
	In vivo Thrombogenicity	Coated Balloon + Catheter Body		Non-thrombogenic
Chemical Characterization	Gas Chromatography - Mass Spectroscopy (GC/MS) for volatile and semi-volatile, organic compounds	X	X	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
	Inductively Coupled Plasma (ICP) Spectroscopy for metallic compounds	X	X	
	Liquid Chromatography - Mass Spectroscopy (LC/MS) for semi-volatile and non-volatile organic compounds	X	X	

*Although a cytotoxic response was noted for the neat extract of the balloon, the results are considered acceptable following extract dilutions and based on acceptable implantation response from the *in vivo* safety study.

The endpoints of sub-chronic toxicity, chronic toxicity and implantation were evaluated as part of *in vivo* studies conducted to evaluate the safety and effectiveness of the device in porcine iliofemoral artery model, as described in Section IX.D, Animal Studies, below. These additional animal studies demonstrated a lack of inflammation and toxicity when the product was used in a clinically-relevant vascular location. A chemical characterization and toxicological risk assessment was also conducted to support systemic toxicity, genotoxicity, and carcinogenicity.

The information provided demonstrates that the Stellarex 035 DCB is biocompatible for its intended use.

B. *In vitro* Bench Testing

Table 5 provides an overview of the functional engineering testing performed with the Stellarex 035 DCB. The table includes the tests performed, the objective of the tests, the acceptance criteria, and the result of the test.

Table 5: Summary of Functional Testing Performed

Test	Testing Objective	Acceptance Criteria (Specification)	Pass/Fail
Dimensional (ID, OD, Crossing Profile)	Demonstrate Stellarex 035 DCB accommodates 0.035" guidewires and 6F sheath compatibility	ID: 0.0360 ± 0.001" OD: 0.068 + 0.002" Crossing Profile: 6 Fr	Pass
Catheter Effective Length	Demonstrate Stellarex 035 DCB length is appropriate for clinical use	80 ± 3cm 135 ± 3cm	Pass
Delivery, Deployment, and Retraction	Demonstrate safe and reliable use of Stellarex 035 DCB following the recommended techniques in the Instructions for Use without damage to the product	Balloon catheter preparation, delivery, balloon inflation/ deflation, and catheter retraction steps must not damage the balloon catheter.	Pass
Balloon Inflation/ Deflation Time	Demonstrate successful inflation and deflation of Stellarex 035 DCB within clinical time limits	Inflation Time: ≤ 60 seconds Deflation Time: ≤ 60 seconds	Pass
Balloon OD/Length	Demonstrate Stellarex 035 DCB meets labeled balloon dimensions	OD: ± 0.5mm of nominal Length: ± 10% of nominal	Pass
Balloon Compliance	Demonstrate Stellarex 035 DCB meets the labeled compliance	Average compliance ≤ 10%	Pass
Balloon Burst Strength	Demonstrate Stellarex 035 DCB is able to withstand inflation pressures that exceed the labeled burst pressures	Balloon burst pressure ≥ rated burst pressure (RBP, atm) Diameter (mm) ↓ / Length (mm): 40 / 60 / 80 / 120 4.0: 20 / 20 / 20 / 20 5.0: 18 / 18 / 18 / 16 6.0: 14 / 14 / 14 / 12	Pass
Balloon Fatigue	Demonstrate Stellarex 035 DCB clinically is able to withstand multiple inflations to RBP	Balloon can meet the 10 cycles of repeated inflation to RBP without failure	Pass
Kink Resistance	Demonstrate Stellarex 035 DCB is able to withstand clinical vessel articulation without kinking	Must not kink at ¾" arch radius supported by wire	Pass

Test	Testing Objective	Acceptance Criteria (Specification)	Pass/Fail
Torque Strength	Demonstrate Stellarex 035 DCB is able to withstand torque forces applied during clinical use	≥720° of rotation	Pass
Bond Tensile Strength	Demonstrate Stellarex 035 DCB is able to withstand forces seen during clinical use	Distal Bond: ≥ 2.25lbf Proximal Bond: ≥ 3.0lbf Manifold Bond: ≥ 3.0lbf	Pass

C. Analytical Testing and Coating Characterizations

Analytical testing was performed to determine the identity, safety, purity and quality of the drug substance (paclitaxel) of the Stellarex 035 DCB, as described in **Table 6.**

Table 6: Summary of Analytical Testing and Coating Characterizations

Test	Description of Test	Acceptance Criteria	Results
Coating Appearance and Visual Rating	Visual inspection was conducted to verify that the Stellarex 035 DCB drug coating meets the appearance and visual rating specifications	Must meet visual standards	Device met established acceptance criteria
Paclitaxel Identification	Test drug substance for identity and ensure conformity to incoming specifications	Identity must be confirmed via two different tests	Drug Substance met established acceptance criteria
Paclitaxel Assay	Quantitative assay to determine the total amount of paclitaxel on the Stellarex 035 DCB	Drug content assay must be within limits	Device met established acceptance criteria
Content Uniformity	Verification of the content uniformity of the paclitaxel coating from balloon to balloon	USP <905>	Device met established acceptance criteria
Related Substances/ Impurities	Quantitative assay to determine the type and amount of impurities and degradation products on the Stellarex 035 DCB	ICH Q3B (R2)	Device met established acceptance criteria
Residual Solvents	Quantitative assay to determine the type and amount of residual solvents on the Stellarex 035 DCB	Residual solvent levels must be within limits	Device met established acceptance criteria
***In Vitro* Elution**	Determination of the *in vitro* release rate of paclitaxel from the Stellarex 035 DCB	USP <711>	Device met established acceptance criteria
Particulate Matter Quantitation	Particulate sizes and counts measured for the Stellarex 035 DCB	Particulate sizes and counts must be within limits	Device met established acceptance criteria

Test	Description of Test	Acceptance Criteria	Results
Endotoxin	Ensures blood-contacting Stellarex 035 DCB is safe for human use	USP <161>	Device met established acceptance criteria
Drug Content Circumferential Uniformity	Measure relative uniformity of drug content around balloon circumference	Testing for characterization purposes only	N/A (Characterization Only)
Drug Content Length Uniformity	Measure relative uniformity of drug content along balloon length	Testing for characterization purposes only	N/A Characterization Only)
Particulate Identification	Chemical identification of the particulate matter for the Stellarex 035 DCB	Testing for characterization purposes only	N/A (Characterization Only)
Particulate Crystallinity	Determination of the percent crystallinity of the particulate matter for the Stellarex 035 DCB	Testing for characterization purposes only	N/A (Characterization Only)
Coating Integrity	Characterization of the drug coating morphology on the surface of the balloon	Testing for characterization purposes only	N/A (Characterization Only)
Coating Thickness	Characterization of the drug coating thickness on the surface of the balloon	Testing for characterization purposes only	N/A (Characterization Only)

D. Animal Studies

Spectranetics conducted the following *in vivo* animal testing in a porcine iliofemoral artery model to evaluate the safety of the Stellarex 035 DCB:

- Four pharmacokinetic studies (time points from 0.5 hours to 180 days) were completed evaluating drug content in plasma, treated iliofemoral arterial tissue, and downstream muscle/organ specimens in swine.
- Five safety studies (time points from 30 to 210 days) were completed providing evidence of drug delivery, tissue response, and safety in swine iliofemoral arteries.

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

A list and description of the animal studies conducted is presented in **Table 7**.

Table 7: Summary of *In Vivo* Animal Studies

Study ID	Count & Animal Type	Local Drug Dose	Balloon Size	Duration & Major Endpoints	Endpoints Met
MPI 2049-001 Biocompatibility & Safety Study	n=12 Yucatan swine	1X 3X	5x40mm 6x40mm	Artery & Downstream Organs Histopathology: 30 days Organs PK: 30 d Plasma PK: 1/3/7/12 h, 1/3/7/14 d	Yes
MPI 2049-002 Biocompatibility & Safety Study	n=38 Yucatan swine	1X 3X	5x40mm 6x40mm	Artery & Downstream Organs Histopathology: 90/180/210 days Organs PK: 90/180/210 d Plasma PK: 1/3/7/12 h, 1/3/7/14 d	Yes
MPI 2049-003 180d PK Study	n=12 Yucatan swine	1X	5x40mm 6x40mm	Artery & Organs PK: 60/90/180 d Plasma PK: 0.5/1/3/7/12 h, 1/3/7/12/28 d	Yes
MPI 2049-004 28d PK Study	n=32 Yucatan swine	1X	5x40mm 6x40mm	Artery & Organs PK: 1/7/12 h, 1/3/7/14/28 d Plasma PK: 0.5/1/3/7/12 h, 1/3/7/12/28 d	Yes
MPI 2049-013 Safety Study	n=10 Yucatan swine	1X	5x40mm 6x40mm	Artery & Downstream Organs Histopathology: 30 days	Yes
MPI 2049-014 28d PK Study	n=40 Yucatan swine	2X	5x40mm 6x40mm	Artery & Organs PK: 1/3/7/14/28 d Plasma PK: 0.5/1/3/7/12 h, 1/3/7/12/28 d	Yes
APS ADO074 Safety Margin PK & Safety Study	n=20 Yorkshire Cross Swine	3X	6x120mm	Artery & Downstream Organs Histopathology: 28/90 days Organs PK: 28/90 d Plasma PK: 1/3/7/12 h, 1/3/7/14/28/60 d	Yes
APS NGX047-IS07 Local and Embolic Safety Study	n=6 Yorkshire Cross Swine	1X 11X	6x120mm	Artery & Downstream Organs Histopathology: 30 days	Yes

The preclinical studies conducted confirm the safety of treatment with the Stellarex 035 DCB. The GLP safety evaluation studies of the Stellarex 035 DCB demonstrated favorable safety parameters as defined by the following:

- Successful balloon deployments in the target artery with major procedural device-related complications, such as acute thrombosis, major bleeding, or critically flow limiting dissection, observed in less than 5% of animals.

- No major angiographic differences were observed between test and control treatment groups. No vessel abnormalities were reported. There was no sign of drug-induced vascular toxicity in any of the study arms.
- The histological assessments of the treated iliofemoral arteries did not reveal any signs of vessel toxicity arising from any of the Stellarex 035 DCB treatment groups (1X, 3X). There was no incidence of excessive neo-intimal formation, medial necrosis, thrombotic occlusions, or aneurysm formation in follow-up studies inclusive of 210-days.
- No macroscopic or clinically-relevant microscopic infarctions caused by device-associated downstream tissue embolic events were reported in any studies.

The pre-clinical pharmacokinetic studies demonstrated effective drug delivery and uptake into the arterial tissues as follows:

- Arterial paclitaxel concentrations were detectable in all studies from 1 hour to 14 days post-procedure. Limited paclitaxel remained at 28 days and reached levels below quantification by 60 to 90 days post-procedure for all samples.
- Plasma paclitaxel concentrations reached their maximum within the first 30 minutes post-device deployment and followed a rapid elimination profile, reaching levels below quantification by 14 to 28 days post-procedure. Plasma concentration profiles were comparable and reproducible from study to study.
- The presence of paclitaxel in major organs or muscles was not associated with any adverse clinical reactions. Systemic concentrations correlated to the size and number of devices used. No explant abnormalities were noted.

Though higher systemic drug exposure levels were observed during study ADO074 and NGX047-IS07, the histopathology data demonstrated an acceptable drug dose and embolic load safety margin for the intended therapeutic dose and indicated range of allowable balloon lengths.

E. Additional Studies

Stability and Shelf Life Studies

Finished product stability studies were conducted according to United States Pharmacopeia (USP) and International Conference on Harmonization (ICH) guidelines to establish the shelf life for the Stellarex 035 DCB. The testing includes an evaluation of potency, impurities, coating appearance, *in vitro* elution, particulates, and sterility.

Appropriate functional engineering tests were also performed on aged product and compared to baseline to ensure that the Stellarex 035 DCB performed acceptably.

The data generated from the stability studies, coupled with the data generated from the shelf life studies, currently supports a 24-month label claim and associated shelf life for the product.

Sterilization

Stellarex 035 DCB is sterilized using ethylene oxide sterilization, which has been validated per AAMI/ISO 11135-1:2007. Testing for ethylene oxide residuals was completed and acceptable per ANSI/AAMI/ISO 10993-7:2008 (R) 2012. Results from sterilization studies show the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. Also, the amounts of bacterial endotoxin are verified on every lot to be within the specification limit.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of percutaneous balloon angioplasty, after predilatation, of de novo and restenotic lesions in native superficial femoral and popliteal arteries with the Stellarex 035 DCB in the USA and Austria under IDE # G120270. Data from this clinical study formed the basis for the PMA approval decision. A summary of the study is presented below.

A. Study Design

Patients were treated between June 18, 2013 and July 29, 2015. The database for this PMA reflected data collected through September 2, 2016 and included 300 patients randomized 2:1 to the Stellarex 035 DCB (n=200) or the control PTA device (n=100). There were 43 investigational sites (41 sites in the United States and 2 sites in Austria).

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.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ILLUMENATE Pivotal Study was limited to patients who met the following inclusion criteria:

   - Symptomatic leg ischemia, requiring treatment of SFA and/or popliteal artery
   - Greater than or equal to 18 years of age
   - Willing to provide informed consent and capable and willing to comply with all the required follow up evaluations within the defined follow-up visit windows
   - Willing to not undergo other planned vascular interventions within 14 days before and/or 30 days after the protocol treatment (Note: successful treatment of ipsilateral and contralateral iliac arteries was allowed prior to enrollment)
   - Life expectancy >1 year

- Rutherford-Becker Clinical Category of 2, 3 or 4
- De novo or restenotic lesion (except for in-stent restenotic lesion) with >70% stenosis within the SFA and/or popliteal arteries in a single limb
- Single lesion which was ≥3 cm and ≤18 cm in length (by visual estimation) [Note: tandem lesions were allowed. A tandem lesion was defined as two distinct lesions with 3 cm or less of healthy vessel separating the two diseased areas. The total cumulative length of the tandem lesions, including the healthy vessel segment, was required to be less than or equal to 18 cm.]
- Lesion treatable by no more than 2 study devices
- Successful guidewire crossing of lesion. The guidewire advancement was required to not be indicative of the presence of fresh thrombus in the lesion.
- Target vessel reference diameter ≥4 mm and ≤6 mm (by visual estimation)
- Inflow artery was patent, free from significant lesion stenosis (≥50% stenosis considered significant) as confirmed by angiography. Treatment of a target lesion was acceptable after successful treatment of inflow artery lesion(s). (Note: successful inflow artery treatment was defined as attainment of residual diameter stenosis <30% without death or major vascular complication)
- Target limb with at least 1 patent (less than 50% stenosis) tibio-peroneal run-off vessel in the target limb confirmed by baseline angiography or prior magnetic resonance (MR) angiography or computed tomography (CT) angiography, within 45 days prior to the index procedure (Note: treatment of outflow disease was not permitted)

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

- Females who were pregnant, lactating, or intended to become pregnant, or males intending to father children during the study
- Known aortic aneurysm(s) >5 cm
- Contraindication to dual anti-platelet therapy
- Known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator could not be adequately pre-treated
- Current participation in an investigational drug or another device study
- History of hemorrhagic stroke within 3 months
- Previous or planned surgical or interventional procedure within 14 days before or 30 days after index procedure (successful treatment of the ipsilateral and contralateral iliac arteries was permitted prior to enrollment)
- Prior endovascular treatment of the target lesion by PTA or any other means of previous endovascular treatment (e.g., stents/stent grafts, cutting balloons, scoring balloons, cryoplasty, thrombectomy, atherectomy, brachytherapy or laser devices) within 6 months of the index procedure, or any previous placement of a bypass graft proximal to the target lesion
- Treatment of lesions in the contralateral limb with the investigation study device
- Use of the investigational study device in other than a single treatment session

- Chronic renal insufficiency (dialysis dependent, or serum creatinine ≥2.5 mg/dL within 30 days of index procedure)
- Significant contralateral or ipsilateral common femoral disease that required intervention during the index procedure
- No normal proximal arterial segment in which duplex ultrasound velocity ratios could be measured
- Known inadequate distal outflow
- Acute or sub-acute thrombus in the target vessel
- Aneurysmal target vessel
- Use of adjunctive therapies (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, brachytherapy) during the study procedure in the target lesion or target vessel
- Treatment of the contralateral limb during the same procedure or within 30 days following the study procedure (exclusive of the iliac arteries, which can be treated prior to enrollment)
- Presence of concentric calcification that precluded PTA pre-dilatation
- Prior stent placement in the target vessel
- Residual stenosis of greater than 70%, stent placement, or flow-limiting (Grade D or greater) dissection following pre-dilatation

2. Follow-up Schedule

All patients are scheduled to return for follow-up office visits at 6, 12, 24, and 36 months postoperatively. 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 will occur at 1, 48 and 60 months to review medication compliance and adverse events. A summary of the patient visits can be found in **Table 8** below. The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 8. Schedule of Events: Baseline through 12 Months

EVENT	Baseline Within 14 days	Procedure	Post-Procedure/ Pre-Discharge	1 Month 30 ± 15 days	6 Months 180 ± 30 days	12 Months 365 ± 45 days	24 Months 730 ± 45 days	36 Months 1095 ± 45 days	48 Months (Phone) 1460 ± 45 days	60 Months (Phone) 1825 ± 45 days	Unscheduled ** (as clinically indicated)
Subject Medical/ Clinical History	✓										
Anticoagulants, Antiplatelets, and Statins	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Subject Informed Consent	✓										
Clinical Inclusion and Exclusion Criteria	✓										
Angiographic Inclusion and Exclusion Criteria		✓									
Pregnancy Test (if applicable)	✓										
Complete Metabolic Panel	✓ (Within 30 days)				✓	✓					
Complete Blood Count	✓ (Within 30 days)				✓	✓					
Peripheral Angiogram with Runoff		✓									
Duplex Ultrasound Examination			✓*		✓	✓	✓	✓	✓		✓
Ankle-Brachial Index	✓		✓*		✓	✓	✓	✓	✓		✓
Rutherford-Becker Classification	✓		✓*		✓	✓	✓	✓	✓		✓
6-Minute Walking Test	✓				✓	✓	✓	✓	✓		✓
WIQ	✓				✓	✓	✓	✓	✓	✓	✓
EQ-5D	✓				✓	✓	✓	✓		✓	✓
Health Economic Evaluation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

EVENT	Baseline Within 14 days	Procedure	Post-Procedure/ Pre-Discharge	1 Month 30 ± 15 days	6 Months 180 ± 30 days	12 Months 365 ± 45 days	24 Months 730 ± 45 days	36 Months 1095 ± 45 days	48 Months (Phone) 1460 ± 45 days	60 Months (Phone) 1825 ± 45 days	Unscheduled ** (as clinically indicated)
Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓	

*One duplex ultrasound, ABI, and RCC must occur within 45 days post-procedure.

**NOTE: While an attempt should be made to collect all non-invasive testing at unscheduled visits or re-interventions, a protocol deviation will not be required if all assessments are not completed. For re-interventions, the angiogram and duplex ultrasound should be completed per the respective core laboratory guidelines.

3. Clinical Endpoints

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 (TLR) through 12 months post-procedure. The primary safety endpoint analysis was performed using the intent-to-treat (ITT) population. A one-tailed alpha of 0.025 and 90% power were employed. 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 duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) ≤ 2.5 and freedom from TLR, as adjudicated by an independent core laboratory. The primary safety endpoint analysis was performed using the ITT population. 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:

$$H_0: \pi DCB \leq \pi PTA$$
$$H_1: \pi DCB > \pi PTA$$

Secondary endpoints: 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 (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 $\leq$ 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 $\leq$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 $\leq$50% (as determined by the angiographic core lab), using the Stellarex 035 DCB test device or PTA control device without a device malfunction after 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.

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

B. Accountability of PMA Cohort

At the time of database lock, of 300 patients enrolled in the PMA study, 96.3% of patients were available for analysis at the 12 month post-operative visit. Follow-up

compliance at the 12-month follow-up visit is presented in **Table 9**. Follow-up compliance within the window was 89.5% for DCB subjects and 90.9% for PTA subjects.

Table 9: Subject Follow-up Compliance Through 12 Months (ITT Set)

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.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. 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 10**.

Table 10: 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

Table 10: Baseline Demographics and Medical History

Characteristic	Stellarex 035 DCB (N=200)	PTA (N=100)	p-value[a]
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			
Peripheral Vascular Disease (PVD)	100% (200/200)	100% (100/100)	N/A
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
Liver Disease	3.5% (7/200)	4.0% (4/100)	1.000
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
Deep Vein Thrombosis	3.0% (6/200)	4.0% (4/100)	0.736
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			0.061
Never Smoked	16.0% (32/200)	25.0% (25/100)	

Table 10: Baseline Demographics and Medical History

Characteristic	Stellarex 035 DCB (N=200)	PTA (N=100)	p-value[a]
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 mm, PTA 88.8 mm; p= 0.105). Reference vessel diameter was smaller in the Stellarex 035 DCB group compared to the PTA group (4.86 mm to 5.15 mm; 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 11**. Angiographic core lab data is presented unless indicated otherwise.

Table 11: 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

Table 11: Baseline Lesion Characteristics

Angiographic Lesion Characteristic[1]	Stellarex 035 DCB (N=200)	PTA (N=100)	p-value[a]
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)	
Number of Patent Run-off Vessels			0.397
0	5.4% (9/166)	1.2% (1/82)	
1	27.1% (45/166)	29.3% (24/82)	
2	31.3% (52/166)	36.6% (30/82)	
3	36.1% (60/166)	32.9% (27/82)	
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 Reference Vessel Diameter (RVD) (mm)	4.91 ± 0.90 (199) 4.88 (2.70, 7.37)	5.17 ± 1.02 (100) 5.18 (3.05, 7.58)	0.024
Post-Procedure Diameter Stenosis (%)	25.2 ± 11.7 (199) 25.0 (-6.7, 58.9)	27.4 ± 10.1 (100) 27.7 (3.0, 51.1)	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[3]	6.0% (12/200)	6.0% (6/100)	1.000

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] 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.

D. Safety and Effectiveness Results

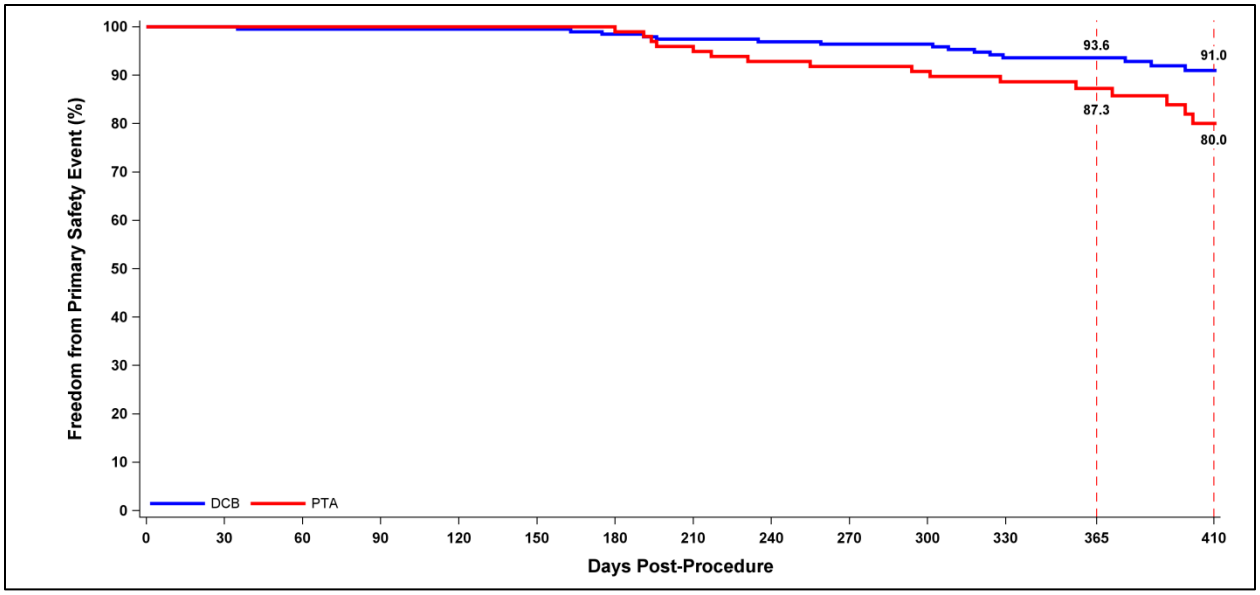
1. Safety Results

The 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). The analysis of safety was based on the intent-to-treat (ITT) cohort of 284 patients/procedures (189 DCB and 95 PTA) available for the 12 month evaluation. Missing data were accounted for using a multiple imputation analysis. Non-inferiority of the primary safety endpoint was tested using the Farrington-Manning approach. The non-inferiority margin of 5% was met, so a superiority test was conducted, as presented below in **Table 12**. Kaplan-Meier Event-Free from Primary Safety Endpoint through 410 days is presented in **Figure 4**.

Table 12: Primary Safety Endpoint

Outcome	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]	Difference [95% CI][a]	p-value[a]
Primary Safety Endpoint[1,3]	92.1% (174/189)	83.2% (79/95)	8.3% [0.03%, 16.57%]	0.0246

[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]Data are based on complete data without multiple imputations and presented as % (n/N).
[3]Non-inferiority on the primary safety endpoint was tested using the Farrington-Manning approach. The noninferiority margin of 5% was met; however, the results shown above are for superiority testing.
[a]Estimate of the difference (DCB-PTA) and 95% CI are based on the model based estimates resulting from multiple-imputation of missing data. p-value is 1-sided for a non-inferiority margin of 5% (for DCB-PTA) and based on the model based estimates resulting from multiple-imputation of missing data.
In the case where duplex ultrasound data was not available, angiographic core laboratory as sessment of restenosis was utilized.
Subjects were counted as failures if they had an event prior to the primary endpoint timepoint. Thus, the numbers in the denominator appears greater than the follow-up compliance.



	Stellarex 035 DCB (N=200)				PTA (N=100)					
Days	**At Risk**	**Number With Event**	**Event Free (%)**	**95% CI (%)**	**At Risk**	**Number With Event**	**Event Free (%)**	**95% CI (%)**	**Difference [95% CI][1]**	**Log-Rank p-value**
0	200	0	100.0	--	100	0	100.0	--	0.0 [0.0, 0.0]	0.025
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]	
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.

Figure 4: Kaplan-Meier Plot Freedom from Primary Safety Event

2. Adverse effects that occurred in the PMA clinical study:

   Serious adverse event rates by MedDRA system organ class (SOC) and preferred term (PT) through 12 months are shown in **Table 13**. A serious adverse event (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. As depicted in Table 13, the rate of serious adverse events was low and comparable between groups. No unanticipated adverse device effects (UADEs) occurred. Device-related adverse events were also comparable (9.5% DCB vs 7.0% PTA) and were all CEC-adjudicated to be procedure-related. These included dissection, stenosis, embolism, and pain in the extremity.

Table 13: Summary of Serious Adverse Events through 12 Months (ITT Set)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
Not Reported	0.5% (1/200)	0.0% (0/100)
Not Yet Coded	1.0% (2/200)	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)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
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)
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)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
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)
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)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
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)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
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)
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)

Event[1]	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]
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) [Events] where the numerator is the number of subjects with at least one event, the denominator is the total number of subjects enrolled, and the events in brackets are the total number of that event type.

3. Effectiveness Results

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). The analysis of effectiveness was based on the ITT cohort of 269 evaluable patients (177 DCB and 92 PTA) at the 12-month time point. Missing data were accounted for using a multiple imputation analysis. In the case where duplex ultrasound data were not available, angiographic core laboratory assessment of restenosis was utilized. Key effectiveness outcomes are presented in **Table 14**. Kaplan Meier Event Primary Patency through 410 days is presented in **Figure 5**. As noted in the data below, the Stellarex DCB was shown have superior effectiveness as compared to PTA.

Table 14: Primary Effectiveness Endpoint

Outcome	Stellarex 035 DCB (N=200)[2]	PTA (N=100)[2]	Difference [95% CI][a]	p-value[a]
Primary Effectiveness Endpoint-Patency at 12 months[1]	76.3% (135/177)	57.6% (53/92)	16.9% [5.1%, 28.7%]	0.003

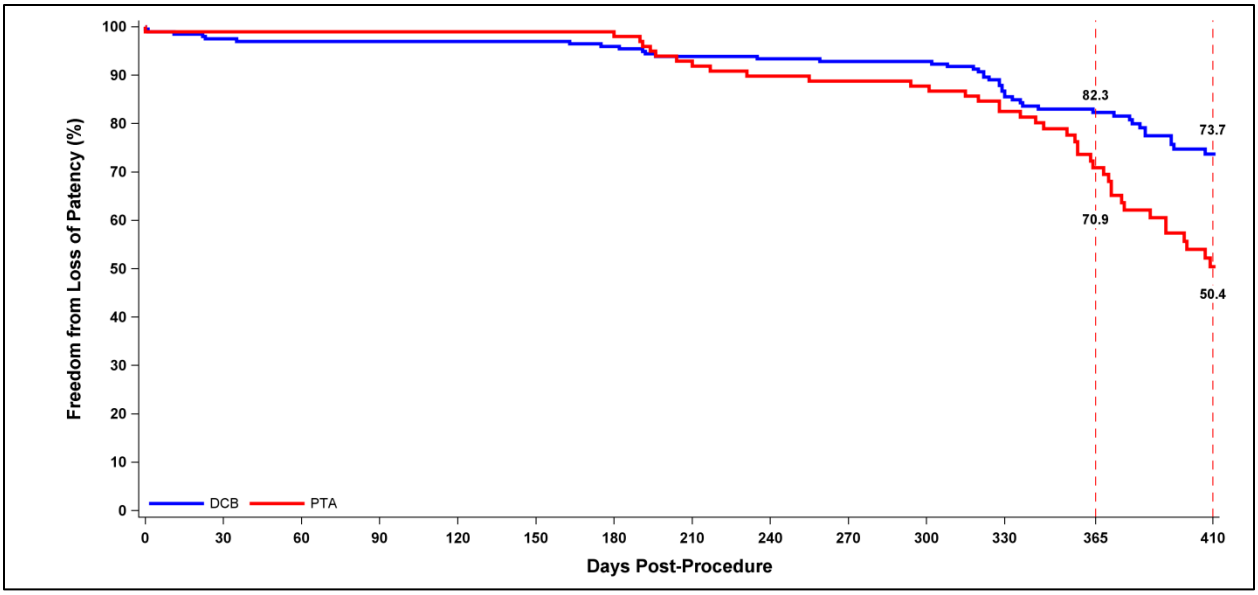
[1]The primary effectiveness endpoint was defined as patency at 12 months. Patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom from clinically-driven target lesion revascularization (CD-TLR) through 12 months (410 days).

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

[a]Estimate of the difference (DCB-PTA) and 95% CI are based on the model based estimates resulting from multiple-imputation of missing data. p-value is 1-sided for a non-inferiority margin of 5% (for DCB-PTA) and based on the model based estimates resulting from multiple-imputation of missing data.

In the case where duplex ultrasound data was not available, angiographic core laboratory ass essment of restenosis was utilized.

Subjects were counted as failures if they had an event prior to the primary endpoint timepoint. Thus, the numbers in the denominator appear greater than the follow-up compliance.



	Stellarex 035 DCB (N=200)				PTA (N=100)					
Days	**At Risk**	**Number With Event**	**Event Free (%)**	**95% CI (%)**	**At Risk**	**Number With Event**	**Event Free (%)**	**95% CI (%)**	**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.

Figure 5: Kaplan-Meier Plot Freedom from Loss of Patency through 12 Months

4. Secondary Endpoint Results:

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 9.5% in the DCB group and 17.9% in the PTA group. All-cause mortality and acute success were similar between the DCB group and PTA group. Select secondary endpoints are summarized in **Table 15**.

Table 15: Secondary Endpoint Results

Major Adverse Events (Secondary Definition)	Stellarex 035 DCB (N=200)[1]	PTA (N=100)[1]	Difference (DCB – PTA)
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) [Events]. 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.

5. Subgroup Analyses:

Gender: A subgroup analysis for gender was conducted to examine its influence on the primary safety and effectiveness endpoints. **Table 16** 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 16: Gender Analyses of Primary Safety and Effectiveness Endpoint (ITT Set)

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**
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).

6. Pharmacokinetic Sub-Study:

The ILLUMENATE PK Study is a prospective, non-randomized, single-arm, multi-center, pharmacokinetic study that describes the pharmacokinetics of paclitaxel in the blood delivered by the Stellarex 035 DCB. Twenty-five (25) subjects were enrolled at two (2) sites in New Zealand. Each enrolled subject will be continued to be followed for 2 years (24 months) after treatment. Determination of circulating plasma paclitaxel concentration occurred immediately after the last DCB deployment and at 1, 4, and 24 hours, plus 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 17** summarizes the pharmacokinetic parameters including maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC_{0-24h}) and terminal elimination half-life ($T_{1/2}$).

Table 17: Summary of Pharmacokinetic Parameters

Parameter	N	Mean	Standard Deviation	CV (%)	Range (Min, Max)
AUC_{0-24h} (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.					

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 186 investigators of which none were full-time or part-time employees of the sponsor, and three had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None of the Investigators
- Significant payment of other sorts: 3 Investigators
- Proprietary interest in the product tested held by the investigator: None of the investigators
- Significant equity interest held by investigator in sponsor of covered study: None of the investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. 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 endpoint was the composite rate 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. The primary safety endpoint rate was 94.1% for the DCB group and 83.3% for the PTA group, for a difference between groups (DCB-PTA) of 10.8%. For the stent cohort, primary safety through 12 months was 87.9% (29/33).

The primary efficacy endpoint was patency at 12 months. Patency was defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR≤2.5 and freedom from CD TLR and was analyzed on a "per lesion" basis if subjects had multiple lesions. Primary patency at 12 months was 83.9% for the DCB group and 60.6% for the PTA group, for a difference of 23.3%. For the stent cohort, primary efficacy through 12 months was 78.8% (26/33).

The primary safety and effectiveness results are represented in **Table 18** and **Table 19**.

Table 18: EU RCT Study Primary Safety Endpoint

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

[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 the end of the 12-month visit window (395 days).
[2]Data are presented per subject as % (n/N)

Table 19: EU RCT Study Primary Efficacy Endpoint

Efficacy Endpoint	Stellarex 035 DCB (N Subjects=222 N Lesions=254)	PTA (N Subjcts=72 N Lesions=79)[2]	Difference (DCB – PTA)
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

B. 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 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 endpoint was the composite rate of freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and CD TLR through 12 months post-procedure. The 12 month primary safety endpoint was based on Kaplan-Meier analysis. The primary safety endpoint rate at 12 months was 94.8%.

The efficacy endpoint was primary patency at 12 months, defined as the absence of target lesion restenosis per duplex ultrasound (PSVR≤2.5) and freedom from CD TLR. The primary patency rate at 12 months was 77.2% (285/369 lesions).

The primary safety and effectiveness results are presented in **Table 20** and **Table 21**.

Table 20: Global Study Primary Safety Endpoint

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

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 21: Global Study Primary Efficacy Endpoint

Efficacy Endpoint	Stellarex 035 DCB (N Subjects=371 N Lesions=417)
Primary Efficacy Endpoint	77.2% (285/369)
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).	

C. 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 (80) 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). Data from peer-reviewed medical literature about bare balloon PTA and published results on drug-coated balloon trials were used to develop the OPC for the evaluation of the study endpoints. 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 loss 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 Events (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 MAEs at 6 months for the Cohort 1 was 4.0%, lower than the objective performance criterion of 30%. The endpoint was met, with an observed MAE rate at 6 months of 6.7% for the Cohort 2 ITT analysis set.

D. Summary of Rare Adverse Events (RAE)

Rare adverse events (RAEs) were evaluated in more than 800 subjects from the ILLUMENATE Pivotal Study, ILLUMENATE EU RCT Study, ILLUMENATE Global Study, PK Study, and FIH Study. Rare adverse events (RAEs) 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 035 DCB subjects, 15 (1.6%) had an ipsilateral embolic event of the target limb and 8 (0.9%) had an arterial thrombosis arterial thrombosis of the treated segment within 365 days. There was no indication these events were related to the paclitaxel drug coating.

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The 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. The ILLUMENATE Pivotal Study met its primary effectiveness endpoint for primary patency at 12 months, demonstrating superiority in the Stellarex 035 DCB test group compared to the PTA control group. The 12-month primary patency rate was 76.3% in the DCB group vs. 57.6% in the PTA group (p=0.003). Secondary effectiveness endpoints, including rate of CD-TLR, showed favorable results for the Stellarex 035 DCB group. In conclusion, the primary effectiveness hypothesis of the study was met, indicating that the Stellarex 035 DCB provides a significantly higher rate of primary patency compared to standard PTA. These results support the effectiveness of the Stellarex 035 DCB for the treatment of symptomatic vascular disease of the superficial femoral and popliteal arteries.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in the clinical studies conducted to support PMA approval, as described above. The ILLUMENATE Pivotal Study met its primary safety endpoint: the Stellarex 035 DCB test group met the pre-defined 5% non-inferiority margin and in a sequential testing procedure, and showed superiority against the PTA control

group. The 12-month freedom from primary safety composite was 92.1% in the DCB group and 83.2% in the PTA group (p=0.0246). Secondary safety endpoints, including MAE rate, demonstrated favorable results for the DCB group. The 12-month major adverse event rate was 9.4% in the DCB group vs. 17.7% in the PTA group. In conclusion, the primary safety hypothesis of the study was met, indicating that the Stellarex 035 DCB provides superior safety than treatment with standard PTA. Additional supporting data from the other Stellarex 035 DCB clinical studies did not detect a significant safety signal with respect to rare or long-term adverse device or drug effects. These results support the safety of the Stellarex 035 DCB for the treatment of symptomatic vascular disease of the superficial femoral and popliteal arteries.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit of the Stellarex 035 DCB improving patients' symptoms and quality of life outweigh the probable risks associated with use of the device. Additional factors to be considered in determining probable risks and benefits for the Stellarex 035 DCB include:

1. The clinical study provided adequate follow-up (12 months) to evaluate safety and effectiveness, with measures taken to assess the impact of missing data.
2. The device is intended for use in subjects with peripheral vascular disease of the superficial femoral and popliteal arteries. The results adequately support general use in the identified population.
3. There are alternative treatments available for this disease, such as percutaneous transluminal angioplasty (PTA) alone, but this treatment has been shown to be superior to PTA alone with regard to safety and effectiveness.
4. Patient risk is minimized by limiting the use to operators who have the necessary training to use the device safely and effectively. Adherence to the recommended periprocedural medication regimens is also stressed.
5. The frequency and types of the adverse events reported throughout the pivotal clinical study are in alignment with what might be expected in the studied patient population and therapeutic area. No unanticipated adverse device effects were reported in the study.

Given the available information above, the data support that the probable benefits outweigh the probable risks for percutaneous transluminal angioplasty, after appropriate vessel preparation, of de novo or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with reference vessel diameters of 4-6 mm.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The clinical study results are comparable to results from other drug-coated balloons with similar indications. Given all of the available data, it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIV. CDRH DECISION

CDRH issued an approval order on July 26, 2017. The final conditions of approval cited in the approval order are described below.

Non-Clinical

The coating uniformity data that was provided for this product has demonstrated variability. The applicant has agreed to optimize the processing (e.g., coating, drying) to achieve a more consistent and uniform coating on the device. Therefore, within 180 days, the applicant has agreed to submit a supplement that includes the following:

- A complete description of the changes in processing that were made to achieve coating uniformity
- Updated redline test methods describing the step-by-step processing methods
- Coating integrity and coating uniformity testing on n=5 each of the extremes plus intermediate device sizes using the new processing technique
- A discussion for why other attributes (e.g., biocompatibility, sterility, engineering) would not be affected by the proposed changes

Clinical:

ODE Lead PMA Post-Approval Study - *ILLUMINATE Continued Follow-Up Study:* This study will evaluate the long-term safety and effectiveness of the Stellarex 035 DCB in 300 subjects from the premarket study (ILLUMINATE trial). The ILLUMINATE trial was designed as a global, multicenter, single-blind, randomized (2:1 Stellarex DCB to PTA) trial. Subjects will be followed annually through 5 years post-procedure with no more than 20% attrition.

The primary effectiveness endpoint is primary patency of the target lesion at 24 months. A minimum of 236 subjects evaluable at 24 months are required to show superiority of

the Stellarex DCB to PTA. This sample size assumes a one-sided 0.025 alpha and at least 80% power.

The primary safety endpoint is a composite of freedom from device- and procedure-related death at 30 days and freedom from target limb major amputation and clinically-driven target lesion revascularization (CD-TLR) at 24 months. A minimum of 206 subjects evaluable at 24 months are required to show non-inferiority of the Stellarex DCB to PTA. This sample size assumes a one-sided 0.025 alpha, at least 80% power and 10% margin.

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

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.