Spectranetics Stellarex 035 DCB Advisory Panel Briefing Package

Executive Summary

This briefing package for the June 19-20, 2019 FDA Circulatory System Devices advisory panel meeting on Paclitaxel (PTX) coated devices for the treatment of peripheral arterial disease describes the Stellarex Drug-Coated Balloon (DCB) product from Spectranetics (now part of the Image Guided Therapy business within Philips). In addition to a description of the Stellarex device, an integrated analysis of all the available clinical data was conducted to evaluate the Stellarex DCB given the recent information about the possible connection between the use of PTX coated devices and increased patient deaths during long-term clinical follow-up. The package is organized as follows:

- Summary of the development history of PTX-coated devices for the treatment of peripheral artery disease and current state of the clinical evidence for DCBs in clinical practice
- Description of the technical characteristics of the Stellarex product
- Detailed description of the Stellarex Clinical Data
- Proposed next steps and conclusions.

The data provided herein provides a comprehensive review of the Stellarex product and the compelling clinical data supporting its safe and effective use in femoropopliteal arteries.

History

Key Points

- ***PTX is the only drug currently used in DCB or DES for femoropopliteal disease.***
- ***The paclitaxel drug dose density, excipient and paclitaxel physical state vary between the currently approved products in the USA.***

The treatment of coronary artery lesions via the use of paclitaxel or -olimus drug-eluting stents (DES) revolutionized the interventional cardiology space in the early 2000s, supported by large-scale randomized trials confirming their superiority over bare metal stents (BMS) and their precursor of percutaneous transluminal coronary angioplasty (PTCA). These outcomes established DES as the standard of care in interventional cardiology.

Based on the remarkable advances in the coronary space, similar drug-eluting technologies have been the subject of research, and subsequent regulatory approval and commercialization, for use in the treatment of Peripheral Artery Disease (PAD). The long-term success of any treatment modality in the femoropopliteal segment is particularly challenging because of the extensive plaque burden and characteristically long segments of stenosis. Complex mechanical forces such

as elongation, compression, torsion, and flexion result in significant stress on any permanent implants. In addition, the time course of femoropopliteal restenosis is more delayed than coronary restenosis. Thus, the drug dosing strategy for a successful peripheral therapy needs to be similar but different from that in the coronary arteries.

Similar to the coronary vasculature, the modality of treatment in the femoral-popliteal artery bed has evolved over time. Randomized trials demonstrated a benefit of BMS when compared to percutaneous transluminal angioplasty (PTA)[1]. However, the risk of stent fracture and significant restenosis due to the unique mechanical forces was shown to be a concern. As an evolution beyond BMS, the development of DES and DCB progressed for the treatment of PAD, with PTX the exclusive drug of choice to-date for all FDA-approved devices.

The PTX mechanism of action for DES and DCB products is the same: inhibition of migration and proliferation of smooth muscle cells to minimize restenosis, while not affecting vascular healing via migration of endothelial cells. The effect of PTX is cytostatic, rather than cytotoxic as is the use of PTX in chemotherapy. [2, 3] Since PTX is lipophilic, following contact with the vessel wall, its activity is dependent on solubilization and transport into the arterial tissue.

Within the peripheral DES space, the delivery and availability of paclitaxel is very different between the two approved devices. For the Cook Medical Zilver PTX, local delivery of a 3.0 $\mu g/mm^2$ drug dose density is achieved without a polymeric matrix, while there is sustained delivery of a 0.167 $\mu g/mm^2$ drug dose density from a polymer matrix for the Boston Scientific ELUVIA. The differences in the local availability of these differing drug doses are evident in their arterial tissue pharmacokinetic profiles over time.[4]

Similar to DES, the amount and availability of paclitaxel differs across the various DCB technologies (FDA approved DCBs: Medtronic IN.PACT Admiral: 3.5 $\mu g/mm^2$, Bard Lutonix: 2.0 $\mu g/mm^2$, Spectranetics Stellarex: 2.0 $\mu g/mm^2$). The excipients present in the coating (Medtronic: urea, Bard: sorbitol, Spectranetics: poly-(ethylene glycol)) facilitate the solubilization of PTX, in order to allow for the biological effect. While all DCB technologies incorporate PTX, the physical state of PTX may vary on the overall spectrum bookended by the two extremes of either fully amorphous or crystalline. These modifications may lead to differing acute PTX transfer

[1] Dake MD, Ansel GM, Jaff MR, et al. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions. J Am Coll Cardiol 2013; 61:2417–27.

[2] Axel DI, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997; 96(2):636-645.

[3] Sollott SJ, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. J Clin Invest 1995; 95(4):1869-1876.

[4] Granada, JF The Science Behind Local Drug-Delivery Technologies: The Benefit of Sustained Paclitaxel Release in the SFA. Supplement to Endovascular Today Europe 2016; 4(6):7-8.

efficiencies from the balloon to the diseased arterial wall, as well as differences in the duration of local PTX tissue exposure. Research suggests an amorphous coating does not stay resident in the vessel at therapeutic levels as long as crystalline paclitaxel morphology, due to the slow dissolution of crystalline paclitaxel into the tissue for sustained release over time.[5]

Summary

While there are many similarities between the various DCB and DES products currently approved for use in treating atherosclerosis of the femoropopliteal artery, there are important distinctions between the products as well. Based on the key design, chemical, and physical differences of these products, it is problematic to evaluate the pooled effect of these products, since there are many uncontrolled variables.

Current state of clinical evidence on safety of DCB clinical practice

Key Points

- ***The 2018 Katsanos et al meta-analysis identified a potential increase in the risk of late mortality when PTX-coated devices are used in the treatment of PAD.***
- ***There is a substantial amount of evidence in the medical literature, which do not identify the increased risk of death raised in the meta-analysis.***

Introduction

A comprehensive literature search was conducted in PubMed, EMBASE, and other databases; including public releases at congresses of eligible randomized controlled trials (RCT's) and meta-analyses to identify relevant datasets pertaining to the use of DCB in PAD. Literature was reviewed for all-cause mortality. Following this review, 17 RCT studies, and 16 systematic reviews and meta-analyses were identified for further study.

Level 1 Oxford Centre for Evidence-Based Medicine (OCEBM) Evidence Review

Of the applicable above the knee (ATK) RCTs identified, 17 of these studies reported all-cause mortality, with follow-up periods ranging from 6 months to 5 years. Twelve (71%) of these studies found no significant differences in mortality for DCB compared with the control group. Three studies were unequivocal in their conclusion. Two RCT's demonstrated a long-term increased risk associated with DCB treatment when compared to control (uncoated PTA).

[5] Granada JF. Future directions, clinical applications and local drug delivery technologies. Presented at the Transcatheter Cardiovascular Therapeutics (TCT) 25th annual scientific symposium; October 27–November 1, 2013; San Francisco, California.

Of the 16 identified systematic reviews and meta-analyses, 15/16 (94%) demonstrated no increased risk of long-term mortality. The one outlier was the Katsanos et al study.[6] The 5 DCB systematic reviews and meta-analyses published in 2019 further demonstrated no significant differences in all-cause mortality risk in the treatment arm compared with uncoated PTA. Included is a large real world, retrospective cohort study of 16,560 patients from the US Medicare database which evaluated patients treated with PTX-coated devices. [7] No other available systematic review or meta-analysis to date has demonstrated or substantiated the significantly increased long-term risk of all-cause death associated with DCB use represented by Katsanos et al.

Summary

The 2018 Katsanos et al meta-analysis identified a potential increased risk of late mortality when PTX coated devices are used in the treatment of PAD. However, a comprehensive literature search, including RCT's and meta-analyses, does not show the same concern. An overwhelming number of Level 1 evidence demonstrated no statistical differences in all-cause mortality between patients treated with DCB for PAD compared with control (uncoated PTA).

Technical Summary of Stellarex

Key Points

- ***Stellarex is coated with a 2.0 µg/mm^2 mixture of amorphous plus crystalline PTX.***
- ***Poly-(ethylene glycol) (PEG) is utilized as an excipient for the Stellarex product.***
- ***The coating was designed to optimize initial and sustained arterial PTX uptake.***
- ***Pre-clinical animal data show focal delivery of the PTX to the artery, with elimination of the drug within 30 days of delivery.***

The design of the Stellarex product includes a paclitaxel dose density of 2.0 µg/mm^2 within the excipient poly-(ethylene glycol) (PEG). The molecular weight of the PEG excipient and its functionality lends itself to the desired adhesion, flexibility and elasticity of the overall coating, helping to prevent premature drug loss during handling, tracking and inflation. The coating of the Stellarex product is a mixture of amorphous as well as crystalline paclitaxel. This hybrid formulation of amorphous plus crystalline PTX results in rapid initial drug uptake into the arterial wall as well as sustained availability, respectively. In addition, the formulation leads to limited PTX washout at the target lesion in the presence of calcium, due to PEG forming strong ionic bonds

[6] Katsanos K, et al. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2018; 7:e011245.

[7] Secemsky EA, et al. Association of Survival With Femoropopliteal Artery Revascularization With Drug-Coated Devices. JAMA Cardiol. 2019; 4(4):332-340.

with hydroxyl apatite, the primary component of calcified atherosclerotic lesions.[8] As discussed earlier, the dose, form of PTX, and excipient is different for each approved product.

Stellarex is available in a variety of balloon sizes to meet the needs of the clinical scenario:

Table 1: Stellarex 035 DCB Commercially Available Balloon Sizes

Lengths (mm)		40	60	80	100	120
Diameters (mm)	4	4x40	4x60	4x80	4x100	4x120
	5	5x40	5x60	5x80	5x100	5x120
	6	6x40	6x60	6x80	6x100	6x120

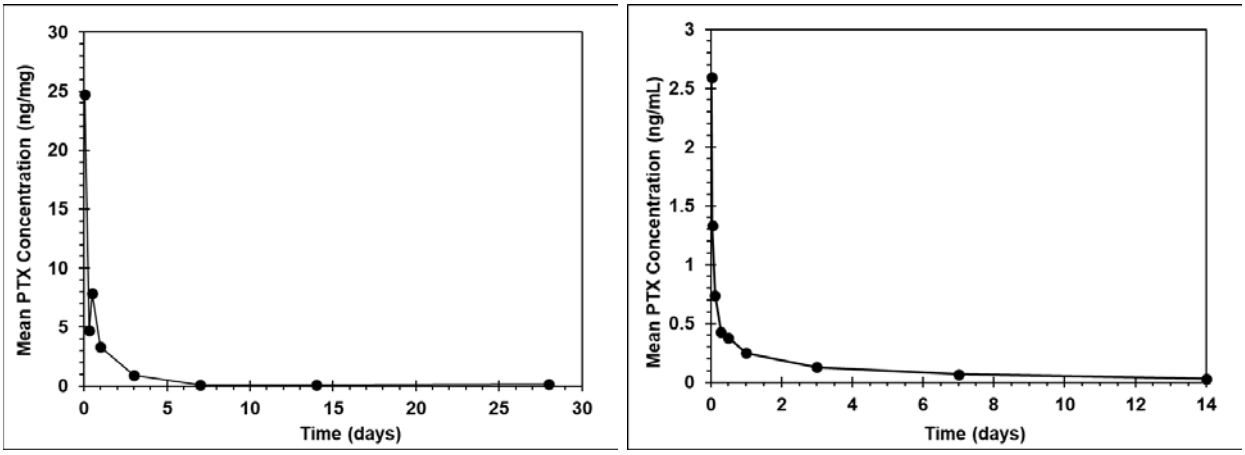
As part of Stellarex product development, device functional testing, biocompatibility evaluations, plus coating characterization studies were completed in order to demonstrate that the product met its design objectives throughout its shelf life. Additionally, animal testing was completed in a porcine iliofemoral artery model to evaluate the safety and bioanalytical efficacy of the Stellarex DCB. Finally, in order to confirm the identity, potency, and purity of finished drug product, a series of tests are performed following the manufacture of every lot of Stellarex product.

The completed animal test results demonstrate the controlled delivery of PTX to the artery wall, with a limited duration of exposure. The limited duration of exposure is of particular interest, as much of the discussions in the scientific community in response to the Katsanos et al meta-analysis have been to consider the potential for a late toxic effect of PTX. As shown in **Figure 1** below for GLP study 2049-004 (on file at Spectranetics), an initial bolus of drug is provided to the artery wall, with a declining concentration profile over the first week and progressing to unmeasurable levels after the first month. Systemic exposure to PTX, as measured in plasma, is limited to the first few days after delivery. Similarly, downstream organ tissues exhibited PTX concentrations orders of magnitude lower than the treated arterial tissue, with durations of exposure comparable to plasma. Across four pharmacokinetic studies and five safety studies, there were no abnormal findings based on clinical pathology, gross necropsy, pathology, or histology assessments for single or multiple DCB inflations per limb in the porcine model.

[8] Venkatasubbu GD, et al. Surface modification and paclitaxel drug delivery of folic acid modified polyethylene glycol functionalized hydroxyapatite nanoparticles. Powder Technology. 2013; 235:437-442.

Figure 1: Animal Study Paclitaxel Concentration Profiles

Porcine Iliofemoral Arterial Tissue **Porcine Plasma (Two 6x40mm DCBs)**



Summary

Based on these findings, the Stellarex product has been well characterized through development and as part of routine production. Animal study results demonstrate the highly localized delivery of PTX to the desired arterial treatment site, with limited systemic exposure. As well, the duration of exposure to PTX is limited to two weeks in plasma and 30 days in arterial tissue.

Stellarex Clinical Data

Key Points

- ***The Stellarex clinical program includes 2 RCTs, which independently and when pooled, show very similar mortality rates in just under 600 patients through 3 years of completed follow-up.***
- ***Analyses across all available Stellarex clinical data demonstrate no indication of a greater propensity for mortality compared to PTA control.***

Overview of the Stellarex ILLUMENATE Clinical Program

The ILLUMENATE clinical program was designed to evaluate the safety and effectiveness of the Stellarex product for use in PAD. There are currently 7 clinical studies in the ILLUMENATE Clinical Program evaluating the Stellarex product in the treatment of femoral and popliteal, or ATK, arteries, listed in **Table 2**. The efficacy parameters include target lesion revascularization in each study. As well, the safety parameters of each study included freedom from device and/or procedure related death, target limb major amputation, or clinically driven target lesion revascularization through a defined follow-up period.

Table 2: Overview of Stellarex ILLUMENATE Femoropopliteal Clinical Program

Study	Study Design	NCT # clinicaltrials.gov	Study Start	Follow Up Period	Patients Planned	(# of sites) Geography	Status
ILLUMENATE FIH	Single-arm	NCT02110524	Dec 2011	24 months	80	(3) Europe	**Completed**
ILLUMENATE EU RCT	RCT	NCT01858363	Nov 2012	60 months	328 (3:1 randomization)	(18) Europe	**Follow-up (3yr complete)**
ILLUMENATE Pivotal	RCT	NCT01858428	June 2013	60 months	300 (2:1 randomization)	(43) USA, Europe	**Follow-up (3 yr complete)**
ILLUMENATE PK	Single-arm	NCT01912937	June 2013	24 months	25	(2) New Zealand	**Completed**
ILLUMENATE Global	Single-arm	NCT01927068	July 2013	60 months	371	(37) Europe, New Zealand, Australia	**Follow-up (3 Year complete)**
ILLUMENATE ISR	Single-arm	NCT01927068	July 2013	36 months	130	(25) Europe, New Zealand, Australia	**Follow-up**
SAVER Registry	Single-arm	NCT02769273	June 2016	36 months	10000	(34) Europe	**Enrolling**

The two RCT studies, **ILLUMENATE EU RCT** and **ILLUMENATE Pivotal**, compare Stellarex DCB to PTA as the control in a 3:1 or 2:1 randomization ratio, respectively, and do not include any cross-over treatments. The trials were powered for efficacy and safety composites, but not for all-cause mortality.

To date, the Stellarex ATK clinical studies have successfully met their individual efficacy and/or safety objectives.

Methodology

This analysis examined the safety profile of the Stellarex product compared to PTA, analyzing patient-level data from the worldwide Stellarex clinical trials. The two RCTs, ILLUMENATE EU RCT and ILLUMENATE Pivotal, were pooled in a homogenous meta-analysis of a single therapeutic device to compare mortality through 3 years between Stellarex (N=419) and PTA control (N=170) cohorts. A separate integrated analysis of mortality rates in ATK lesion patients treated with Stellarex from all seven studies was also evaluated as supportive information to validate the safety conclusions in a larger sample (N=2523). For this patient level clinical study analysis, Spectranetics utilized an independent third party (Syntactx) to conduct a thorough assessment of mortality within the Stellarex ATK clinical program. The results were also confirmed/validated by a second independent biostatistics and data management group (NAMSA) to ensure accuracy of the methodology and the integrity of the data.

Quality of the Data

A two-stage method to pool the individual patient data was performed using Stata/IC (version 15.1, StataCorp LLC, College Station, TX, USA). The I^2 statistic, a percent calculation to assess the variation across studies used for pooling, was measured. The I^2 statistic was 0.0%, confirming homogeneity for the two Stellarex RCTs. The I^2 statistic was 47.3% when all 7 studies were included, suggesting a moderate level of homogeneity. After elimination of the ILLUMENATE PK study from the analysis, the I^2 statistic decreased to 38.6%, indicating homogeneity was improved.

All trials in the ILLUMENATE study program have been and are being conducted according to Good Clinical Practice (GCP). All trials have been approved by an independent institutional review board (IRB) or ethics committee (EC). All patients have provided written informed consent before being enrolled. Adverse events are reported by the site investigators, sites are monitored, and information was/is source verified for data accuracy, integrity and completeness. Adverse events occurring within the specified follow-up period are independently adjudicated by a blinded Clinical Events Committee, (CEC) comprised of varied specialists.

Overall, the follow-up compliance has been adequate wherein the number of LTFU (lost to follow up) patients was relatively low in both RCT's, as shown in **Table 3**.

Table 3: Overview of RCT Patient Disposition - Patient Withdrawal and Lost-to-Follow-up

ILLUMENATE EU RCT	**Randomized Cohort**		
36 Month (1095 Days ± 60 Days)	**DCB (N=222)**	**PTA (N=72)**	**Total[1] (N=294)**
Withdrawn	23 (10.4%)	13 (18.1%)	36 (12.2%)
Lost-to-follow-up	10 (4.5%)	1 (1.4%)	11 (3.7%)
ILLUMENATE Pivotal	**ITT Cohort**		
36 Month (1095 Days ± 60 Days)	**DCB (N=200)**	**PTA (N=100)**	**Total (N=300)**
Withdrawn	16 (8.0%)	5 (5.0%)	21 (7.0%)
Lost-to-follow-up	4 (2.0%)	3 (3.0%)	7 (2.3%)

[1]7 subjects were randomized to receive study treatment but were exited from the study due to not receiving a study device (DCB or PTA).

ILLUMENATE European (EU) Randomized Clinical Trial (RCT) Study Clinical Study Report: Tables, Listings, and Figures for PAS CSR and Month 36 Analyses. July 6, 2018

ILLUMENATE Pivotal Study Clinical Study Report: Tables, Listings, and Figures for PAS CSR and Month 36 Analyses. November 30, 2018

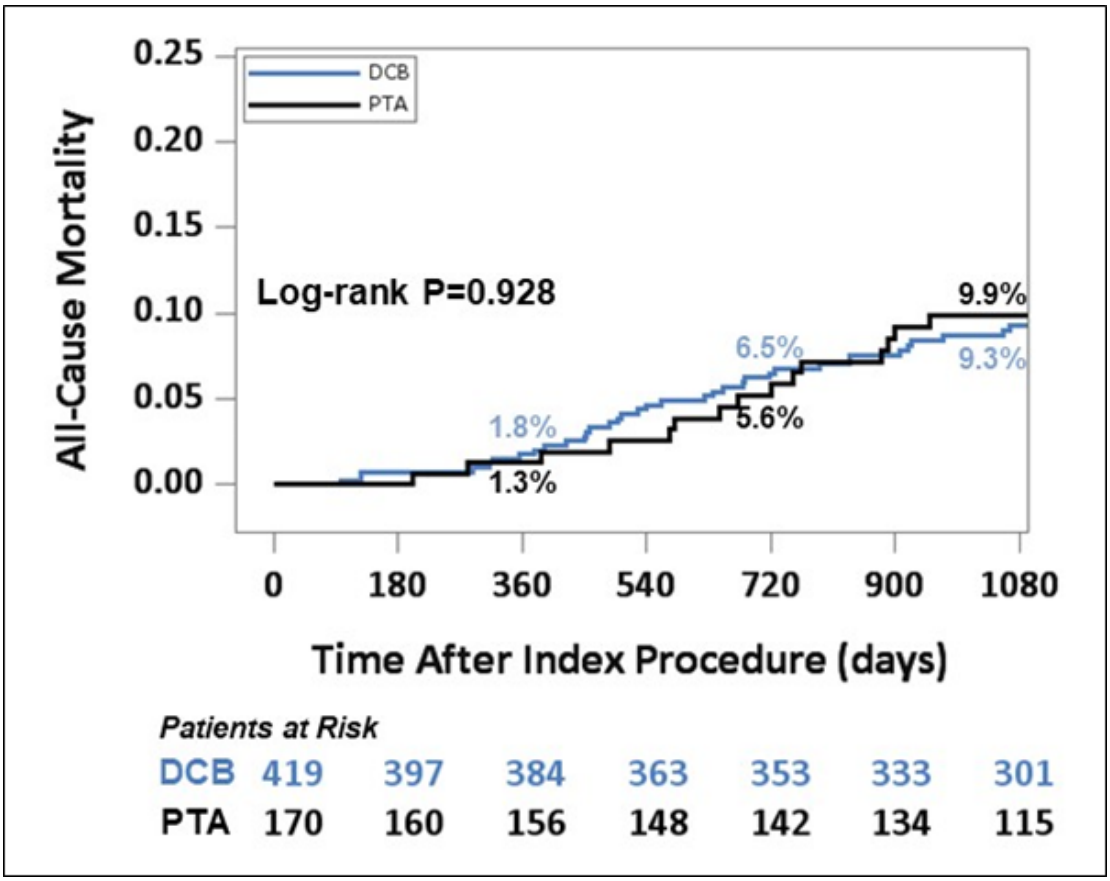
Results

Pooled Analysis of the 2 RCT's - ILLUMENATE EU-RCT and ILLUMENATE Pivotal

In comparing mortality after treatment with DCB versus PTA, data were aggregated from the 2 RCTs comprising 419 DCB and 170 PTA patients. Demographic and baseline characteristics were similar in the DCB and PTA arms of both studies, with two exceptions. Patients in the pooled DCB arm were slightly younger (67.4 ± 9.7 vs. 69.4 ± 9.4 years, DCB vs. PTA, P = 0.024) and were more often smokers (86.6% vs. 78.8%, DCB vs. PTA, P = 0.024). The median exposure of PTX in the DCB patients was 3.9 mg (interquartile range 2.6 mg to 6.5 mg).

In the 589 patients enrolled in the RCT trials, death occurred in 35/419 DCB patients (8.4%) and 15/170 PTA patients (8.8%) within 3 years of the index procedure. There was no significant difference in all-cause mortality between the two cohorts through the available follow-up period of 3 years (Figure 1, P=0.928, log-rank test). The 1-year (360-day) Kaplan-Meier estimate of all-cause mortality was 1.8% ± 0.7% (estimate ± standard error) in the DCB cohort and 1.3% ± 0.9% in the PTA cohort. At 2 years (720 days), all-cause mortality was 6.5% ± 1.3% in the DCB cohort versus 5.9% ± 1.9% in the PTA cohort. At 3 years (1080 days), all-cause mortality was 9.3% ± 1.5% in the DCB cohort and 9.9% ± 2.4% in the PTA cohort. These Kaplan-Meier estimates are presented graphically in **Figure 2**.

Figure 2: All-cause mortality in the pooled randomized clinical trials



Integrated Analysis of all ILLUMENATE Studies

In addition to the analysis of the pooled RCTs, an additional integrated analysis of all Stellarex clinical studies as described earlier, was also conducted. As there were no deaths reported in the ILLUMENATE PK study, it could be considered an outlier, and an integrated analysis without this study was completed.

While not included in the integrated analysis, it is noted that the ILLUMENATE PK trial of 25 patients evaluated the pharmacokinetics of paclitaxel in the bloodstream following clinical use of the Stellarex product. PTX clearance was evaluated, with all patients having detectable levels of drug immediately after the last DCB deployment followed by biphasic clearance. Measured levels were rapidly declining in the first hour, while paclitaxel concentrations after 24 hours were below the lower limit of quantification (<0.100 ng/mL) in 96% (24/25) patients.

Excluding the ILLUMENATE PK study, the integrated analysis rather focused on patient level data from the remaining six studies including both RCTs, the 3 single-arm studies, and the 1 registry. Combining these studies provided 2495 patients with 2325 of those treated with Stellarex and 170 with PTA control. In the cohort of 2325 DCB-treated patients, 80 deaths (3.4%) occurred through 3 years. The 1-, 2-, and 3-year estimates of all-cause mortality are shown in **Table 4**.

Table 4: All-Cause Mortality Rates: Pooling 6 Studies (Excludes ILLUMENATE PK)

All-Cause Mortality	Pooled RCTs		P Value	All Studies
	DCB KM Estimate n=419	PTA KM Estimate n=170		DCB KM Estimate n=2325
			0.928	
1-year	1.8%	1.3%		2.0%
2-year	6.5%	5.6%		5.6%
3-year	9.3%	9.9%		8.0%
Syntactx, (New York, New York) independent analysis of Stellarex ATK Clinical Program (2019)				

A breakdown of mortality into cardiovascular-related and non-cardiovascular is also provided in **Table 5**, including patients from the ILLUMENATE PK study.

Table 5: Cardiovascular and Non-Cardiovascular Mortality Rates: Pooling all 7 Studies (Includes ILLUMENATE PK)

Mortality	Pooled RCTs		P Value	Pooled Studies
	DCB KM Estimate n=419	PTA KM Estimate n=170		DCB KM Estimate n=2351
Cardiovascular			0.33	
1-year	0.5%	0%		0.1%
2-year	1.0%	1.4%		1.3%
3-year	1.9%	2.8%		1.9%
Non-Cardiovascular			0.67	
1-year	1.3%	1.3%		1.5%
2-year	5.6%	4.6%		4.2%
3-year	7.5%	7.3%		6.1%
Presented at LINC 2019				

Adjudicated Causes of Death

The causes of death are summarized in **Table 6**, as categorized by MedDRA SOC. The CEC-adjudicated cause of death through 3 years was cardiovascular in nature in 19 patients (24%) and non-cardiovascular in nature in 61 patients (76%). Among the non-cardiovascular-related deaths in the DCB patients, 17 (21%) were of undetermined cause at the time of this analysis. Of the 15 deaths in the PTA cohort, the adjudicated cause of death was cardiovascular in 4 (27%) patients and non-cardiovascular in the remaining 11 (73%) patients. The higher proportion of deaths of undetermined cause in the non-randomized DCB cohort was due to yet undetermined causes of death in the ongoing SAVER registry.

The most common CEC-adjudicated cause of death in the integrated analysis of all 6 studies after DCB treatment was a cardiac disorder, responsible for 19/80 deaths (23.8%), followed by neoplasms (18/80 deaths, 22.5%). In the RCT cohort for the pooled RCT's, neoplasms were the most common cause of death (12/35, 34.3%), followed by cardiac disorders (8/35, 22.9%), while in the PTA cohort, general disorders were the most common cause of death (5/15, 33.3%), followed by cardiac disorders (4/15, 26.7%) and neoplasms (2/15, 13.3%). While there is a difference in mortality from neoplasm between the two groups, it is unknown if these were pre-existing at baseline. Therefore, no definitive rationale can be described for the variance between the groups. There were no device or procedure-related deaths in the entire series of 2523 patents.

Table 6: Causes of death in patients treated with paclitaxel-coated balloons as adjudicated by the Clinical Events Committee (MedDRA System-Organ Classes).

Cause of Death	All Studies*	Non-RCTs*	Pooled RCTs	
	DCB N=2325	DCB N=1906	DCB N=419	PTA N=170
Cardiac disorders	19/80 (24%)	11/45 (24%)	8/35 (23%)	4/15 (27%)
Gastrointestinal disorders	1/80 (1%)	0/45 (0%)	1/35 (3%)	1/15 (7%)
General disorders	8/80 (10%)	5/45 (11%)	3/35 (9%)	5/15 (33%)
Hepatobiliary disorders	1/80 (1%)	0/45 (0%)	1/35 (3%)	1/15 (7%)
Infections and infestations	5/80 (6%)	2/45 (4%)	3/35 (9%)	0/15 (0%)
Injury/poisoning/procedural	1/80 (1%)	0/45 (0%)	1/35 (3%)	0/15 (0%)
Metabolism and nutritional	1/80 (1%)	0/45 (0%)	1/35 (3%)	0/15 (0%)
Neoplasms benign, malignant	18/80 (23%)	6/45 (13%)	12/35 (34%)	2/15 (13%)
Nervous system disorders	1/80 (1%)	1/45 (2%)	0/35 (0%)	0/15 (0%)
Renal and urinary disorders	0/80 (0%)	0/45 (0%)	0/35 (0%)	1/15 (7%)
Respiratory/thoracic/mediastinal	7/80 (9%)	3/45 (7%)	4/35 (11%)	1/15 (7%)
Vascular disorders	1/80 (1%)	0/45 (0%)	1/35 (3%)	0/15 (0%)
Undetermined	17/80 (21%)	17/45 (38%)	0/35 (0%)	0/15 (0%)
Total deaths through 3 years	80/2325 (3.4%)	45/1906 (2.4%)	35/419 (8.4%)	15/170 (8.8%)

* Data comprises pooled datasets. There were no deaths in the 28 patients excluded from the pooled analysis. Syntactx, (New York, New York) independent analysis of Stellarex ATK Clinical Program (2019)

Predictors of death were assessed using hazard ratios (HR) and Cox proportional hazards modeling, shown in **Table 7**. The analysis identified age (HR 1.06, 95% confidence interval (CI): 1.04-1.08, P<0.001), diabetes (HR 1.42, 95% CI: 1.01-2.00, P=0.043), congestive heart failure (HR 1.88, 95% CI: 1.12-3.16, P=0.017), and renal insufficiency (HR 2.00, 95% CI: 1.33-3.01, P<0.001) to be the predictors of mortality using this methodology. Exposure to PTX was concluded as not being a predictor of mortality.

Table 7: Multivariable Cox Proportional Hazards Model for Mortality

Covariate	Coefficient	St Error	Hazard Ratio (95% CI)	P Value
Without Forcing Drug Dose into the Model				
Age (per year)	0.06015	0.00980	1.062 (1.042, 1.083)	<0.001
Congestive Heart Failure	0.61897	0.26493	1.857 (1.105, 3.121)	0.020
Diabetes	0.35554	0.17446	1.427 (1.014, 2.009)	0.042
Renal Insufficiency	0.69192	0.20886	1.998 (1.327, 3.008)	0.001
With Drug Dose Forced into the Model				
Age (per year)	0.06058	0.00985	1.062 (1.042, 1.083)	<0.001
Congestive Heart Failure	0.63782	0.26578	1.892 (1.124, 3.186)	0.016
Diabetes	0.36778	0.17481	1.445 (1.025, 2.035)	0.035
Renal Insufficiency	0.70674	0.20933	2.027 (1.345, 3.056)	<0.001
Paclitaxel Dose (per mg)	0.03442	0.02877	1.035 (0.978, 1.095)	0.232
Syntactx, (New York, NY) independent analysis of Stellarex ATK Clinical Program (2019)				

Clinical Conclusions

This analysis of patient-level data from the 2 randomized controlled trials of the Stellarex product shows that there is no statistically significant difference in mortality at 1, 2 and 3 years between the Stellarex treatment groups and the PTA control groups. In an integrated analysis of 6 Stellarex studies, the results were consistent with that reported in the RCT analysis, showing no increase in patient mortality attributed to the Stellarex product. This larger sample size analysis provides validation of the mortality rate reported in the pooled RCT analysis. The clinical risk-benefit analysis for the use of Stellarex product in the treatment of atherosclerosis of the femoropopliteal segment is not changed by this data analysis when compared to the original risk-benefit analysis leading to PMA approval.

There have been no reports of device-related mortality in any of the Stellarex studies, all of which had independent third party CEC's. The 2 RCT's also had independent DSMB's (data safety monitoring boards) as did the ILLUMENATE Global, ILLUMENATE ISR and the ILLUMENATE PK studies.

This data analysis from the Stellarex ATK clinical trials further establishes the safety profile of the Stellarex product, with no greater propensity for patient mortality indicated.

Proposed Next Steps

Spectranetics proposes the following next steps be considered by the advisory panel:

1. **Guideline Enhancement:** Review and update as needed to clarify the appropriate follow-up for PAD patients to optimally manage the overall complexity and range of co-morbidities found in this patient population.
2. **Strengthen Future PAD studies:** Ensure consistent follow-up and visit compliance in both control and treatment arms, as appropriate. Ensure detailed reporting of contralateral limb revascularization and pharma regimen used. Provide additional guardrails to minimize loss to follow-up, in particular for mortality outcomes (e.g., update informed consent language to allow withdrawal from study procedures but continued visibility to vital status).
3. **Interrogation of Existing Large datasets:** As an achievable goal, we support an industry-wide partnership with key stakeholders (physician societies, FDA, etc.) to further interrogate existing, large, observational datasets (e.g., CMS data) to confirm lack of a mortality signal over an extended period (through 5 years).

Overall Conclusions

1. **All Paclitaxel-coated devices for PAD are different:** In response to the Katsanos et al meta-analysis, Spectranetics conducted a complete review of the Stellarex product and clinical program results. In reviewing this history of paclitaxel-coated devices, the observation was made that all of the approved devices in the USA are different in the dose and form of paclitaxel, and in carrier excipient.
2. **Paclitaxel for the Stellarex product is not observed beyond 30 days:** Preclinical and clinical pharmacokinetic studies of the Stellarex product show that paclitaxel levels are no longer measurable after 30 days in target arterial tissue, while clearance from the bloodstream leads to non-measureable systemic levels in less than 30 days.
3. **No mortality signal through 3 years:** Multiple analyses of the Stellarex clinical data, across 2 RCTs and 5 single-arm trials, consistently show equivalent mortality rates, with no indication of a signal towards an increased risk of mortality. The mortality rates are balanced between DCB treatment and uncoated PTA control in the RCTs, and mortality rates are consistent to the RCTs in the integrated analysis of all 7 Stellarex trials in over 2300 patients.