The Latest in DCB Evidence

ILLUMENATE Global confirms findings of ILLUMENATE FIH

BY PROF. THOMAS ZELLER, MD

The advent and growth of drug-eluting technologies have raised the bar and expectations for clinical evidence requirements. This is forcing all stakeholders, from manufacturers to health care providers and payers, to collaborate toward meaningful trials to fully appreciate and justify the "why," "when," and "at what cost" so that modern combination technologies may best fit into the treatment of peripheral artery disease. Although there are currently more than 10 drug-coated balloon (DCB) technologies available in Europe, only a few manufacturers are conducting clinical trials of various sizes and levels of rigor.

Pharmacokinetic (PK) and proof-of-concept studies represent the appropriate first step of any research plan, and well-designed randomized controlled trials should follow. These types of trials should be powered on an objective primary patency endpoint and accompanied by a comprehensive array of secondary endpoints including clinical and functional metrics. These trials should be followed by real-world and real practice evidence from large-scale registries. Finally, health economic evidence should be an integral part of these trials, with the important mandate to understand the affordability of these technologies within various health care environments and across different geographical regions.

In this context, the ILLUMENATE trial series (composed of ILLUMENATE first-in-human [FIH][1]; ILLUMENATE Pivotal[2]; ILLUMENATE PK[3]; ILLUMENATE EU-RCT[4]; and ILLUMENATE Global[5]) represents an exemplary case of a clinical program with breadth and quality. Each DCB brand should commit to this same breadth and quality in order to reveal the full potential, best indications, and major limitations within the wide peripheral artery disease clinical and anatomical spectrums.

The ILLUMENATE series was designed to evaluate the safety and performance of the Stellarex DCB (Spectranetics Corporation). The Stellarex DCB is a 0.035-inch guidewire-compatible angioplasty catheter coated with paclitaxel (2 µg/mm^2 balloon surface) and polyethylene glycol, an excipient that facilitates the transfer of the paclitaxel into the vessel wall.

ILLUMENATE FIH

ILLUMENATE FIH,[1] the first completed and published study from the ILLUMENATE series, is a multicenter, single-arm study characterized by high scientific rigor as typical of pivotal randomized trials. Independent imaging evaluation was provided by external angiographic and duplex ultrasound core laboratories, adjudication of clinical events by a clinical events committee (CEC), and full source data verification conducted by external monitors. Eighty patients were enrolled and treated with the Stellarex DCB for stenosis or occlusion of femoropopliteal arteries in patients with symptoms of claudication or rest pain (Rutherford categories 2–4).

ILLUMENATE FIH was the first DCB trial to offer insight on the role of predilatation. Two patient cohorts were subsequently enrolled: one with predilatation (n = 50) and one without predilatation (n = 30). Primary patency and freedom from target lesion revascularization (TLR) for 12 and 24 months are illustrated in Figures 1 and 2. Although the outcomes through 2 years were similar between the two groups, it's notable that the rates of postdilatation (35.1% vs 12.1%) and stent placement (8.1% vs 5.2%) were higher in the direct cohort as compared with the predilatation cohort. While predilatation may be optional in simple lesions, these findings suggest predilatation reduces the need for postdilatation and stenting. Predilatation

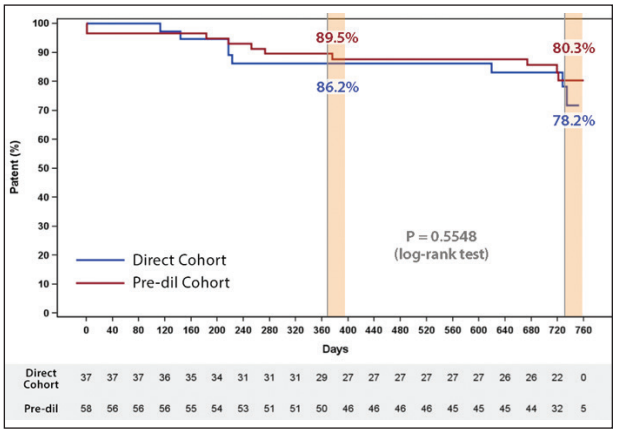

Figure 1. ILLUMENATE FIH outcomes: freedom from loss of primary patency through 24 months.[6]

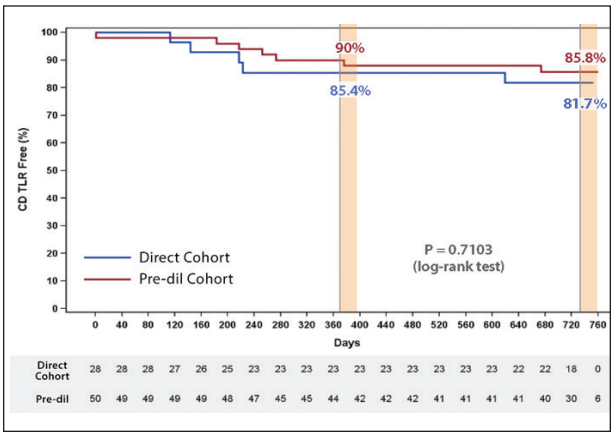

Figure 2. ILLUMENATE FIH outcomes: freedom from CD-TLR through 24 months.[6]

is still highly recommended in total occlusions and in the presence of calcification.

ILLUMENATE GLOBAL STUDY

Recently presented at the Charing Cross Symposium, interim results of the ILLUMENATE GLOBAL study add to the current evidence base of the Stellarex DCB and suggest consistency with the promising results in the ILLUMENATE FIH study.[1]

The ILLUMENATE Global study is a prospective, single-arm, multicenter study that enrolled 371 patients at 37 centers in Europe, Australia, and New Zealand. All subjects enrolled were treated with the Stellarex DCB and will be followed for up to 5 years. It is important to distinguish this single-arm study from other global registries. Unlike most global registries, this study is being conducted with the highest level of data collection rigor. The study includes an angiographic core laboratory (Beth Israel Deaconess Medical Center, Boston, MA), duplex ultrasound core laboratory (VasCore, Boston, MA), independent monitoring of all data, and oversight by a CEC and data safety monitoring board to ensure data are unbiased and accurate.

The primary safety endpoint is freedom from device and procedure-related death through 30 days postprocedure and freedom from target limb major amputation and clinically driven TLR (CD-TLR) through 12 months. The primary effectiveness endpoint is primary patency at 12 months. Primary patency is defined as the absence of restenosis per duplex ultrasound (peak systolic velocity ≤ 2.5) and freedom from CD-TLR.

Key inclusion criteria included the following: Rutherford category 2 to 4, target limb has at least one patent (< 50% stenosis) runoff vessel to the foot, and the patient has one or two target lesions with a cumulative length ≤ 20 cm. Key exclusion criteria included in-stent restenosis, severe calcification that precludes adequate percutaneous transluminal angioplasty treatment, and lesions that would require adjunctive therapies such as atherectomy catheters or scoring balloons. Follow-up assessments include a duplex ultrasound for patency assessment, functional outcome questionnaires (EQ-5D and Walking Impairment Questionnaire), an ankle-brachial index assessment, and adverse event evaluations.

The interim analysis included 153 patients with 174 lesions. Per angiographic core laboratory assessment, the mean lesion length was 7.3 cm, 25.6% were total occlusions, and 42.4% had severe calcification. Postdilatation was performed in 25.3% of lesions, and the provisional stent rate was 12.6%. The freedom from a composite primary safety event rate was 91% (Figure 3).

The primary patency rate, per core lab adjudication and Kaplan-Meier estimate, was 84.7% at day 365

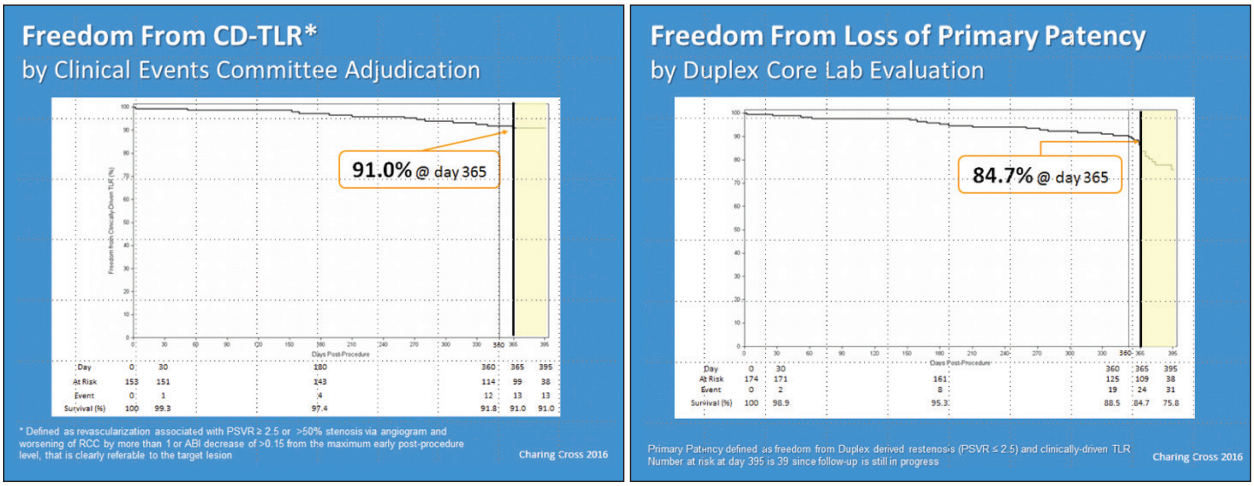

Figure 3. ILLUMENATE Global interim results released at the Charing Cross Symposium in London, UK.[7]

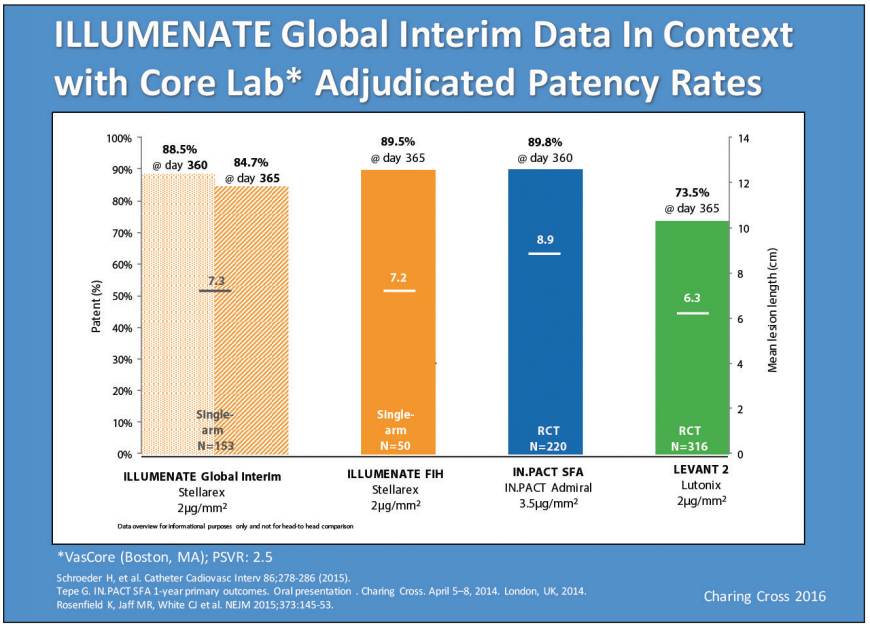

Figure 4. Core-lab adjudicated primary patency rates from DCB trials: the ILLUMENATE Global interim primary patency rate is consistent with the primary patency rate observed in the ILLUMENATE FIH study, which is comparable to the IN.PACT SFA study and favorable compared to the LEVANT 2 study.[7]

(Figure 3), which is in line with the 89.5% patency rate observed in ILLUMENATE FIH.[1] The freedom from CD-TLR rate, per CEC adjudication and Kaplan-Meier estimate, was 91% at day 365, also similar to the 90% rate observed in ILLUMENATE FIH.

While the data are still only interim, compared with other core laboratory-adjudicated patency data (Figure 4), 84.7% is favorable compared to the LEVANT 2 study[8] and comparable to the rate observed in the IN.PACT SFA study.[9,10]

The two randomized controlled trials, ILLUMENATE Pivotal and ILLUMENATE EU-RCT, are fully enrolled and currently in the follow-up phase. The data are highly anticipated and expected to be released later this year.

CONCLUSIONS

ILLUMENATE Global interim results suggest consistent outcomes with the final results observed in the ILLUMENATE FIH study and are comparable with the highest reported core lab–adjudicated DCB patency rates. Overall, the ILLUMENATE series of studies represents one of the broadest and highest-quality clinical evidence programs within the entire endovascular therapy landscape. Notably, the ILLUMENATE program includes two rigorously conducted randomized controlled trials with more than 600 patients, and results from these trials are expected to be released later this year. ■

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