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The ILLUMENATE SFA Clinical Program

Data on the Stellarex DCB for treatment of femoropopliteal arterial disease.

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Drug-coated balloons (DCBs) are becoming a more widely accepted and preferred first-line therapy for the treatment of peripheral artery disease. As such, there is a continued effort and investment by industry to evolve and improve on the efficacy of DCBs through optimization of the coating characteristics. Modern DCB goals are to maximize drug transfer to the target lesion while minimizing systemic drug loss. Due to differences in coatings and drug transfer capabilities, robust clinical evidence is required for each DCB; clinical data from one DCB cannot be generalized to another. The Stellarex DCB (Spectranetics Corporation) is the newest DCB on the market in the United States. The novel coating consists of paclitaxel and polyethylene glycol (PEG).

The ILLUMENATE SFA clinical program was designed to evaluate the safety and performance of the Stellarex DCB and includes five studies with more than 1,200 patients (Figure 1). All studies are being conducted with robust controls including angiographic and duplex ultrasound core laboratory oversight, clinical events committee adjudication, and 100% monitoring of source data to confirm accuracy of the databases. Importantly, this program includes two separately conducted randomized controlled trials, the ILLUMENATE European randomized clinical trial (EU RCT) and the ILLUMENATE Pivotal trial.

ILLUMENATE EU RCT

ILLUMENATE EU RCT was the first randomized study of the Stellarex DCB following the promising early results of the ILLUMENATE first-in-human study.[1] Recently, 12-month results from the ILLUMENATE EU RCT study were published in *Circulation*.[2] In total, 294 patients were randomized to treatment with the Stellarex DCB (n = 222 patients, 254 lesions) or percutaneous transluminal angioplasty (PTA) (n = 72 patients, 79 lesions). Key baseline data can be found in Table 1.

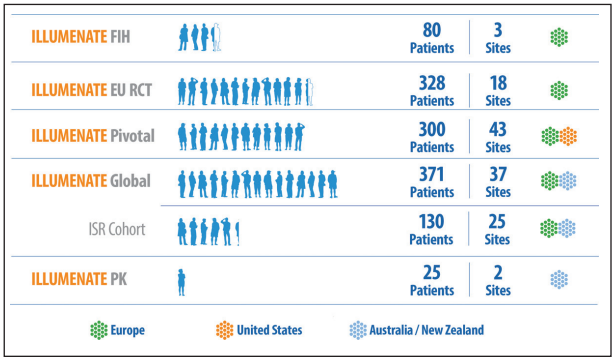

Figure 1. The ILLUMENATE clinical SFA program.

The primary safety endpoint was a composite of freedom from device- and procedure-related death through 30 days postprocedure and freedom from major target limb amputation and clinically driven target lesion revascularization (CD-TLR) through 12 months postprocedure. The primary safety endpoint was met and superiority was demonstrated; freedom from a primary safety event was 94.1% (193/205) with DCB and 83.3% (50/60) with PTA, for a difference of 10.8% (95% confidence interval, 0.9%–23%). The primary effectiveness endpoint was primary patency at 12 months, which was met. Superiority of Stellarex over PTA was achieved (83.9% [188/224] vs 60.6% [40/66]; $P < 0.001$). The primary patency rate per Kaplan-Meier esti-

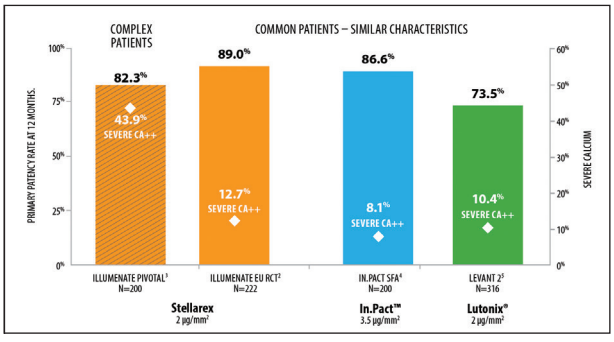

Figure 2. Twelve-month patency rates across similarly designed and conducted RCTs.*

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TABLE 1. ILLUMENATE EU RCT KEY BASELINE CHARACTERISTICS

Lesion (Per Core Lab)	Stellarex n = 254 Lesions	PTA n = 79 Lesions	*P* Value
Lesion length (cm)	7.2 ± 5.2 (250)	7.1 ± 5.3 (79)	0.878
Total occlusions	19.2 (48/250)	19 (15/79)	0.967
Severe calcification	12.7 (32/251)	10.1 (8/79)	0.533
Baseline diameter stenosis	78.7 ± 16 (250)	80.8 ± 15.7 (79)	0.297
Demographics	**Stellarex n = 222 Patients**	**PTA n = 72 Patients**	***P* Value**
Age (y)	66.8 ± 9.2 (222)	69 ± 8.6 (72)	0.079
Male	72.1 (160/222)	68.1 (49/72)	0.514
Rutherford clinical category ≥ 3	84.6 (187/221)	78.9 (56/71)	0.260
Diabetes	37.4 (83/222)	36.1 (26/72)	0.846
Previous or current smoker	89.2 (198/222)	83.3 (60/72)	0.188

Values are mean ± SD or % (n/N).

mate at day 365 was 89% for Stellarex versus 65% for PTA (log rank, $P < 0.001$), the highest published 1-year primary patency rate in any DCB RCT (Figure 2). As expected, the higher patency rate resulted in CD-TLR rates that were significantly lower in the Stellarex cohort (5.9% vs 16.7%; $P = 0.014$). At 12 months, a similar percentage of patients in both the DCB and PTA cohorts had improvements in ankle-brachial index (83.9% and 76.8%), Rutherford classification (89.2% and 86.2%), and walking distance (77.1% and 72.1%). Importantly, these similar outcomes were achieved with a significantly lower rate of CD-TLR in the DCB cohort. This has potential implications from both a cost-effectiveness and quality-of-life perspective.

Recently, the 24-month outcomes were reported and the significant treatment effect was sustained out to 2 years with no indication of late catch-up.[6] Patients treated with the Stellarex DCB maintained a significantly higher primary patency rate of 75.2% versus 61.2% (log-rank *P* value, 0.004) per Kaplan-Meier estimate at day 730. The exact patency rates, calculated as the ratio of event-free patients divided by evaluable patients, through the full 2-year follow-up window of 790 days was 75.9% (145/191) versus 61% (36/59) ($P = 0.025$). Similarly, the rate of CD-TLRs was significantly lower in the Stellarex group (12.1% vs 30.5%; $P < 0.001$) (Figure 3). These long-term results of the ILLUMENATE EU RCT trial validate the initial findings from the ILLUMENATE first-in-human study that demonstrated primary patency rates of 89.5% at 12 months and 80.3% at 24 months.[1]

ILLUMENATE PIVOTAL

The ILLUMENATE Pivotal study is an investigational device exemption study being conducted in the United States and supported approval of Stellarex DCB by the US Food and Drug Administration.[7] This study randomized 300 patients to treatment with Stellarex (n = 200) or standard PTA (n = 100). The primary safety endpoint was freedom from device- and procedure-related death through 30 days, as well as freedom from major target limb amputation and CD-TLR through 12 months. The primary effectiveness endpoint was primary patency through 12 months.

The two cohorts were well matched and included a high rate of diabetic patients (50%), women (41%), and

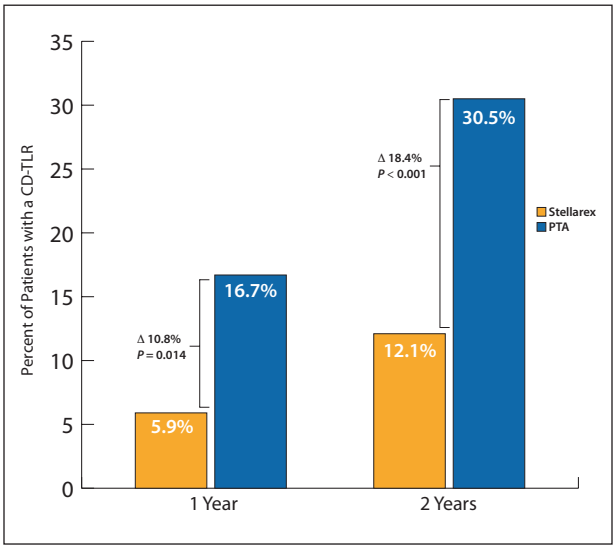

Figure 3. Rates of CD-TLR at 1 and 2 years in the ILLUMENATE EU RCT trial. A significantly lower rate of CD-TLRs was observed in the Stellarex group out to 2 years, with the treatment effect increasing from 1 to 2 years.

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TABLE 2. ILLUMENATE PIVOTAL STUDY KEY BASELINE CHARACTERISTICS

Lesion (Per Core Lab)	**Stellarex n = 200 Lesions**	**PTA n = 100 Lesions**	***P* Value**
Lesion length (cm)	8 ± 4.5 (199)	8.9 ± 4.6 (100)	0.105
Total occlusions	19 (38/200)	18 (18/100)	0.834
Severe calcification	43.9 (87/198)	43 (43/100)	0.877
Baseline diameter stenosis	73.9 ± 17 (200)	74.8 ± 17 (100)	0.673
Demographics	**Stellarex n = 200 Patients**	**PTA n = 100 Patients**	***P* Value**
Age (y)	68.3 ± 10.3 (200)	69.8 ± 9.8 (100)	0.225
Female	44 (88/200)	36 (36/100)	0.185
Rutherford clinical category ≥ 3	68.5 (137/200)	65 (65/100)	0.542
Diabetes	49.5 (99/200)	52 (52/100)	0.683
Previous or current smoker	84 (168/200)	75 (75/100)	0.061
Ankle-brachial index	0.75 ± 0.21 (193)	0.76 ± 0.2 (100)	0.508
Renal insufficiency	18 (36/200)	16 (16/100)	0.666
Body mass index ≥ 30 kg/m^2	39.5 (79/200)	30 (30/100)	0.107

Values are mean ± SD or % (n/N).

those with calcified lesions (43.9%); the mean lesion length was 8.3 cm (data by group in Table 2). This patient population presented with more comorbidities than the ILLUMENATE EU RCT cohort. When comparing the DCB cohorts from both trials, more pivotal patients were reported to have renal insufficiency (18% vs 9%), diabetes (50% vs 37%), previous coronary revascularization (45% vs 21%), and a body mass index ≥ 30 kg/m^2 (40% vs 26%).

The primary safety endpoint was met and superiority was achieved (92.1% vs 83.2%; superiority, $P = 0.246$). The primary effectiveness endpoint was also met and superiority was demonstrated (76.3% for DCB vs 57.6% for PTA; $P = 0.003$). Primary patency per the Kaplan-Meier estimate was significantly higher for Stellarex versus PTA (82.3% vs 70.9%; $P = 0.002$). Likewise, the rate of CD-TLR was significantly lower in the DCB cohort (7.9% vs 16.8%; $P = 0.023$).

Similar to what was observed in the ILLUMENATE EU RCT study, the improvements in clinical/functional assessments were comparable between cohorts, but this was achieved in the DCB cohort with half as many revascularizations. In total, 73% of patients in both cohorts had an improvement in walking distance as assessed by the 6-minute walk test at 12 months as compared to baseline, and the walking impairment question composite scores were improved in 78% of patients in both cohorts.

There has been a lot of discussion around the potential mechanisms that contributed to the success of the Stellarex DCB despite the high preponderance of female patients, diabetics, and patients with calcified lesions enrolled. We know several features such as drug dose, coating formulation (crystalline or amorphous), and type of excipient affect the pharmacokinetic profile and potentially have an impact on the amount of drug that is transferred to the wall of the artery.[8] The Stellarex DCB incorporates a low dose (2 µg/mm^2) of paclitaxel in a hybrid formulation made of both amorphous and crystalline paclitaxel molecules, combined with PEG (the excipient). The hybrid formulation likely helps maintain coating integrity (an attribute of the amorphous state) while allowing for sustained drug tissue release (due to the more crystalline molecules).[8] PEG is a polymer

with a high molecular weight, which means that it has some mechanical properties (eg, durability and adhesion) that allow the coating to maintain its integrity through typical balloon deformation such as flexion and elongation.[9] Additionally, PEG has been reported to have a high affinity to hydroxylapatite, which is a primary structural component in calcified atherosclerotic lesions.[10] The hybrid coating in combination with PEG's durability is a likely contributor to the drug transfer efficiency of the Stellarex DCB. The affinity of PEG to hydroxylapatite may maintain this transfer efficiency by limiting washout in the presence of calcified lesions; however, further studies are needed to evaluate the role of excipients in drug transfer efficiency in severely calcified lesions.

The results from this study were validated by the results of the ILLUMENATE Global study (n = 371, single-arm DCB), which reported an 81.4% primary patency rate at 12 months in a population that included complex lesions with 31.3% chronic total occlusions and 40.8% severe calcium.[11]

The ILLUMENATE series of studies are robust and are generating consistent and compelling data. The Stellarex DCB should be considered as a first-line treatment option for femoropopliteal lesions. ■

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*Studies shown are not head-to-head comparisons, and data presented cannot be directly compared. Calcium definitions may vary from study to study, and the rates presented herein are based on those used and reported in each respective study. "Complex patients" refers to high rates of severe calcium, diabetes, and renal insufficiency estimates. Primary patency is based on Kaplan-Meier estimate.

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