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The Stellarex Difference: Critical Components of an Optimal DCB

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Since the first prototype of a paclitaxel drug-coated balloon (DCB) was developed, we have learned that DCB performance is built on a critical balance of multiple factors that include the right coating morphology, the right excipient, and an optimal drug dose. Following in-vitro and preclinical tests, performance must ultimately be demonstrated by rigorous, well-designed, and well-conducted clinical trials.

The Stellarex™ DCB (Spectranetics Corporation) carefully balances these critical factors and has been demonstrated as safe and effective in common to complex patients by the durable and consistent clinical results of the ILLUMENATE trials (Figure 1).[1-4]

THE ACTIVE DRUG PACLITAXEL

Paclitaxel is lipophilic and characterized by high fat affinity, meaning it is naturally captured by the fatty tissue constituents. It is also hydrophobic, meaning it does not bind with aqueous media such as blood.

Due to its lipophilic properties, paclitaxel is captured by tissue after exposure to or direct contact with the vessel wall. In order to apply its antirestenotic action, paclitaxel must be in an available form so that it binds to and stabilizes arterial smooth muscle cell microtubules. Animal studies suggest that following transfer, paclitaxel must stay resident in the vessel, acting as a drug reservoir, to exert action through the critical 30-day restenosis window.[5,6]

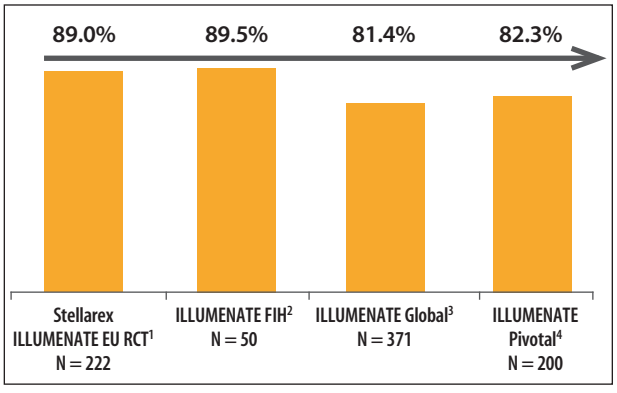

Figure 1. Consistent patency rates (based on Kaplan-Meier estimates) were observed across four separate studies with Stellarex at 12 months.

CRYSTALLINE VERSUS AMORPHOUS PACLITAXEL

There are different types of coating formulations and coating processes for a DCB; each brand of DCB has its own unique formulation and coating process. As a result, paclitaxel morphology on the balloon surface can range from amorphous to crystalline. Having an optimal mix of amorphous and crystalline paclitaxel along with the right excipient is necessary for an efficacious DCB.

Amorphous paclitaxel morphology is durable during tracking and it effectively transfers drug to the vessel wall. Research suggests an amorphous coating does not stay resident in the vessel at therapeutic levels as long as crystalline paclitaxel morphology.[7]

Crystalline paclitaxel morphology is more brittle than an amorphous morphology during tracking but also allows for effective drug transfer. Research indicates that it resides in the vessel at therapeutic levels out to the 30-day restenotic window. Research shows crystalline paclitaxel dissolves into the tissue slowly for sustained release over time.[7] Figure 2 demonstrates the different pharmacokinetic properties of the different paclitaxel morphologies. After being transferred to the vessel wall, crystalline paclitaxel may form "drug depots," which may help in sustained release (Figure 3).[8]

The Stellarex DCB has an optimal mix of amorphous and crystalline paclitaxel (Figure 4), merging the characteristics of both amorphous and crystalline paclitaxel morphologies. Research performed on animal studies

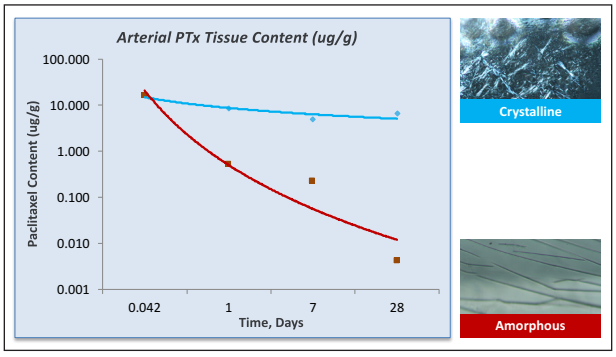

Figure 2. Pharmacokinetic properties by paclitaxel morphology. Porcine model data on file at Spectranetics (reference study).

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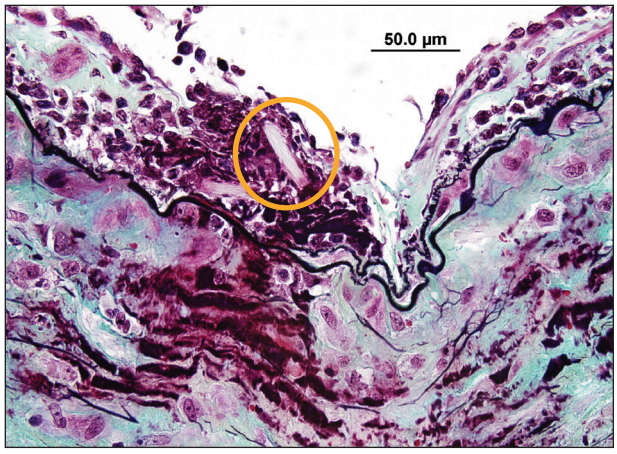

Figure 3. Histopathologic image of paclitaxel drug depot in a porcine model. Porcine model data on file at Spectranetics.

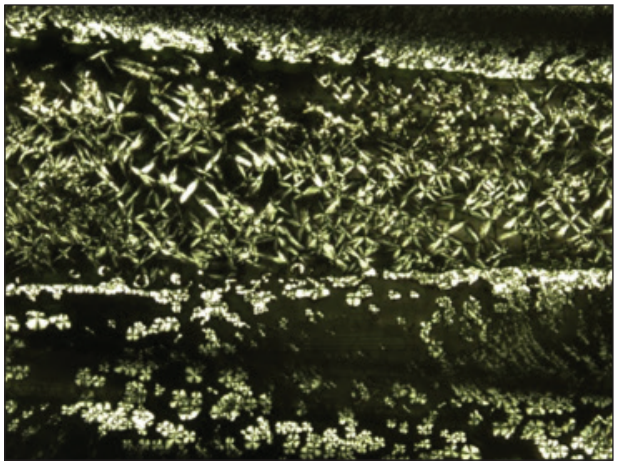

Figure 4. Stellarex EnduraCoat Technology under optical microscopy.

indicate that the Stellarex coating formulation creates a durable coating that helps prevent drug loss during handling and transit to the treatment site and provides uniform drug transfer with drug residency at a therapeutic dose throughout or passing the 30-day restenotic window.

THE EXCIPIENT

DCBs require paclitaxel to remain on the balloon surface during transit to the treatment site and be released when inflated and in contact with the vessel wall. An excipient is intended to help facilitate/maximize paclitaxel adherence to the balloon during transit and transfer from the balloon to the tissue once the balloon is inflated. The type and quantity of excipient are important design factors; this ensures that paclitaxel is not excessively and prematurely lost once in contact with the bloodstream before the balloon is inflated at the treatment site.

Stellarex uses polyethylene glycol (PEG) as the excipient. PEG is a hydrophilic polymer, meaning it has affinity for water. PEG has a large molecular weight of 8,000, which is designed to dissolve slowly, keeping the drug protected during use. This may allow Stellarex more time to track to the lesion without losing drug prematurely. The combination of PEG and water results in a plasticized coating with attractive mechanical properties (eg, adhesion, flexibility, elasticity, and elongation) for adaptability during balloon deformation such as flexion, torsion, and compression. This increases the durability of the coating, making it less likely to flake off during handling, tracking, and inflation. Additionally, PEG's hydrophilic properties render it durable to most chemical reactions. It is also a nontoxic excipient that has been used in topical, oral, and intravenous applications for decades. This nontoxic, durable excipient acts as a reliable carrier of paclitaxel. Therefore, a DCB with PEG, such as Stellarex, is designed to have a low drug dose and allow for a therapeutic dose to reach the target lesion.

Excipients exert their actions in different ways. Hydrophilic excipients such as PEG or urea are polar molecules that act as inert fillers; once hydrated, they swell and start a process of separating paclitaxel molecules to free them from each other, hence increasing their bioactive surface and augmenting absorption onto the arterial wall. Although urea is also water soluble, it doesn't exhibit the polymer mechanical properties that PEG exerts, possibly rendering it less durable. Polysorbate (the excipient for the Lutonix DCB [Bard Peripheral Vascular, Inc.]) has been claimed to act as an emulsifier. When emulsifiers are combined with a more amorphous paclitaxel morphology, paclitaxel dissolution can be accelerated, which may lead to less drug being available over time. Using PEG as an excipient allows the Stellarex DCB to balance coating durability and the transfer efficiency of paclitaxel.

The coating solution of paclitaxel and PEG, along with the proprietary manufacturing process for the Stellarex DCB, is the EnduraCoat™ Technology. The EnduraCoat Technology allows the Stellarex DCB to achieve durable and consistent clinical outcomes with a low-dose drug.

TREATMENT IN CALCIUM

Treatment success in calcium has been touted as the Achilles' heel of DCB therapy. However, Stellarex has shown clinical efficacy in a patient population with high rates of severe calcium.

In the ILLUMENATE Pivotal trial, Stellarex achieved primary patency of 82.3% in the most complex patient

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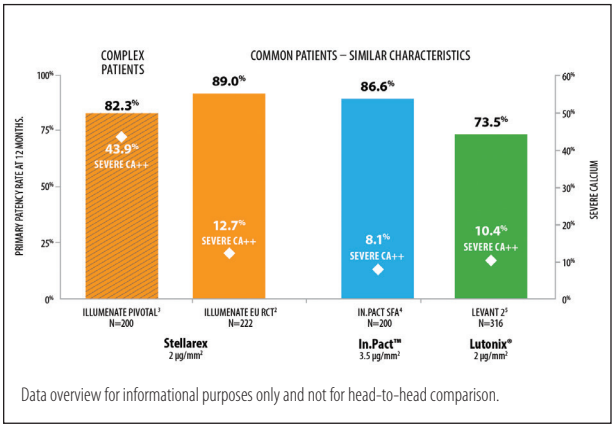

Figure 5. Reported patency rates from available DCB trials.

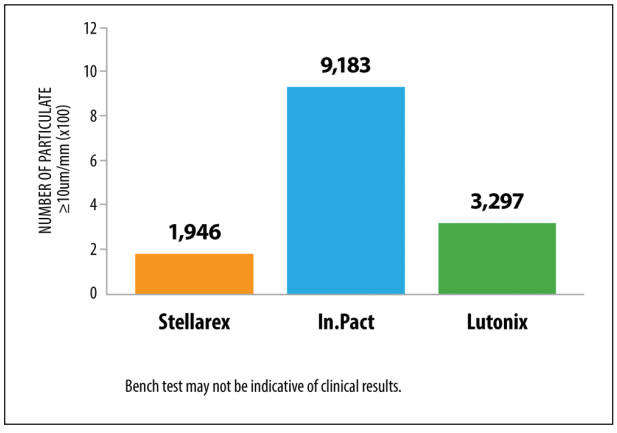

Figure 6. Particulates lost after tracking and inflation. Data on file at Spectranetics.*

population and the highest rates of severely calcified lesions ever reported in a published DCB randomized controlled trial (Figure 5).[4]

The success of Stellarex in calcified lesions may be attributed to the excipient PEG. PEG has a high affinity to hydroxylapaptite (HAp), the primary component of calcified atherosclerotic lesions.[11] PEG will form ionic bonds with HAp, which may limit the amount of paclitaxel washoff in calcified lesions.[11]

DISTAL EMBOLIZATION

The downstream effect of paclitaxel during DCB use must be clearly understood as it relates to safety concerns associated with DCBs. Specifically, the downstream effect of paclitaxel in the presence of foot ulcers may impede wound healing and ultimately affect limb salvage. Therefore, it is crucial for any given DCB to incorporate the smallest dose possible to achieve clinical efficacy in order to reduce the possible safety risks posed by downstream effects of paclitaxel. In order to prove the downstream safety effect of paclitaxel while using Stellarex, 5.5 times the particulate limit from the largest balloon was tested in animal studies to find no downstream safety issues as demonstrated by all gross pathology and histopathology safety outputs.

COATING DURABILITY

High coating durability is the result of extensive drug formulation coating process optimization to enhance performance on the Stellarex-specific balloon material. The ultimate objective was twofold: (1) to obtain excellent drug adherence during balloon preparation and handling, insertion through the introducer, and transit through the vasculature to the target lesion, and (2) to maximize drug release to the vessel wall once the balloon is inflated.

The coating durability of Stellarex is confirmed by quantitative particulate testing after tracking the DCB through an anatomical vascular model.[12] This testing supports that Stellarex limits drug particle loss compared to other DCB competitors with the same (and higher) drug dose. In a comparative assessment, Stellarex resulted in 79% fewer particles produced during tracking than the In.Pact Admiral DCB (Medtronic) and 41% fewer particles than the Lutonix DCB (Figure 6).

THE STELLAREX DIFFERENCE

DCB performance relies on the optimal mix of amorphous and crystalline paclitaxel, a durable excipient, and an optimal drug dose. The balance of these critical factors determines the clinical results and safety profile.

A DCB such as the Stellarex DCB, with an optimal mix of both amorphous and crystalline paclitaxel, maintains durability during tracking and is designed for effective drug transfer and provides drug residency through the 30-day restenosis window. The EnduraCoat Technology allows the Stellarex DCB to achieve durable and consistent clinical outcomes combined with a low drug dose.

The Stellarex DCB has shown a top-tier 12-month primary patency rate of 89% for common patients and a primary patency rate of 82.3% in complex patients with the highest rate of severely calcified lesions of 43.9% in core lab–adjudicated randomized controlled trials (Figure 5).[1,4] The ILLUMENATE first-in-human study demonstrated a primary patency rate of 80.3% at 2 years, suggesting durability of this treatment option.[2] ■

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*Competitor studies are independent clinical trials with different protocols and definitions. Therefore, they 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. Primary patency based on Kaplan-Meier estimates.

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