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 Name and Address: Philips Image Guided Therapy Corporation
6655 Wedgwood Road N, Suite 105
Maple Grove, MN 55311 USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160049/S015

Date of FDA Notice of Approval: March 25, 2022

The original PMA (P160049) was approved on July 26, 2017, and 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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Stellarex™ 0.035" OTW Drug-coated Angioplasty Balloon.

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*, restenotic, or in-stent restenotic lesions up to 180 mm in length in 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 antiplatelet and/or anticoagulation therapy.
- Women who are breastfeeding, pregnant or are intending to become pregnant or men intending to father children.
- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries.

- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Stellarex 0.035" OTW drug-coated angioplasty balloon instructions for use (IFU).

V. 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-complaint balloon and an atraumatic tapered tip. The balloon is coated with a proprietary coating containing the drug paclitaxel (see **Figure 1**).

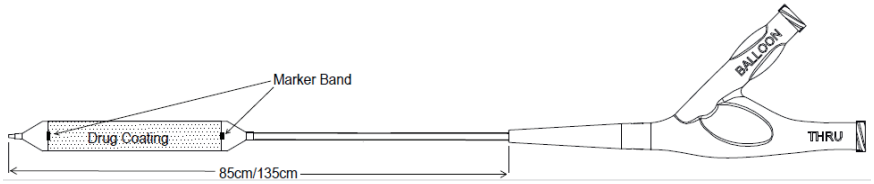

Figure 1: Stellarex 035 DCB Schematic

PTA Catheter Component
The Stellarex 035 DCB is available in balloon lengths ranging from 40 mm to 200 mm, balloon diameters ranging from 4.0 mm to 6.0 mm, and 80 cm and 135 cm catheter working lengths. The Stellarex 035 DCB is compatible with 0.035" guidewires and 6F introducer sheaths.

Drug Component
The Stellarex 035 DCB is coated with EnduraCoat technology, a proprietary coating with a nominal drug dose density of 2µg/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 total paclitaxel dose per balloon size is provided in **Table 1**.

Table 1: Nominal Paclitaxel Content (µg) by Balloon Size

Diameter (mm)	Balloon Length (mm)						
	40	60	80	100	120	150	200
4.0	1,124	1,674	2,211	2,759	3,307	4,161	5,428
5.0	1,335	1,998	2,636	3,245	3,880	4,882	6,443
6.0	1,619	2,410	3,174	3,957	4,721	5,911	7,812

Active Pharmaceutical Ingredient (API) – Paclitaxel
The API of the Stellarex 035 DCB is paclitaxel. Paclitaxel is a FDA approved drug, indicated for the treatment of multiple cancers including breast and ovarian cancer. 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*. The chemical formula is $C_{47}H_{51}NO_{14}$. The chemical structure of paclitaxel is illustrated in **Figure 2**.

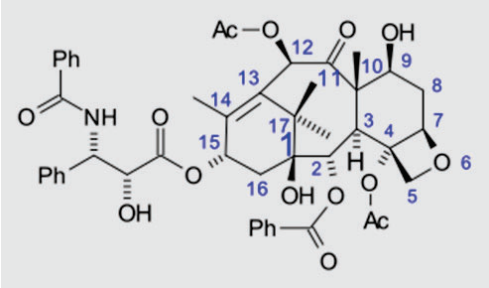

Figure 2: Paclitaxel Chemical Structure

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**.

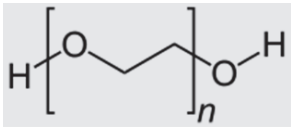

Figure 3: PEG Chemical Structure

Mechanism of Action

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

VI. ALTERNATE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of *de novo*, restenotic, and in-stent restenotic lesions in the superficial femoral and popliteal arteries:

- Non-invasive treatment (risk factor modification, exercise, and/or drug therapy)
- Minimally invasive treatment (plain old balloon angioplasty, bare metal or drug-eluting stent, or 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 received CE Mark on December 31, 2014, and the original PMA (P160049) was approved on July 26, 2017. **Table 2** lists the countries in which the Stellarex 035 DCB is commercially available. The Stellarex 035 DCB has not been withdrawn from marketing for any reason related to safety or effectiveness.

Table 2: Stellarex 035 DCB Commercial Availability

Austria	Denmark	Israel	Mexico	South Africa
Belgium	Estonia	Italy	Myanmar	Spain
Brazil	Finland	Jordan	Netherlands	Sweden
Brunei	France	Latvia	Norway	Switzerland
Bulgaria	Germany	Lebanon	Panama	Taiwan
Cambodia	Greece	Liechtenstein	Poland	Turkey
Canada	Haiti	Lithuania	Portugal	United Arab Emirates
Chile	Hong Kong	Luxembourg	Romania	United Kingdom
Croatia	Hungary	Macao	Saudi Arabia	United States
Cyprus	Iceland	Malaysia	Slovakia	
Czech Republic	Ireland	Malta	Slovenia	

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

For the specific adverse events that occurred in the in-stent restenosis (ISR) clinical study, see **Table 11** in Section X.

IX. SUMMARY OF NONCLINICAL STUDIES

No changes have been made to the Stellarex 035 DCB design or specifications to support this indications expansion, thus all bench testing, animal studies and shelf life testing previously provided are applicable to use of the Stellarex 035 DCB for the treatment of in-stent restenosis in the superficial femoral and popliteal arteries. The SSED containing these studies is available on the CDRH website. To support the treatment of in-stent restenosis, the in-stent bench testing summarized in **Table 3** was performed.

Table 3: Bench Testing Summary

Test	Summary	Acceptance Criteria	Results
Balloon Burst Strength (in stent)	Balloon is inflated incrementally while constrained until burst.	Balloon burst pressure ≥ rated burst pressure (RBP, atm) Diameter (mm) / Length (mm): 40, 60, 80, 100, 120, 150, 200 4: 20, 20, 20, 20, 20, 20, 20 5: 18, 18, 18, 18, 16, 16, 16 6: 14, 14, 14, 14, 12, 12, 11	Results met the acceptance criteria
Balloon Fatigue (in stent)	Balloon is inflated to RBP, held, and deflated for a total of 10 cycles while constrained.	Balloon withstands 10 cycles without failure.	Results met the acceptance criteria
Particulate Matter (in stent)	Particulate levels quantified per simulated use tracking and deployment within a stent.	Particulate sizes and counts must be within limits	With stent results were similar to without stent results

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study, ILLUMENATE Global, which included an ISR cohort (I-Global ISR), to establish a reasonable assurance of safety and effectiveness of percutaneous transluminal angioplasty, after appropriate vessel preparation, of in-stent restenotic lesions in the superficial femoral or popliteal arteries with the Stellarex 035 DCB in Australia, Europe and New Zealand. The study was conducted in accordance with 21 CFR Parts 50, 54, 56, 812, and 814, the Declaration of Helsinki, ICH GCP, ISO 14155, and the study protocol.

The applicant also performed an observational study, Stellarex Vascular E-Registry (also referred to as SAVER), in Europe for treatment with the Stellarex 035 DCB in superficial femoral and/or popliteal arteries in a real-world, claudicant or ischemic rest pain patient population per the institution's standard practice. A subset of patients enrolled in SAVER were treated for ISR (referred to as SAVER ISR).

Data from both clinical studies were the basis for the Panel Track Supplement approval decision. A summary of the I-Global ISR and SAVER ISR clinical studies is presented below.

A. Study Design

ILLUMENATE Global ISR

Patients were treated between September 2016 and March 2019. The database for this Panel Track Supplement reflected data collected through December 10, 2020, and included 129 patients. There were 21 investigational sites.

The study was a prospective, single-arm, multi-center study performed to assess the safety and effectiveness of the Stellarex 035 DCB for the treatment of ISR lesions in the superficial femoral and/or popliteal arteries. The primary safety and effectiveness endpoints were evaluated at 12 months by comparison to pre-defined literature derived performance goals (PG). The performance goals were set based on an analysis of published ISR clinical data and modeled the VIVA Physician's, Inc. recommendation for bare metal stent trials with the performance goal for effectiveness set at 2X PTA[1].

1. Clinical Inclusion and Exclusion Criteria

Enrollment in I-Global ISR was limited to patients who met the following inclusion criteria:

General Inclusion Criteria

1. Symptomatic leg ischemia, requiring treatment of the SFA and/or popliteal artery;
2. Rutherford Clinical Category of 2, 3 or 4;
3. Age 18-85 years old;
4. Life expectancy > 1 year;
5. Willing to provide informed consent and willing and capable to comply with the required follow-up evaluations and medication regimen;
6. History of previous femoropopliteal nitinol stenting suspect for in-stent restenosis;
7. Resting ankle-brachial index (ABI) (<0.9) or an abnormal exercise ABI (<0.9) if resting ABI is normal. Patients with incompressible arteries (ABI >1.2) must have a toe-brachial index (TBI) <0.7 in the target limb;

Angiographic Inclusion Criteria

1. Angiographic evidence of significant restenosis (≥50% by visual estimate) within a previously deployed femoropopliteal bare nitinol stent(s) including ISR Class I, II or III;
2. Target limb with at least one patent (<50% stenosis tibio-peroneal run-off vessel to the foot confirmed by baseline angiography or magnetic resonance angiography or computed tomography angiography;
3. Total target treatment length of in-stent restenosis ≥ 4.0 cm in length and may include a single lesion or a multifocal lesion within the femoropopliteal segment (this includes the proximal, mid, and/or distal SFA and P1, P2 and/or P3 segment of the popliteal artery); Edge

[1] Rocha-Singh KJ, et al. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheterization and Cardiovascular Interventions 2007; 69(6):910-919.

restenosis may be treated provided the lesion extends no more than 3 cm outside the margin of the stent (proximal and/or distal margin);
4. Reference vessel diameter of 4 to 6 mm by visual estimate;
5. Successful guidewire crossing of the lesion(s).

Patients were not permitted to be enrolled in I-Global ISR if they met any of the following exclusion criteria:

General Exclusion Criteria

1. Female who is pregnant, of childbearing potential and not taking adequate contraceptive measures, or nursing, or male intending to father children during the study;
2. Significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy.
3. Known intolerance to study medications, paclitaxel or contrast agents that in the opinion of the investigator cannot be adequately pre-treated;
4. Current participation in an investigational device or drug study;
5. History of hemorrhagic stroke within 3 months including those within <60 days with an unresolved walking impairment;
6. Surgical or endovascular procedure of target limb within 3 months prior to the index procedure;
7. Planned surgical intervention (requiring hospitalization) or endovascular procedure within 30 days after the index procedure;
8. Previous peripheral bypass affecting the target limb;
9. Unstable angina pectoris, myocardial infarction within 60 days, liver failure, renal failure or chronic kidney disease (dialysis dependent, or serum creatinine ≥ 2.5 mg/dL) within 30 days of the index procedure;
10. History of previous femoropopliteal stenting in the target lesion with drug eluting stents or covered stents (endografts);

Angiographic Exclusion Criteria

1. Ipsilateral and/or contralateral iliac (or common femoral) artery stenosis ≥ 50% diameter stenosis that is not successfully treated prior to index procedure (e.g., where a perforation occurred requiring a covered stent) or with final residual stenosis ≥ 30% documented by angiography;
2. Identification of any lesion of the native vessel (excludes ISR) above the target stent in the femoropopliteal segment > 50% that is not successfully treated prior to index procedure (e.g., complication requiring additional treatment) or with final residual stenosis > 30% documented by angiography;
3. Acute or sub-acute intraluminal thrombus in the target vessel;
4. Aneurysm (at least twice the reference vessel diameter) in the target vessel, abdominal aorta, iliac, or popliteal arteries;
5. Perforation, dissection or other injury of the access or target vessel requiring stenting or surgical intervention prior to enrollment;

6. No normal arterial segment proximal to the target lesion in which duplex ultrasound velocity ratios can be measured;
7. Use of adjunctive therapies (i.e., laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy) during the study procedure;
8. Grade 4 or 5 stent fracture affecting target stent or proximal to the target stent, or where evidence of stent protrusion into the lumen is noted on angiography in 2 orthogonal views.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1, 6, 12, 24 and 36 months. The pre-operative and postoperative evaluations are summarized in **Table 4**. Adverse events were recorded at all visits.

Table 4: Follow-up Schedule and Evaluations

Evaluation	Baseline (within 30 days prior to procedure)	Procedure	Discharge	1 Month (15 – 45 days)	6 Months (150 – 210 days)	12 Months (335 – 395 days)	24 Months (670 – 790 days)	36 Months (1,035 – 1,155 days)
Informed Consent	X							
Medical History and Physical Exam	X							
Laboratory Tests	X[1]							
Concomitant Medication Use	X		X	X	X	X	X	X
Rutherford Clinical Category (RCC)	X		X[2]		X	X	X	X
Walking Impairment Questionnaire (WIQ)	X				X	X	X	X
EQ-5D Questionnaire	X				X	X	X	X
Ankle Brachial Index (ABI)/ Toe Brachial Index (TBI)[3]	X		X[2]		X	X	X	X
Angiogram		X						
Duplex Ultrasound			X[2]		X	X	X	X
Adverse Event Evaluation		X	X	X	X	X	X	X

[1] within 7 days prior to enrollment
[2] One duplex ultrasound, ABI, and RCC within 45 days post-procedure
[3] TBI if applicable

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

*Primary Safety Endp*oint: 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, which is called 'freedom from safety composite events' in the following text.

H_0: $\pi_s \leq PGs$

H_1: $\pi_s > PGs$

Where π_s is the proportion of subjects experiencing 'freedom from safety composite events' and PGs is the safety performance goal of 65%. This PGs weights the response of PTA subjects from eight ISR studies (50.1%) with the response of DCB subjects from six ISR studies (82.4%) and the response of Stellarex 035 DCB ISR subjects in the Stellarex Vascular E-Registry (SAVER) 84%).

For CD-TLR, a revascularization of the target lesion was considered clinically-driven if the peak systolic velocity ratio (PSVR) was ≥ 2.5 by duplex ultrasound or if angiography showed a percent diameter stenosis >50% and there was worsening of the Rutherford Clinical Category (RCC) or Ankle Brachial Index (ABI) that was clearly referable to the target lesion. Worsening was defined as deterioration indicated by an increase in the RCC by more than 1 category (>1 category) from the earliest post-procedural measurement, or deterioration in the ABI by more than 0.15 from the maximum early post-procedural level.

Primary Effectiveness Endpoint: Primary patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from clinically driven target lesion revascularization (CD-TLR).

H_0: $\pi_e \leq PGe$

H_1: $\pi_e > PGe$

Where π_e is the proportion of subjects experiencing primary patency at 12 months post-procedure and PGe is the effectiveness performance goal of 64%.

Secondary Endpoints: The secondary effectiveness endpoint is freedom from TLR at 12 months post procedure.

H_0: $\pi_{es} \leq PGes$

H_1: $\pi_{es} > PGes$

Where π_{es} is the proportion of subjects experiencing freedom from TLR at 12 months post-procedure and PGes is the secondary effectiveness performance goal of 76%.

The secondary endpoints are listed below:

- Major adverse event rate (composite of cardiovascular death, major target limb amputation, and CD-TLR) at 1, 6, 12, 24 and 36 months
- Adverse events rate at 1, 6, 12, 24 and 36 months
- CD-TLR rate at 6, 12, 24 and 36 months
- Rate of CD-TVR rate at 6, 12, 24 and 36 months
- Major target limb major amputation rate at 6, 12, 24 and 36 months
- All-cause mortality rate at 6, 12, 24 and 36 months
- Rate of arterial thrombosis of treated segment at 1, 6, 12, 24 and 36 months
- Rate of ipsilateral embolic events of the study limb within 30 days post procedure
- Primary patency rate at 6, 12, 24 and 36 months
- Change in Ankle-Brachial Index (ABI) from baseline to 6, 12, 24 and 36 months
- Change in walking impairment questionnaire (WIQ) from baseline to 6, 12, 24 and 36 months
- Change in Rutherford Clinical Category (RCC) from baseline to 6, 12, 24 and 36 months
- Change in EQ-5D from baseline to 6, 12, 24 and 36 months

Taking into consideration both the co-primary safety and effectiveness endpoints and assuming a 15% attrition rate, a sample size of 129 was determined to be adequate for the primary hypotheses based on the required enrolled 118 DCB subjects. The overall power of the study was 85%.

The primary analyses for safety and effectiveness were based on a modified intention-to-treat (mITT) principle, whereby all subjects enrolled who did not receive a bailout stent were analyzed regardless of treatment received. The primary endpoints were analyzed as dichotomous (success/failure) based on each subject's observed status at 12 months on a two-sided 95% confidence interval. The primary endpoints were also evaluated using Kaplan-Meier survival analysis. The secondary effectiveness endpoint was based on non-missing data and assessed by constructing two-sided 95% confidence intervals about the estimates of the 12-month freedom from TLR rate using the exact binomial method.

With regards to success/failure criteria, the study was considered successful if both of the primary endpoints were met. The primary safety and effectiveness endpoints were considered met if the lower 95% confidence limit was greater than each corresponding performance goal.

Stellarex Vascular E-Registry (SAVER) ISR

The SAVER is a prospective, international, multi-center, single-arm, observational registry intended to assess the Stellarex 035 DCB in a real-world setting, according to

the Instructions for Use and institutions' standard treatment practice. As of August 2021, of 1,960 patients enrolled in SAVER across Europe (57 sites), 343 patients were treated with the Stellarex 035 DCB for ISR in the superficial femoral or popliteal arteries (referred to as SAVER ISR). At database lock on August 26, 2021, 325 patients were eligible for the 12 month visit. Follow-up time points and assessments were per each site's standard practice and were not mandated by the protocol due to the non-interventional nature of the study. The protocol recommended follow-up through 36 months.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in SAVER was not limited to protocol specific criteria due to the non-interventional nature of the study. All patients included in the SAVER ISR analysis were treated with the Stellarex 035 DCB for ISR in the superficial femoral or popliteal arteries. The target population was open to RCC 2-6 for SAVER ISR.

Recommended inclusion criteria were as follows:

- Patients intended to be treated with Stellarex 035 DCB for de-novo or restenotic lesions of the femoro-popliteal arteries;
- Rutherford Clinical Category (RCC) 2-4 indicated for endovascular treatment according to local applicable guidelines;
- Age ≥18 years old;
- Life expectancy > 1 year;
- Willing to provide written informed consent prior to enrollment in the study (as applicable);
- Willing to come on site or to be contacted by phone for the follow-up;

Recommended exclusion criteria were as follows:

- Patients with any medical condition that would make him/her inappropriate for treatment with Stellarex 035 DCB per Instructions for Use (IFU) or investigator's opinion.
- Patient already enrolled in other investigational (interventional) studies that would interfere with study endpoints.
- Patients that in the judgment of the investigator would need treatment below the knee before and/or during the index procedure.

2. Follow-up Schedule

The recommended follow-up visits assessments (not protocol mandated) are summarized in **Table 5**. Patients were scheduled to return for follow-up examinations according to each site's standard practice. Depending on the site's standard practice, follow-up visits may be conducted during an office visit or by telephone.

Table 5: SAVER Recommended Follow-up Visit Assessments

Recommended Assessment[1]	Visit						
	Baseline	Procedure	Discharge	1 Year	2 Years	3 Years	Unscheduled Follow-up
Informed Consent	X						
Medical History	X						
Procedural data		X					X
Angiographic data		X					X
Rutherford Clinical Category (RCC) Assessment	X		X	X	X	X	X
Ankle Brachial Index (ABI)	X		X	X	X	X	X
Duplex Ultrasound[2]				X			X
Selection of Adverse Events Evaluation[3]	X	X	X	X	X	X	X
Walking Impairment Questionnaire (WIQ) and/or 6 minute Walking Test	X			X	X	X	X
EQ-5D or SF36 Questionnaire	X			X	X	X	X

[1] Per institution's standard practice
[2] DUS imaging cohort (subset of sites and patients)
[3] Death, target vessel and target lesion revascularization, and amputation

Adverse events were adjudicated by an independent CEC and revascularizations were assessed by an angiographic core laboratory. A duplex ultrasound (DUS) imaging cohort was included for sites that performed this diagnostic test as per the institution's standard practice. These images were assessed by a DUS core laboratory. Data management and biostatistical analyses were performed by Philips.

3. Clinical Endpoints

SAVER does not have pre-defined hypothesis testing for determination of success/failure. Descriptive statistics were used to present the data and summarize the results. Discrete variables were presented using frequency distributions and cross tabulations. Continuous variables were summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values. Planned statistical time points included baseline, procedure, discharge, 30 days post procedure, 12, 24 and 36 months. Although there was not a planned 30 day visit, adverse event data was collected, which included amputations, major re-interventions, and deaths. As those events have a reported date, the endpoint was calculated through an imputation analysis. For endpoints analyzed with Kaplan-Meier time to event methods, analysis time points corresponding to 12 months was presented at 365 days. Kaplan-Meier estimates were presented with the corresponding 95% log-log confidence interval and Greenwood's estimate of the standard error was used. Primary safety and effectiveness were analyzed as dichotomous

(success/failure). The following events were collected, adjudicated by CEC, and included in the analysis:

- Death
- Target Vessel Revascularization (TVR)
- Target Lesion Revascularization (TLR)
- Major amputation of the target limb

Primary Safety Endpoint: The primary safety endpoint was assessed by clinical peripheral artery disease based on the RCC score, either RCC 2-3 (Cohort 1) and RCC 4-6 (Cohort 2).

RCC 2-3: 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.

A revascularization of the target lesion is considered clinically-driven (CD) if the PSVR is ≥ 2.5 by duplex ultrasound or if angiography shows a percent diameter stenosis >50% and there are symptoms attributable to increased ischemia or worsening of ABI that is clearly referable to the target lesion. Worsening is defined as deterioration in the Ankle Brachial- Index (ABI) by more than 0.15 from the maximum early post-procedural level.

RCC 4-6: Freedom from Composite MALE + POD at 30 days defined as:

- Major Adverse Limb Event (MALE), defined as the composite of either major amputation or major re-intervention through 30 days of the index procedure. Major re-intervention is defined as creation of a new surgical bypass graft, the use of thrombectomy or thrombolysis or a major surgical graft revision such as a jump graft or an interposition graft.
- Perioperative Death (POD) through 30 days.

Primary Effectiveness Endpoint: The primary effectiveness endpoint was freedom from CD-TLR at 12 months post-procedure which was adjudicated by the CEC.

Secondary Endpoints: Other secondary endpoints assessed included:

- All-cause mortality at 12 months
- Cardiovascular death at 12 months
- Device or procedure related death at 30 days
- Procedural complication defined as occurrence of death, stroke, myocardial infraction, emergent surgical revascularization, significant distal embolization in target limb, or thrombosis of target vessel through the end of the procedure
- Major target limb amputation at 12 months
- CD-TLR rate at 12 months
- CD-TVR at 12 months

- Major Adverse Event (MAE) rate through 12 months post-procedure, defined as a composite rate of cardiovascular death, major target limb amputation, and CD-TLR
- Primary patency rate at 12 months (DUS imaging cohort with evaluable data)
- Change in Rutherford Clinical Category (RCC) from baseline to 12 months
- Change in Ankle-Brachial Index (ABI) from baseline to 12 months

B. Accountability of PMA Cohort

At the time of database lock for the I-Global ISR study, of the 129 patients enrolled, 93.8% (121/129) of patients were eligible for analysis at the 12-month post-operative visit. At the time of the SAVER database lock, of the 343 patients treated with the Stellarex 035 DCB for femoropopliteal ISR, 94.8% (325/343) of patients were eligible for the 12-month visit. Follow-up compliance through 12 months is presented in **Table 6**.

Table 6: Follow-up Compliance through 12 Months

12 Month (365 Days ± 30)	I-Global ISR (ITT) (N=129)	I-Global ISR (mITT) (N=122)	SAVER ISR (N=343)
Eligible Subjects[1]	93.8% (121/129)	94.3% (115/122)	94.8% (325/343)
Study Exits[2]	8	7	18
Death[2]	3	3	10
Withdrawn[2]	3	2	4
Lost-to-follow-up[2]	2	2	3
Missed Visits	3	3	Not applicable
Site Terminated Study	Not applicable	Not applicable	1

[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.

C. Study Population Demographics and Baseline Parameters

The demographics of the study populations are typical for in-stent restenosis procedures performed in Europe. Subject baseline demographics, medical history, and risk factors for the I-Global ISR and SAVER ISR patients are summarized in **Table 7**.

Numerically, compared to the I-Global ISR patients, the SAVER ISR patients had higher RCC scores (indicating a more severe clinical status), more popliteal lesions, and appeared to have more than one lesion treated per patient.

Table 7: Baseline Demographics and Clinical Characteristics

Demographics and Characteristics	I Global ISR (N Subjects=129 N Lesions=131[2]) ITT Set	SAVER ISR (N Subjects=343 N Lesions=397)
Baseline Clinical Characteristics		
Age (years)	69.0 ± 9.4 (129) 68.0 (46.0, 91.0)	70.7 ± 9.5 (206) 71.0 (49.0, 92.0)
Male	64.3% (83/129)	64.1% (220/343)
Body Mass Index (BMI)	28.2 ± 4.5 (129) 27.8 (16.7, 37.8)	27.2 ± 4.6 (312) 26.9 (15.2, 46.5)
Ankle-Brachial Index	0.66 ± 0.18 (118) 0.69 (0.00, 1.10)	0.64 ± 0.23 (175) 0.63 (0.00, 1.81)
Rutherford Clinical Category		
2	25.6% (33/129)	17.6% (60/340)
3	66.7% (86/129)	65.3% (222/340)
4	7.0% (9/129)	11.2% (38/340)
5	0.8% (1/129)	5.9% (20/340)
Medical History/Risk Factors		
Hypertension	79.1% (102/129)	81.4% (271/333)
Hyperlipidemia/ Hypercholesterolemia	78.3% (101/129)	72.9% (239/328)
Coronary Heart Disease		
Myocardial Infarction (MI)	16.3% (21/129)	12.1% (40/330)
Angina Pectoris	7.8% (10/129)	7.3% (24/330)
Congestive Heart Failure (CHF)	8.5% (11/129)	4.5% (15/330)
Previous Percutaneous or Surgical Coronary Revascularization	27.1% (35/129)	30.3% (100/330)
Renal Insufficiency	15.5% (20/129)	5.1% (17/331)
Diabetes	38.0% (49/129)	37.7% (126/334)
Type I	0.0% (0/129)	4.5% (15/334)
Type II	38.0% (49/129)	33.2% (111/334)
Smoker		
Never Smoked	17.8% (23/129)	28.3% (90/318)
Previous or Current Smoker	82.2% (106/129)	71.7% (228/318)
Previous Treatment for In-Stent Restenosis in the Target Limb	33.3% (43/129)	NA[3]
Previous Limb Amputation	2.3% (3/129)	NA[3]
Previous Amputation on the Study Limb	0.8% (1/129)	NA[3]
Previous Intervention of the Lower Limb	NA[3]	96.7% (321/332)
Previous Intervention of the Study Limb	NA[3]	93.1% (308/331)
Angiographic Lesion Characteristics as defined by QA[1]		

Table 7: Baseline Demographics and Clinical Characteristics

Demographics and Characteristics	I Global ISR (N Subjects=129 N Lesions=131[2]) ITT Set	SAVER ISR (N Subjects=343 N Lesions=397)
Study Limb (per subject)[3]		
Left	49.6% (64/129)	52.8% (181/343)
Right	50.4% (65/129)	47.2% (162/343)
Number of Lesions (per subject)[3]		
1	99.2% (128/129)	85.1% (292/343)
2	0.8% (1/129)	14.0% (48/343)
3	0.0% (0/129)	0.9% (3/343)
Lesion Location (Most Proximal)		
Proximal SFA	32.1% (42/131)	36.0% (143/397)
Mid SFA	35.1% (46/131)	51.4% (204/397)
Distal SFA	26.0% (34/131)	41.8% (166/397)
Proximal Popliteal	6.1% (8/131)	21.2% (84/397)
Mid Popliteal	0.8% (1/131)	10.1% (40/397)
Distal Popliteal	0.0% (0/131)	3.0% (12/397)
Lesion Length (mm)	129.9 ± 90.3 (131) 98.6 (13.5, 393.7)	133.3 ± 91.8 (397) 110.0 (8.0, 440.0)
Diameter Stenosis (%)	78.0 ± 17.9 (131) 75.2 (37.0, 144.6)	87.4 ± 12.9 (378) 90.0 (1.0, 100.0)
Total Occlusion (100% Stenosis)	23.7% (31/131)	28.7% (112/390)
Calcification		
None/Mild	67.7% (88/130)	67.8% (246/363)
Moderate	25.4% (33/130)	22.0% (80/363)
Severe	6.9% (9/130)	10.2% (37/363)
TASC II Lesion Classification		
Type A	42.7% (56/131)	NA[3]
Type B	25.2% (33/131)	NA[3]
Type C	16.0% (21/131)	NA[3]
Type D	16.0% (21/131)	NA[3]
Procedural Characteristics		
Pre-Dilatation Performed[2]	98.5% (128/130)	88.2% (224/254)
Post-Dilatation Performed[2]	19.2% (25/130)	17.9% (71/397)
Bailout Stent[2] (per lesion)	5.4% (7/130)	18.1% (71/392)
Post-Procedure Diameter Stenosis %)	26.0 ± 11.1 (128) 25.5 (2.5, 58.7)	8.03 ± 11.13 (351) 5.00 (0.00, 90.00)
Atherectomy	Not permitted	24.5% (62/253)
Scoring Balloon	Not permitted	0.8% (2/251)
Cutting Balloon	Not permitted	0.8% (2/251)
Lesion Success	98.3% (119/121)	97.7% (343/351)
Procedural Success	98.3% (117/119)	96.9% (340/351)

Table 7: Baseline Demographics and Clinical Characteristics

Demographics and Characteristics	I Global ISR (N Subjects=129 N Lesions=131[2]) ITT Set	SAVER ISR (N Subjects=343 N Lesions=397)
Continuous data are presented as Mean ± SD (N), Median (Min, Max). Categorical data are presented as % n/N . [1] Angiographic core laboratory reported data except where indicated otherwise. [2] Two subjects had two lesions which was a protocol deviation. [3] Data was not collected.		

D. Safety and Effectiveness Results

1. Safety Results

I-Global ISR

Unless otherwise noted, the analysis of safety was based on the Modified Intention-to-Treat (mITT) cohort of 122 patients available for the 12-month evaluation. The mITT reflects all patients in the Intention-to-Treat (ITT) population who did not receive a bailout stent and did not receive provisional treatment for >50% residual stenosis post all assigned treatment of bailout stenting. The key safety outcome for this study is presented in **Table 8**. The Kaplan-Meier estimates of freedom from primary safety events are summarized in **Figure 4** and **Table 9**. Adverse events are reported in **Table 11**.

The primary safety endpoint literature derived performance goal was 65%. At 12 months, 84.1% of patients met the primary safety endpoint with a 95% two-sided exact confidence limit of 77.28% to 90.88% ($p<0.001$). Estimates were based on results following multiple imputations for missing data. The primary safety endpoint was met, with the lower confidence limit above the performance goal. The Kaplan-Meier estimate of freedom from primary safety events at 12 months (395 days) was 85.3% (77.4, 90.6), which is supportive for the primary analysis. There were no procedure-related deaths through 30 days post-procedure and no target limb major amputations through 12 months. All primary safety events were CD-TLR through 12 months post-procedure.

Table 8: I-Global ISR Primary Safety Endpoint Results (mITT Set)

Primary Safety Endpoint[1]	DCB (N=122)[2]	95% CI p-value[3]	Performance Goal
	84.1%	77.28%, 90.88% <0.001	65%
[1] Defined as 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. Subjects with a primary safety event within the end of the 12 month window (395 days) are considered failures of the primary safety endpoint regardless if the subject has a completed 12 month follow-up visit.			

[2] Estimate is based on results following multiple imputation for missing data.
[3] The two-sided 95% CI and one-sided p-value are the model based estimates following multiple imputation of missing data. P-value is 1-sided for comparison against the performance goal of 65%.

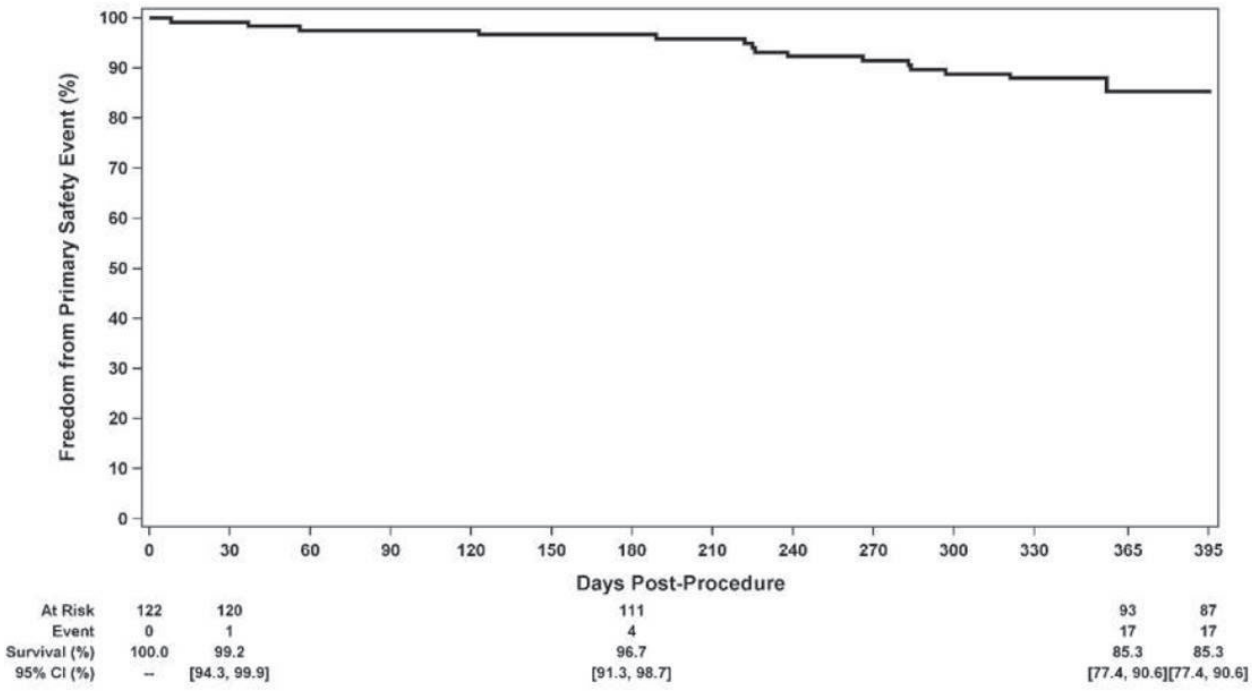

Figure 4: Kaplan-Meier Plot Freedom from Primary Safety Events (mITT Set)

Table 9: Kaplan-Meier Data Freedom from Primary Safety Events (mITT Set)

	DCB (N=122)					
Days	**At Risk**	**Number with Event**	**Event Free (%)**	**95% CI of Event Free Rate (%)**	**Event Rate (%)**	**95% CI of Event Rate (%)**
0	122	0	100.0	--	0.0	--
30	120	1	99.2	[94.3, 99.9]	0.8	[0.1, 5.7]
180	111	4	96.7	[91.3, 98.7]	3.3	[1.3, 8.7]
365	93	17	85.3	[77.4, 90.6]	14.7	[9.4, 22.6]
395	87	17	85.3	[77.4, 90.6]	14.7	[9.4, 22.6]

Freedom from 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 through 12 months post-procedure.

SAVER ISR

No hypothesis testing was pre-specified for SAVER ISR. The primary safety outcomes presented in **Table 10** reflect subjects treated for ISR lesions in the superficial femoral and/or popliteal arteries. There were no device or procedure related deaths through 30 days and no major amputations through 12 months. Adverse events are reported in **Table 12**.

Table 1: SAVER ISR Primary Safety Endpoint Results

Primary Safety Endpoint	Analysis Cohort	
	Cohort 1 (RCC 2-3) [1]	Cohort 2 (RCC 4-6) [2]
Primary Safety Endpoint	85.8% (205/239) [80.7, 89.9]	98.1% (52/53) [89.9, 100.0]
[1] Primary Safety Endpoint for Cohort 1 (RCC 2-3): defined as freedom from device/procedure related death through 30 Days, and freedom from target limb major amputation and freedom from CD-TLR through 12 Months by CEC. Data are presented as % of subjects event free (Number of subjects event free/Number of subjects with event or last study contact at Day 335 or later), with 95% exact confidence limits. [2] Primary Safety Endpoint for Cohort 2 (RCC 4-6): defined as freedom from Composite MAE (major amputation or major re-intervention), and POD (peri-operative death) through 30 days. Data are presented as % of subjects event free (Number of subjects event free/Number of subjects with event or last study contact at Day 30), with 95% exact confidence limits.		

Adverse effects that occurred in the PMA clinical study:

I-Global ISR

A serious adverse event was defined as an event that led to: a death; a serious deterioration in the subject's health that resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, in-patient or prolonged hospitalization, or medical or surgical intervention to prevent a life-threatening illness or injury, or permanent impairment to a body structure or body function; or fetal distress, fetal death or a congenital abnormality or birth defect. Serious adverse event rates by MedDRA system organ class and preferred term through 12 months are provided in **Table 11**. All serious adverse events were adjudicated by the CEC. At 12 months, events occurring at a rate >5% included device occlusion, intermittent claudication, and peripheral artery stenosis.

Table 2: Serious Adverse Events through 12 Months (ITT Set)

Event[1]	6 Months[2] (N=129)[3]	12 Months[2] (N=129)[3]
CARDIAC DISORDERS	3.1% (4/129) [4]	8.5% (11/129) [11]
ACUTE MYOCARDIAL INFARCTION	0.0% (0/122) [0]	0.8% (1/129) [1]
ANGINA PECTORIS	0.0% (0/122) [0]	0.8% (1/129) [1]
ATRIAL FIBRILLATION	0.0% (0/122) [0]	0.8% (1/129) [1]
CARDIAC FAILURE	0.0% (0/122) [0]	0.8% (1/129) [1]
CARDIOMYOPATHY	0.8% (1/129) [1]	0.8% (1/129) [1]
CORONARY ARTERY DISEASE	1.6% (2/129) [2]	3.1% (4/129) [4]
MYOCARDIAL INFARCTION	0.8% (1/129) [1]	0.8% (1/129) [1]
TACHYARRHYTHMIA	0.0% (0/122) [0]	0.8% (1/129) [1]
EYE DISORDERS	0.0% (0/122) [0]	0.8% (1/129) [1]
EYELID PTOSIS	0.0% (0/122) [0]	0.8% (1/129) [1]

Table 2: Serious Adverse Events through 12 Months (ITT Set)

Event[1]	6 Months[2] (N=129)[3]	12 Months[2] (N=129)[3]
GASTROINTESTINAL DISORDERS	0.0% (0/122) [0]	3.1% (4/129) [4]
BARRETT'S OESOPHAGUS	0.0% (0/122) [0]	0.8% (1/129) [1]
DYSPEPSIA	0.0% (0/122) [0]	0.8% (1/129) [1]
GASTRITIS	0.0% (0/122) [0]	0.8% (1/129) [1]
OESOPHAGEAL RUPTURE	0.0% (0/122) [0]	0.8% (1/129) [1]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5.4% (7/129) [7]	10.1% (13/129) [15]
DEVICE OCCLUSION	2.3% (3/129) [3]	5.4% (7/129) [9]
GENERAL PHYSICAL HEALTH DETERIORATION	0.8% (1/129) [1]	0.8% (1/129) [1]
HERNIA	0.8% (1/129) [1]	0.8% (1/129) [1]
IMPAIRED HEALING	0.8% (1/129) [1]	0.8% (1/129) [1]
PYREXIA	0.8% (1/129) [1]	0.8% (1/129) [1]
STENT MALFUNCTION	0.0% (0/122) [0]	1.6% (2/129) [2]
HEPATOBILIARY DISORDERS	0.8% (1/129) [1]	0.8% (1/129) [1]
CHOLANGITIS	0.8% (1/129) [1]	0.8% (1/129) [1]
INFECTIONS AND INFESTATIONS	3.9% (5/129) [5]	6.2% (8/129) [8]
BRONCHITIS	0.8% (1/129) [1]	0.8% (1/129) [1]
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	0.0% (0/122) [0]	0.8% (1/129) [1]
PNEUMONIA	2.3% (3/129) [3]	3.1% (4/129) [4]
PYELONEPHRITIS	0.8% (1/129) [1]	0.8% (1/129) [1]
STAPHYLOCOCCAL BACTERAEMIA	0.0% (0/122) [0]	0.8% (1/129) [1]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	5.4% (7/129) [7]	14.0% (18/129) [18]
ARTERIAL RESTENOSIS	1.6% (2/129) [2]	3.1% (4/129) [4]
PATELLA FRACTURE	0.0% (0/122) [0]	0.8% (1/129) [1]
PERIPHERAL ARTERIAL REOCCLUSION	0.0% (0/122) [0]	0.8% (1/129) [1]
PERIPHERAL ARTERY RESTENOSIS	1.6% (2/129) [2]	4.7% (6/129) [6]
RIB FRACTURE	0.8% (1/129) [1]	0.8% (1/129) [1]
SUBDURAL HAEMATOMA	0.0% (0/122) [0]	0.8% (1/129) [1]
VASCULAR PSEUDOANEURYSM	0.0% (0/122) [0]	0.8% (1/129) [1]
WOUND	0.8% (1/129) [1]	0.8% (1/129) [1]
WOUND HAEMORRHAGE	0.8% (1/129) [1]	1.6% (2/129) [2]
INVESTIGATIONS	0.8% (1/129) [1]	1.6% (2/129) [3]
ANGIOGRAM	0.8% (1/129) [1]	0.8% (1/129) [1]

Table 2: Serious Adverse Events through 12 Months (ITT Set)

Event[1]	6 Months[2] (N=129)[3]	12 Months[2] (N=129)[3]
LIVER FUNCTION TEST ABNORMAL	0.0% (0/122) [0]	0.8% (1/129) [1]
LYMPH NODES SCAN ABNORMAL	0.0% (0/122) [0]	0.8% (1/129) [1]
METABOLISM AND NUTRITION DISORDERS	0.8% (1/129) [1]	0.8% (1/129) [1]
HYPOGLYCAEMIA	0.8% (1/129) [1]	0.8% (1/129) [1]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1.6% (2/129) [2]	3.1% (4/129) [6]
BACK PAIN	0.0% (0/122) [0]	1.6% (2/129) [3]
LUMBAR SPINAL STENOSIS	0.0% (0/122) [0]	0.8% (1/129) [1]
PAIN IN EXTREMITY	1.6% (2/129) [2]	1.6% (2/129) [2]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1.6% (2/129) [2]	2.3% (3/129) [3]
ENDOMETRIAL CANCER	0.8% (1/129) [1]	0.8% (1/129) [1]
LUNG ADENOCARCINOMA	0.0% (0/122) [0]	0.8% (1/129) [1]
LUNG NEOPLASM	0.8% (1/129) [1]	0.8% (1/129) [1]
NERVOUS SYSTEM DISORDERS	2.3% (3/129) [3]	4.7% (6/129) [7]
CAROTID ARTERY STENOSIS	0.8% (1/129) [1]	1.6% (2/129) [2]
CARPAL TUNNEL SYNDROME	0.0% (0/122) [0]	0.8% (1/129) [2]
CEREBROVASCULAR ACCIDENT	0.8% (1/129) [1]	0.8% (1/129) [1]
DIZZINESS	0.8% (1/129) [1]	0.8% (1/129) [1]
RADICULOPATHY	0.0% (0/122) [0]	0.8% (1/129) [1]
PSYCHIATRIC DISORDERS	0.8% (1/129) [1]	0.8% (1/129) [2]
AGGRESSION	0.0% (0/122) [0]	0.8% (1/129) [1]
SUICIDAL IDEATION	0.8% (1/129) [1]	0.8% (1/129) [1]
RENAL AND URINARY DISORDERS	0.8% (1/129) [1]	3.1% (4/129) [4]
HAEMATURIA	0.0% (0/122) [0]	0.8% (1/129) [1]
NEPHROLITHIASIS	0.0% (0/122) [0]	0.8% (1/129) [1]
RENAL FAILURE	0.0% (0/122) [0]	0.8% (1/129) [1]
RENAL FAILURE ACUTE	0.8% (1/129) [1]	0.8% (1/129) [1]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0.0% (0/122) [0]	1.6% (2/129) [2]
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0.0% (0/122) [0]	0.8% (1/129) [1]
PNEUMOTHORAX	0.0% (0/122) [0]	0.8% (1/129) [1]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0.8% (1/129) [1]	0.8% (1/129) [1]

Table 2: Serious Adverse Events through 12 Months (ITT Set)

Event[1]	6 Months[2] (N=129)[3]	12 Months[2] (N=129)[3]
SKIN ULCER	0.8% (1/129) [1]	0.8% (1/129) [1]
SURGICAL AND MEDICAL PROCEDURES	0.8% (1/129) [1]	1.6% (2/129) [2]
ALCOHOL DETOXIFICATION	0.0% (0/122) [0]	0.8% (1/129) [1]
TENDON OPERATION	0.8% (1/129) [1]	0.8% (1/129) [1]
VASCULAR DISORDERS	13.2% (17/129) [25]	21.7% (28/129) [45]
ARTERIAL STENOSIS	0.0% (0/122) [0]	0.8% (1/129) [1]
ARTERIOSCLEROSIS	0.0% (0/122) [0]	0.8% (1/129) [1]
FEMORAL ARTERY DISSECTION	0.8% (1/129) [1]	0.8% (1/129) [1]
FEMORAL ARTERY OCCLUSION	1.6% (2/129) [2]	3.1% (4/129) [4]
HAEMATOMA	0.0% (0/122) [0]	0.8% (1/129) [1]
HYPOTENSION	0.8% (1/129) [1]	0.8% (1/129) [1]
INTERMITTENT CLAUDICATION	2.3% (3/129) [3]	5.4% (7/129) [8]
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	0.8% (1/129) [1]	0.8% (1/129) [1]
PERIPHERAL ARTERY STENOSIS	8.5% (11/129) [15]	13.2% (17/129) [24]
PERIPHERAL EMBOLISM	0.8% (1/129) [1]	0.8% (1/129) [1]
PERIPHERAL ISCHAEMIA	0.8% (1/129) [1]	0.8% (1/129) [1]
VESSEL PERFORATION	0.0% (0/122) [0]	0.8% (1/129) [1]
Total	31.8% (41/129) [62]	51.9% (67/129) [134]

[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 is based on the event verbatim term provided by the CEC. Otherwise, the MedDRA coding is based on the site-reported event verbatim term.
[2] 6 months includes all events through 210 days; 12 months includes all events through 395days.
[3] 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.

SAVER ISR

Complaints were collected through the vigilance system reported according to country specific requirements. For the purpose of SAVER adverse effects endpoints, death, TVR, TLR and amputation of the target limb were collected through an EDC system and adjudicated by the CEC. These events are summarized in **Table 12**.

Table 3: SAVER ISR CEC Adjudicated Adverse Events through 12 Months

Clinical Event	ISR Subjects (N = 343)
Major Adverse Event (MAE)[1]	12.5% (43/343)

Clinical Event	ISR Subjects (N = 343)
Death	1.7% (6/343)
Cardiovascular	0.3% (1/343)
Non-Cardiovascular	1.5% (5/343)
Procedure Related	0.0% (0/343)
Study Device Related	0.0% (0/343)
Amputation Performed on Index Limb	0.0% (0/343)
Major Amputation	0.0% (0/343)
Minor Amputation	0.0% (0/343)
TLR	12.5% (43/343)
Clinically Driven	12.2% (42/343)
Non-Clinically Driven	0.3% (1/343)
TVR	0.3% (1/343)
Clinically Driven	0.3% (1/343)
Non-Clinically Driven	0.0% (0/343)
[1] MAE: Defined as CD-TLR, major amputation of the treated limb, or cardiovascular death. Number of events are cumulative.	

2. Effectiveness Results

I-Global ISR

The primary effectiveness endpoint was primary patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from CD-TLR. The primary effectiveness endpoint literature derived performance goal was 64% (reflects 2X PTA) and only addresses the primary patency component.

The analysis of primary effectiveness was based on 122 evaluable patients at the 12-month time point. The effectiveness outcomes are presented in **Table 13** (mITT set), **Table 14** (Kaplan-Meier estimate mITT set), and **Table 15** (mITT and complete case set). As presented in **Table 13**, 58.8% of patients had primary patency at 12 months with a 95% two-sided exact confidence limit of 49.21% to 68.43%. Since the lower confidence limit (LCL) lies below the performance goal, the primary effectiveness endpoint was not met. The Kaplan-Meier freedom from loss of primary patency through 12 months presented in **Figure 5** and **Table 14** was 66.6% (57.1%, 74.5% at 395 days.

Table 4. Primary Effectiveness Endpoint Results (mITT Set)

Primary Effectiveness Endpoint[1,2]	Results		Performance Goal
	DCB (N=122)[3]	95% CI p-value[4]	
	58.8%	49.21%, 68.43% 0.855	64%

[1] The primary effectiveness endpoint was patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR = 2.5 and freedom from CD-TLR.
[2] Subjects with a primary effectiveness event within 12 months (395 days) are considered as failures of the endpoint regardless if the subject has a 12 month follow-up visit. Subjects are considered a success for the endpoint when there was with a valid image with the 12 month window showing absence of restenosis and no prior CD-TLR.
[3] Estimates are based on results following multiple imputation for missing data.
[4] The two-sided 95% CI and one-sided p-value are the model based estimates following multiple imputation of missing data. P-value is 1-sided for comparison against the performance goal of 64%.

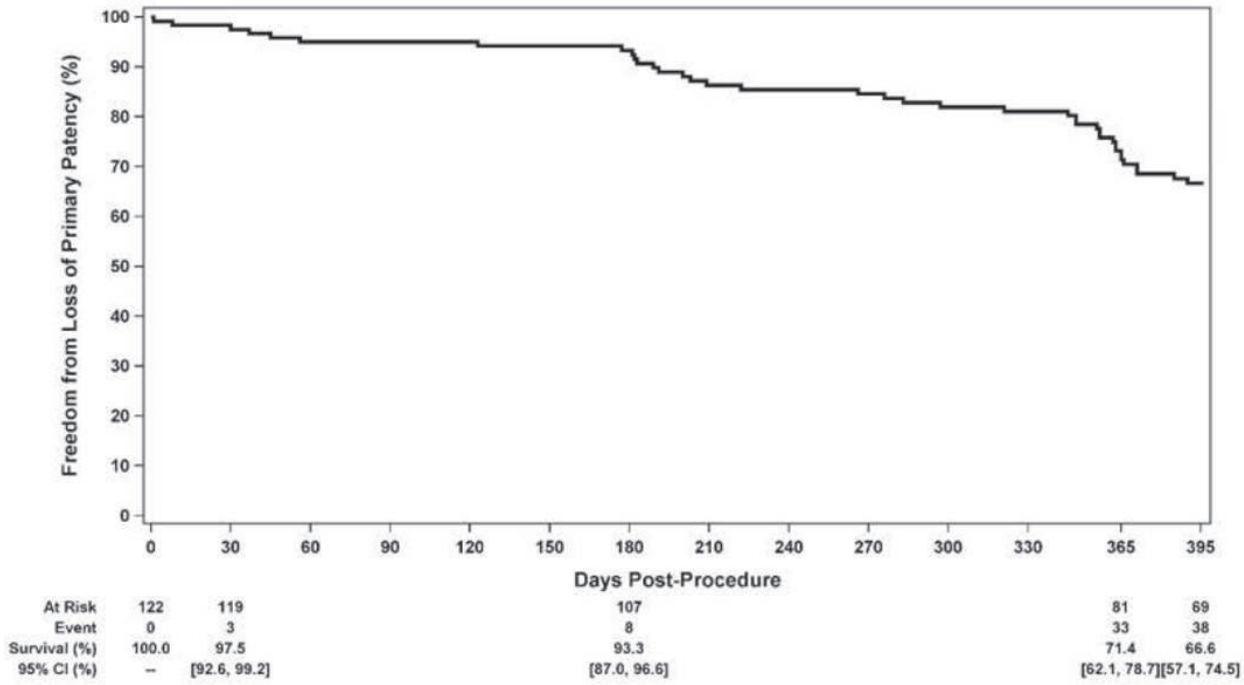

Figure 5. Kaplan-Meier Plot Freedom from Loss of Primary Patency through 12 Months (395 days) (mITT Set)

Table 5. Kaplan-Meier Freedom from Loss of Primary Patency through 12 Months (end of window) (mITT Set)

DCB (N Subjects=122, N Lesions=124)				
Days	**At Risk**	**Number with Event**	**Event Free (%)**	**95% CI of Event Free Rate (%)**
0	122	0	100.0	--
30	119	3	97.5	[92.6, 99.2]
180	107	8	93.3	[87.0, 96.6]
365	81	33	71.4	[62.1, 78.7]
395	69	38	66.6	[57.1, 74.5]

DCB (N Subjects=122, N Lesions=124)				
Days	**At Risk**	**Number with Event**	**Event Free (%)**	**95% CI of Event Free Rate (%)**
Freedom from loss of primary patency was defined as absence of target lesion restenosis (as assessed by the duplex ultrasound core laboratory based on PSVR ≤ 2.5) and freedom CD-TLR. In the case where duplex ultrasound data were not available, angiographic results assessed by the angiographic core laboratory were utilized. Lesions with follow-up within or past the 12 month visit window that were free from CD-TLR but without an evaluable assessment of target lesion restenosis were censored at the time of last contact.				

The primary effectiveness component analyses are presented in **Table 15,** showing the impacts of imaging-driven patency and freedom from CD-TLR (ITT) on primary effectiveness.

Table 6. Primary Effectiveness Endpoint Components (Complete Case Set)

Primary Effectiveness Endpoint[1,2]	**DCB**		
	ITT (N=129)[3]	**mITT (N=122)[3]**	**PP (N=81)[3]**
Primary Effectiveness Endpoint Success	60.2% (59/98) [49.8, 70.0]	59.6% (56/94) [49.0, 69.6]	66.7% (54/81) [55.3, 76.8]
Freedom from target lesion restenosis determined by duplex ultrasound PSVR ≥ 2.5 through 12 months post-procedure	73.0% (65/89) [62.6, 81.9]	72.9% (62/85) [62.2, 82.0]	72.8% (59/81) [61.8, 82.1]
Freedom from CD-TLR through 12 months post-procedure	85.2% (104/122) [77.7, 91.0]	85.2% (98/115) [77.4, 91.2]	88.9% (72/81) [80.0, 94.8]

[1] The primary effectiveness endpoint was patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤2.5 and freedom from CD-TLR.
[2] Subjects with a primary effectiveness event within 12 months (395 days) are considered as failures of the endpoint regardless if the subject has a 12 month follow-up visit. Subjects are considered a success for the endpoint when there was with a valid image with the 12 month window showing absence of restenosis and no prior CD-TLR.
[3] Data are reported without imputation for missing data. Numbers are % (n/N). The 95% exact Clopper-Pearson confidence interval is presented for the overall effectiveness endpoint. 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.
ITT = Intention-to-Treat (all subjects who successfully completed the preliminary qualification procedures and were subsequently enrolled to receive the Stellarex DCB)
mITT = Modified Intention-to-Treat (all ITT subjects who did not receive a bailout stent and did not receive provisional treatment for >50% residual stenosis post all assigned treatment or bailout stenting.
PP = Per Protocol (ITT subjects who had no bail-out stenting and no major protocol deviations defined by the study management team)

Secondary Effectiveness Endpoint

Secondary effectiveness endpoints with analysis at 12 months included freedom from TLR, and changes in ankle-brachial index, walking impairment questionnaire, EQ-5D quality of life, and Rutherford-Becker clinical category.

Freedom from TLR

Freedom from TLR was analyzed using a 76% performance goal for secondary effectiveness (PGes). The analysis was based on 122 subjects for the mITT set and 129 subjects for the ITT set. The results are presented in **Table 16** (mITT set), **Table 17** (Kaplan-Meier estimate mITT set), and **Table 18** (Kaplan-Meier estimate ITT set). Seven subjects were excluded from mITT analyses due to bailout stenting.

As shown in **Table 16**, the secondary effectiveness outcome was not met with 83.5% (95% CI 75.4, 89.7; one-sided p-value 0.0302) compared to the performance goal (PG) of 76%. The same result is provided in **Table 17** for the Kaplan-Meier estimate. The Kaplan-Meier analyses of the ITT set is provided in **Table 18** and shows freedom from TLR is 84.5% with a 95% CI of 76.8% to 89.8%.

Table 7. Secondary Effectiveness Endpoint Freedom from TLR (mITT Set)

Secondary Effectiveness Endpoint	DCB (N=122)[a]	95% CI p-value[a]	Performance Goal
Freedom from TLR at 12 Months	83.5% (96/115)	[75.4, 89.7] 0.0302	76%

[a] Data are reported without imputation for missing data. Numbers are % (n/N). The 95% exact Clopper-Pearson confidence interval is presented. The numerator is the number of subjects without 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. P-value is the one-sided comparison to the performance goal of 76%.

Table 8. Kaplan-Meier Freedom from TLR (mITT Set)

DCB (N=122)						
Days	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	Event Rate (%)	95% CI of Event Rate (%)
0	122	0	100.0	--	0.0	--
30	120	1	99.2	[94.3, 99.9]	0.8	[0.1, 5.7]
180	111	4	96.7	[91.3, 98.7]	3.3	[1.3, 8.7]
365	91	19	83.5	[75.4, 89.2]	16.5	[10.8, 24.6]

Table 9. Kaplan-Meier Freedom from TLR (ITT Set)

DCB (N=129)						
Days	At Risk	Number With Event	Event Free (%)	95% CI of Event Free Rate (%)	Event Rate (%)	95% CI of Event Rate (%)
0	129	0	100.0	--	0.0	--

DCB (N=129)						
Days	**At Risk**	**Number With Event**	**Event Free (%)**	**95% CI of Event Free Rate (%)**	**Event Rate (%)**	**95% CI of Event Rate (%)**
30	127	1	99.2	[94.6, 99.9]	0.8	[0.1, 5.4]
180	118	4	96.8	[91.8, 98.8]	3.2	[1.2, 8.2]
365	96	19	84.5	[76.8, 89.8]	15.5	[10.2, 23.2]

Change in Ankle-Brachial Index

Change in ankle-brachial index (ABI) was determined by subject, comparing the ABI pre-procedure to the ABI at 12 months. The results are presented in **Table 19**. For the mITT Set, ABI was improved for 80.6% of subjects, with a mean improvement of 0.19. Results were similar for the ITT Set. For two subjects with non-compressible arteries, toe-brachial index (TBI) improved by 0.15 at 12 months. Results were similar for the ITT Set.

Table 1910: Change in Ankle-Brachial Index

Characteristic	**ITT Set (N=129)**		**mITT Set (N=122)**	
	Baseline[4]	**12 Months**	**Baseline[4]**	**12 Months**
ABI	0.66 ± 0.18 (118) 0.69 (0.00, 1.10)	0.87 ± 0.21 (108) 0.88 (0.00, 1.70)	0.67 ± 0.17 (111) 0.69 (0.26, 1.10)	0.87 ± 0.21 (103) 0.88 (0.00, 1.70)
Non-Compressible[1]	1.7% (2/120)	2.7% (3/111)	1.8% (2/113)	2.8% (3/106)
Change in ABI from Baseline[2]	--	0.20 ± 0.25 (108) 0.21 (-0.63, 1.14)	--	0.19 ± 0.25 (103) 0.20 (-0.63, 1.14)
Improved	--	81.5% (88/108)	--	80.6% (83/103)
No Change	--	0.0% (0/108)	--	0.0% (0/103)
Worsened	--	18.5% (20/108)	--	19.4% (20/103)
TBI[3]	0.40 ± 0.09 (2) 0.40 (0.34, 0.47)	0.55 ± 0.30 (2) 0.55 (0.34, 0.76)	0.40 ± 0.09 (2) 0.40 (0.34, 0.47)	0.55 ± 0.30 (2) 0.55 (0.34, 0.76)
Change in TBI[3] from Baseline[2]	--	0.15 ± 0.20 (2) 0.15 (0.00, 0.29)	--	0.15 ± 0.20 (2) 0.15 (0.00, 0.29)
Improved	--	100% (2/2)	--	100% (2/2)
No Change	--	0.0% (0/2)	--	0.0% (0/2)
Worsened	--	0.0% (0/2)	--	0.0% (0/2)

Continuous data are presented as Mean ± SD (N), Median (Min, Max). Categorical data are presented as % (n/N).

For each analysis time point, only subjects with data available at both baseline and follow-up are included.

[1]Non-compressible includes subjects for which ABI could not be obtained due to non-compressible arteries as reported on the case report form.

[2]Within-patient changes calculated as follow up visit value minus baseline value. Improved is change >0, Worsened is change <0, No Change is change=0.

[3]Toe-brachial index summarized only when ankle-brachial index could not be obtained due to non-compressible arteries.

[4]Baseline was performed but 6 or 12 months follow-up was not available.

Change in Walking Impairment Questionnaire Scores

The walking impairment questionnaire (WIQ) was used to assess the subject's perception of walking distance, walking speed, and stair climbing ability. The WIQ scores were reported on a 100-point scale without units and is similar to reporting a percentage of the best-case scenario (defined as no difficulties for all distance, speed, or stair climbing assessed). Changes in WIQ scores were determined by subject, where the baseline scores were compared to the scores at 12 months. The composite WIQ score is the average of the walking distance, walking speed, and stair climbing scores. The results are presented in **Table 20**.

For the mITT Set, improvements were observed at 12 months for walking distance (78.2% of subjects), walking speed (70.3% of subjects), stair climbing (68.0% of subjects). Composite WIQ scores at 12 months were improved for 76.0% of subjects and worsened for 24.0% of subjects. Results were similar for the ITT Set.

Table 110: Change in Walking Impairment Questionnaire Scores

Characteristic	ITT Set (N=129)		mITT Set (N=122)	
	Baseline[2]	12 Months	Baseline[2]	12 Months
EQ-5D Index	0.70 ± 0.21 (126) 0.71 (0.00, 1.00)	0.82 ± 0.20 (118) 0.81 (0.08, 1.00)	0.69 ± 0.21 (119) 0.71 (0.00, 1.00)	0.81 ± 0.21 (112) 0.81 (0.08, 1.00)
Change in EQ-5D Index from Baseline[1]	--	0.12 ± 0.24 (118) 0.07 (-0.52, 0.75)	--	0.12 ± 0.24 (112) 0.07 (-0.52, 0.75)
Improved	--	57.6% (68/118)	--	58.0% (65/112)
No Change	--	22.0% (26/118)	--	21.4% (24/112)
Worsened	--	20.3% (24/118)	--	20.5% (23/112)
EQ Visual Analog Scale	65.3 ± 15.6 (126) 70.0 (10.0, 95.0)	73.2 ± 15.7 (118) 75.0 (10.0, 100.0)	65.1 ± 15.7 (119) 70.0 (10.0, 95.0)	72.9 ± 16.1 (112) 75.0 (10.0, 100.0)
Change in EQ Visual Analog Scale from Baseline[1]	--	8.0 ± 18.3 (118) 9.0 (-40.0, 70.0)	--	7.9 ± 18.5 (112) 8.5 (-40.0, 70.0)
Improved	--	61.9% (73/118)	--	60.7% (68/112)
No Change	--	12.7% (15/118)	--	13.4% (15/112)
Worsened	--	25.4% (30/118)	--	25.9% (29/112)

Continuous data are presented as Mean ± SD (N), Median (Min, Max . Categorical data are presented as % (n/N). For each analysis time point, only subjects with data available at both baseline and follow-up are included.
[1]Within-patient changes will be calculated as follow up visit value minus baseline value. Improved is change >0, Worsened is change <0, No Change is change=0.
[2]Baseline was performed but 6 or 12 months follow-up was not available.

Change in EQ-5D – Quality of Life

The EQ-5D was used to assess subject-reported quality of life. The EQ-5D index scores include 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D visual analog scale (VAS) is a global assessment of health status with 0 being "worst imaginable health

state" and 100 being "best imaginable health state." The changes in the EQ-5D Index and VAS scores were determined by subject, where baseline scores were compared to scores at 12 months. The results are presented in **Table 21.** For the mITT Set, for the subjects with EQ-5Q assessments at baseline and follow-up, the mean change (improvement) in the EQ-5D Index scores was 0.12 at 12 months with 58.0% improved, and a 7.9 mean change in the EQ VAS with 60.7% improved. Results were similar for the ITT Set.

Table 121: Change in EQ-5D

Characteristic	ITT Set (N=129)		mITT Set (N=122)	
	Baseline[2]	12 Months	Baseline[2]	12 Months
EQ-5D Index	0.70 ± 0.21 (126) 0.71 (0.00, 1.00)	0.82 ± 0.20 (118) 0.81 (0.08, 1.00)	0.69 ± 0.21 (119) 0.71 (0.00, 1.00)	0.81 ± 0.21 (112) 0.81 (0.08, 1.00)
Change in EQ-5D Index from Baseline[1]	--	0.12 ± 0.24 (118) 0.07 (-0.52, 0.75)	--	0.12 ± 0.24 (112) 0.07 (-0.52, 0.75)
Improved	--	57.6% (68/118)	--	58.0% (65/112)
No Change	--	22.0% (26/118)	--	21.4% (24/112)
Worsened	--	20.3% (24/118)	--	20.5% (23/112)
EQ Visual Analog Scale	65.3 ± 15.6 (126) 70.0 (10.0, 95.0)	73.2 ± 15.7 (118) 75.0 (10.0, 100.0)	65.1 ± 15.7 (119) 70.0 (10.0, 95.0)	72.9 ± 16.1 (112) 75.0 (10.0, 100.0)
Change in EQ Visual Analog Scale from Baseline[1]	--	8.0 ± 18.3 (118) 9.0 (-40.0, 70.0)	--	7.9 ± 18.5 (112) 8.5 (-40.0, 70.0)
Improved	--	61.9% (73/118)	--	60.7% (68/112)
No Change	--	12.7% (15/118)	--	13.4% (15/112)
Worsened	--	25.4% (30/118)	--	25.9% (29/112)

Continuous data are presented as Mean ± SD (N), Median (Min, Max . Categorical data are presented as % (n/N). For each analysis time point, only subjects with data available at both baseline and follow-up are included.
[1]Within-patient changes will be calculated as follow up visit value minus baseline value. Improved is change >0, Worsened is change <0, No Change is change=0.
[2]Baseline was performed but 6 or 12 months follow-up was not available.

Change in Rutherford-Becker Clinical Category

Change in Rutherford-Becker Clinical Category (RCC) classification was determined for each subject by comparing the baseline RCC to that at 12 months. Changes in RCC are presented in **Table 22**. For the mITT Set, the most common RCC was 3 (66.9%) at baseline and 0 (58.8%) at 12 months, and the mean change from baseline was (-)2.1 with 87.7% of subjects improved at 12 months. The changes in RCC were similar for the ITT Set.

Table 132: Change in Rutherford-Becker Clinical Category

Characteristic	ITT Set (N=129)		mITT Set (N=122)	
	Baseline[2]	12 Months	Baseline[2]	12 Months
Rutherford-Becker Clinical Category (RCC)				
0	0.0% (0/128)	59.2% (71/120)	0.0% (0/121)	58.8% (67/114)
1	0.0% (0/128)	22.5% (27/120)	0.0% (0/121)	22.8% (26/114)

Characteristic	ITT Set (N=129)		mITT Set (N=122)	
	Baseline[2]	12 Months	Baseline[2]	12 Months
2	25.8% (33/128)	10.0% (12/120)	26.4% (32/121)	9.6% (11/114)
3	67.2% (86/128)	7.5% (9/120)	66.9% (81/121)	7.9% (9/114)
4	6.3% (8/128)	0.0% (0/120)	5.8% (7/121)	0.0% (0/114)
5	0.8% (1/128)	0.8% (1/120)	0.8% (1/121)	0.9% (1/114)
Average Classification	2.8 ± 0.6 (128) 3.0 (2.0, 5.0)	0.7 ± 1.0 (120) 0.0 (0.0, 5.0)	2.8 ± 0.6 (121) 3.0 (2.0, 5.0)	0.7 ± 1.0 (114) 0.0 (0.0, 5.0)
Change in RCC from Baseline[1]	--	-2.1 ± 1.1 (120) -2.0 (-4.0, 1.0)	--	-2.1 ± 1.1 (114) -2.0 (-4.0, 1.0)
Improved	--	88.3% (106/120)	--	87.7% (100/114)
No Change	--	9.2% (11/120)	--	9.6% (11/114)
Worsened	--	2.5% (3/120)	--	2.6% (3/114)

Continuous data are presented as Mean ± SD (N), Median (Min, Max . Categorical data are presented as % (n/N). For each analysis time point, only subjects with data available at both baseline and follow-up are included.
[1]Within-patient changes will be calculated as follow up visit value minus baseline value. Improved is change <0, Worsened is change >0, No Change is change=0.
[2]Baseline was performed but 6 or 12 months follow-up was not available.

SAVER ISR

Analysis of the SAVER ISR primary effectiveness endpoint was based on 282 evaluable ISR patients at 12 months. The freedom from CD-TLR rate at 12 months was 85.1% as presented in **Table 27**. The freedom from TLR rate at 12 months was 84.8% as presented in **Table 28**. The LCLs of freedom from CD-TLR (80.4%) and freedom from TLR (80.0%) are above the secondary endpoint 76% PG for the I-Global ISR study.

Table 27. Primary Effectiveness Endpoint

Freedom from CD-TLR at 12 months	Success % (n/N)[a]	95% CI[a]
	85.1% (240/282)	80.4%, 89.1%

[a] Data are presented as % of subjects event free (Number of subjects event free/Number of subjects with event or last study contact at Day 335 or later), with 95% exact confidence limits.

Table 28. Secondary Effectiveness Endpoint

Outcomes	ISR (N=343)
Freedom from TLR at 12 months	84.8% (239/282) [80.0%, 88.7%]

3. Subgroup Analyses

I-Global ISR

For the I-Global ISR, the preoperative characteristics listed in **Table 29** were evaluated for potential association with primary endpoint outcomes. The subgroup analyses showed no evidence of a difference in treatment effect for the primary safety endpoint, except for lesion length (<200 mm vs ≥ 200 mm) which indicated that longer lesions ≥ 200 mm) are less likely to meet the

success criteria, e.g., a lower rate of freedom from CD-TLR. However, this likelihood was based on a small (n<50) subgroup analysis.

Table 149. I-Global ISR Subgroup Analyses (mITT)

Subgroup	Parameter	Primary Endpoint	
		Safety	Effectiveness
Age (years)	< 65	82.9% (34/41) [67.9, 92.8]	59.4% (19/32) [40.6, 76.3]
	≥ 65	86.5% (64/74) [76.5, 93.3]	59.7% (37/62) [46.4, 71.9]
Gender	Female	85.7% (36/42) [71.5, 94.6]	57.1% (20/35) [39.4, 73.7]
	Male	84.9% (62/73) [74.6, 92.2]	61.0% (36/59) [47.4, 73.5]
Maximum Lesion Length (mm)	< 200	91.0% (81/89) [83.1, 96.0]	66.7% (48/72) [54.6, 77.3]
	≥ 200	65.4% (17/26) [44.3, 82.8]	36.4% (8/22) [54.6, 77.3]
Maximum Reference Vessel Diameter (mm)	< 4	75.0% (12/16) [47.6, 92.7]	42.9% (6/14) [17.7, 71.1]
	≥ 4 <5	86.0% (43/50) [73.3, 94.2]	51.3% (20/39) [17.7, 71.1]
	≥ 5 <6	90.2% (37/41) [76.9, 97.3]	75.8% (25/33) [17.7, 71.1]
	≥6	75.0% (6/8) [34.9, 96.8]	62.5% (5/8) [24.5, 91.5]

SAVER ISR

No subgroup analysis was performed for the SAVER ISR dataset.

4. 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 Part 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 21 investigators. None of the investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The ILLUMENATE Global ISR cohort primary effectiveness outcome for primary patency at 12 months was 58.8% (95% CI 49.21%, 68.43%; one-sided p-value 0.855) compared to the literature derived performance goal of 64%, which was set based on 2X patency of PTA (as reported by VIVA Physician's Inc; discussed in Section X.A. above). Since the lower confidence limit (49.21%) lies below the performance goal (64%), the primary effectiveness endpoint was not met. The secondary effectiveness outcome of freedom from TLR at 12 months was 83.5% and was not met with 95% CI 75.4% to 89.7%; one-sided p-value 0.0302) compared to the performance goal of 76%. Although the primary effectiveness endpoint was not met, a favorable nominal outcome over the literature-derived primary patency rate of 32% for PTA was demonstrated.

The SAVER ISR cohort outcome for freedom from CD-TLR at 12 months was 85.1% (95% CI 80.4%, 89.1% . Freedom from TLR at 12 months was 84.8% (95% CI 80.0%, 88.7%). Although the SAVER ISR did not have any pre-defined endpoints, the TLR rates are above the performance goal established for the secondary endpoint in the I-Global ISR study. The SAVER ISR real-world evidence supports the effectiveness of the Stellarex 035 DCB for the treatment of ISR.

In general, the totality of evidence supports effectiveness for the treatment of ISR.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies submitted in the original PMA as well as data collected in the clinical study conducted to support ISR approval as described above. The ISR cohort of the ILLUMENATE Global study met its 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 CD-TLR through 12 months post-procedure. At 12 months, 84.1% of patients met the primary safety endpoint with a 95% two-sided exact confidence limit of 77.28% to 90.88% ($p<0.001$) compared to the performance goal of 65%. For both the ILLUMENATE Global study and SAVER ISR, there were no procedure-related deaths through 30 days and no target limb major amputations through 12 months. The SAVER ISR primary safety endpoint based on RCC was 85.8% (RCC 2-3) and 89.1% (RCC 4-6). The results

support the safety of the Stellarex 035 DCB for the treatment of ISR in the superficial femoral and popliteal arteries.

C. Benefit-Risk Determination

The probable benefits of this device are also based on data collected in clinical studies conducted to support PMA approval as described above. A favorable nominal outcome over the literature-derived primary patency rate for PTA was demonstrated at 12 months for the ILLUMENATE Global ISR cohort. Additional benefits demonstrated at 12 months for ILLUMENATE Global ISR cohort included improvement in ankle-brachial index, walking impairment (walking distance, walking speed, and stair climbing ability), quality of life, and Rutherford-Becker Clinical Category. The real-world evidence from the SAVER ISR study demonstrated freedom from CD-TLR at 12 months.

The probable risks of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The types and occurrence rates of adverse events which occurred in the study were consistent with the clinical condition of the patient population treated, natural progression of peripheral artery disease, and similar percutaneous transluminal angioplasty procedures.

The device is already approved for use in *de novo* and restenotic lesions and the expanded Indications for Use does not change the benefit-risk profile related to the late mortality signal for Paclitaxel-coated devices.

Additional factors to be considered in determining probable risks and benefits for the Stellarex 0.035" OTW Drug-coated Angioplasty Balloon include:

- The I-Global ISR study was a single-arm study without a direct comparator in the patient population.
- Enrollment in the study was limited to specific inclusion and exclusion criteria.
- Percutaneous transluminal angioplasty is an available alternative treatment.
- 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.

1. Patient Perspective

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

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for percutaneous transluminal angioplasty (PTA), after appropriate vessel preparation of *de novo*, restenotic, or in-

stent restenotic lesions up to 180 mm in length in superficial femoral or popliteal arteries with reference vessel diameters of 4-6 mm.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Stellarex 035 DCB for the treatment of ISR when used in accordance with the indications for use. The results from the clinical study and real-world evidence demonstrate the benefit of the Stellarex 035 DCB for treatment of ISR lesions and the rates and types of adverse events are consistent with other available treatments for this patient population. 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.

XIII. CDRH DECISION

CDRH issued an approval order on March 25, 2022.

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

XIV. 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.

XV. REFERENCES

1. Rocha-Singh KJ, et al. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheterization and Cardiovascular Interventions 2007; 69(6):910-919.