

ELUVIA™
Drug-Eluting Vascular Stent System

MAY 2022

DEVICE NAME: ELUVIA™ Drug-Eluting Vascular Stent System
TECH NAME: DRUG ELUTING VASCULAR STENT SYSTEM
TRADE NAME: Eluvia
DATE OF APPROVAL: September 24, 2018

Development:

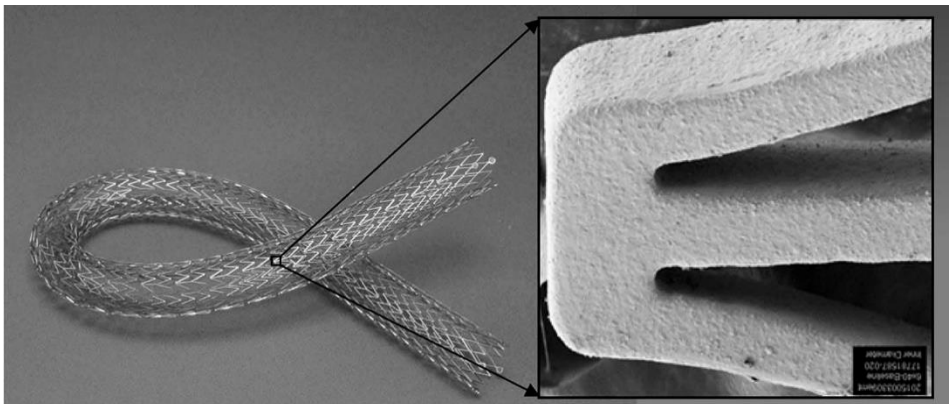
AN OVERVIEW OF HOW ELUVIA WORKS

ELUVIA's innovative engineering design includes:

The Eluvia™ stent was designed to perform in the unique environment of the SFA. Its polymeric coating allows for paclitaxel elution over a long period of time to overlap the timeline associated with peripheral arterial restenosis.

The Eluvia™ stent comprises a self-expanding nitinol stent platform with a coating composed of a polymer system with an antiproliferative active pharmaceutical agent. The geometry of the base stent is such that it provides sufficient force and flexibility to the scaffold while ensuring that it can withstand the mechanical forces of the femoropopliteal segment, in addition to providing uniform drug coverage along the artery length and around its circumference.

The stent coating consists of a primer layer, poly n-butyl methacrylate (PBMA), which promotes adhesion of the active layer. The active layer is composed of the fluoropolymer PVDF-HFP [poly(vinylidene fluoride co-hexafluoropropylene)] and the antiproliferative agent paclitaxel.



The table below details that ELUVIA's polymer matrix makes it unique compared with other paclitaxel peripheral devices and differentiates drug eluting from drug coated devices. ELUVIA's fundamentally different polymer-based coating design, which encapsulates the amorphous form of the drug within the

polymer matrix. This polymer matrix underlies different drug release mechanisms and low particulate burden. ELUVIA utilizes the lowest total dose and dose density among all peripheral paclitaxel devices which results in the lowest drug dose and only device with a sustained elution profile. ELUVIA's biostable polymer does not break down whereas DCB excipients break down and contribute to downstream particulates. Thus, ELUVIA has the lowest particulate burden by orders of magnitude, and therefore the lowest downstream embolic risk.

	Paclitaxel-Eluting	Paclitaxel-Coated			
	Boston Scientific ELUVIA DES	Cook Zilver PTX Stent	DCB		
			Medtronic IN.PACT	BD Lutonix	Phillips Stellarex
Biostable Polymer	✓				
Excipient			✓	✓	✓
Amorphous Coating Morphology	✓	✓			
Paclitaxel Dose Density (µg/mm ²)	0.167	3	3.5	2	2
Total Dose (6 mm x 120 mm)	409 µg	1103 µg	8448 µg	4500 µg	4721 µg
Diffusion-Controlled Elution	✓				
Particulate Counts* (≥10µm size)	1381	11,928	567,432	210,320	193,968

Eluvia is delivered via a trans-femoral approach. It comes in a pre-loaded delivery system. The ELUVIA stent system is a device/drug combination product composed of two components: a device (stent system) and a drug coating (a formulation of paclitaxel contained in a polymer matrix).

DEVICE COMPONENT DESCRIPTION

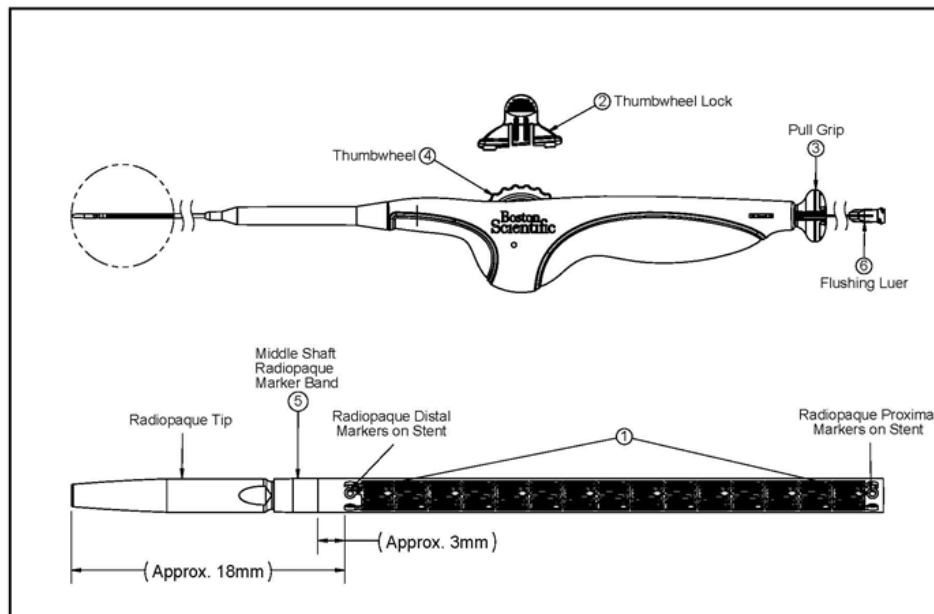
The stent system is comprised of two components: the implantable endoprosthesis and the stent delivery system. The stent is a laser cut self-expanding stent composed of a nickel titanium alloy (nitinol). On both the proximal and distal ends of the stent, radiopaque markers made of tantalum increase visibility of the stent to aid in placement. The stent is constrained within a 6F (2.1 mm maximum OD) delivery system. The delivery system is a triaxial design with an outer shaft to stabilize the stent delivery system, a middle shaft to protect and constrain the stent, and an inner shaft to provide a guidewire lumen. The delivery system is compatible with 0.035 in (0.89 mm) guidewires.

When ready to be implanted, the stent is deployed by retracting the middle shaft (Reference Figure below) of the delivery system. A radiopaque marker at the distal end of the delivery system aids in visibility during deployment. As the stent is exposed to body temperature, it expands to appose the vessel wall.

The ELUVIA Drug-Eluting Stent is available in a variety of diameters and lengths. The delivery system is also offered in two working lengths (75 cm and 130 cm).

DRUG COMPONENT DESCRIPTION:

The ELUVIA Stent is a stent with a drug/polymer coating. The coating comprises two layers, an inner primer layer and an outer polymer matrix that contains an active pharmaceutical ingredient.



Value to Healthcare:

Eluvia is the only peripheral drug-eluting stent with polymer-controlled drug release, designed to sustain drug release to match the restenotic process in the Superficial Femoral Artery. Clinical evidence shows superiority versus other stent technologies, including bare metal stents (without a drug) and the only other drug-coated stent on the market, Zilver PTX. Clinical evidence shows superior efficacy outcomes for Eluvia, including vessel patency as well as lower repeat procedures for vessel revascularization.

Healthcare System Benefits:

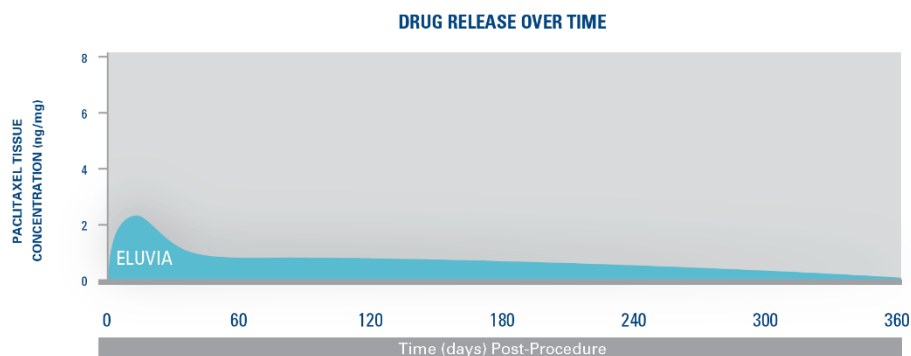
Reinterventions on patients are incredibly taxing for the entire healthcare system. The US SFA market is estimated to be \$600M in 2019 with ~25% of those costs associated with reintervention (up to \$150M). When factoring in the total procedural costs, this drives the 2019 US SFA market estimate above \$1B and the reintervention cost to ~\$250M+. In a clinical trial, reinterventions are documented as Clinically Driven Target Lesion Revascularization (CD-TLR).

DESIGN HISTORY

The Eluvia™ Drug-Eluting Vascular Stent was designed to address demands specific to treating above-the-knee peripheral artery lesions, taking into consideration the mechanical and pathological conditions unique to this anatomy. Coronary arteries and the SFA are both considered muscular arteries, but the mechanical environment of the femoropopliteal segment differs dramatically from that of the coronary arteries. As the largest unsupported artery in the body, the SFA undergoes repetitive deformations along multiple axes during movements such as walking, sitting, standing, or climbing

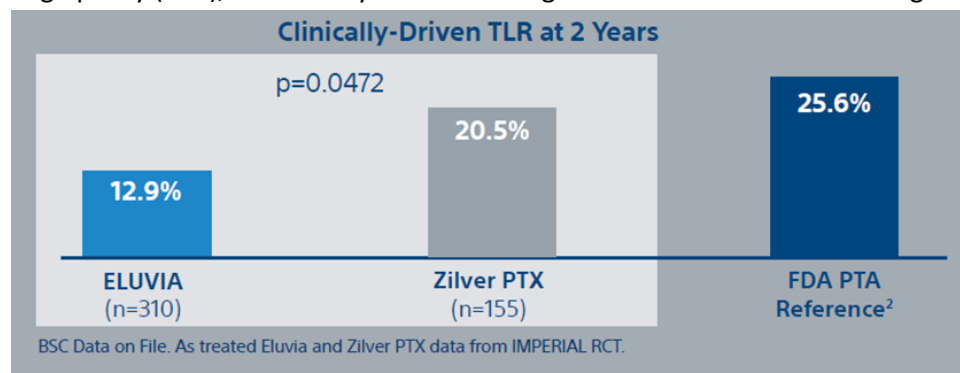
stairs. This challenging mechanical environment highlights the need for a durable scaffold to predictably deliver an active pharmaceutical agent to the diseased vessel. Along with the differences in mechanical environments, preclinical studies indicate that the SFA has a lower ratio of collagen to elastin compared with coronary vessels, which may contribute to differential disease progression. Additionally, bone-like osteoid metaplasia present in the calcified SFA mandates that the dosing of the active pharmaceutical agent is appropriate to mitigate neointimal proliferation. Disease progression was also a consideration for the design of a purpose-built drug-eluting stent for the SFA. Restenosis after endovascular therapy follows a predictable response akin to wound healing, the time course of which is dictated by the biological milieu. In the coronary environment, this time period is 60–90 days. However, the timing of restenosis in the challenging SFA environment seems to follow a longer duration. The implications of these differences for drug delivery are central to how coatings for drug-eluting stents are designed. Paclitaxel, a microtubule stabilizer, was chosen for its demonstrated antirestenotic effect on peripheral arteries. Although ‘-limus’ drugs (e.g., everolimus, sirolimus) are effective in coronary arteries, previous attempts to use them in the SFA have been ineffective. The failure of previous attempts with ‘-limus’ analogs in the SFA may have been confounded by design factors such as lack of durability of the base scaffold, use of polymers that lacked good biocompatibility, or selection of a drug-elution profile that did not match the restenotic cascade. The dosing strategy was based on recognition that coronary and femoropopliteal arteries have similar cell biology and respond with similar antiproliferative mechanisms upon exposure to paclitaxel. However, peripheral atherosclerotic disease contains more calcium and less lipid than coronary lesions, and the SFA is more prone to chronic occlusions. To counteract reduced paclitaxel bioavailability in the SFA due to these differences in tissue and disease composition, a dosing approach including a relatively greater total amount of released drug was adopted. Release profiles of multiple paclitaxel doses were evaluated preclinically before a dose of 0.167 μg paclitaxel/ mm^2 stent surface area was chosen for clinical testing. A polymeric carrier was chosen in order to provide control over the dose and duration of drug release. The base polymer (PBMA) and the fluoropolymer PVDF-HFP comprise the same polymer system as is present on the Promus Element (Boston Scientific, Marlborough, MA) and the Xience V (Abbot Vascular, Abbott Park, IL) drug-eluting coronary stents and thus its clinical safety has been studied in more than 100,000 patients. Biocompatibility of the PBMA plus PVDF-HFP system was also demonstrated in preclinical studies. The polymer demonstrated a good vascular safety profile in a porcine coronary artery stenting model and did not inhibit endothelialization (i.e., healing) in a rabbit peripheral artery stenting model or promote thrombus formation in a bench blood loop model. The ability to alter the polymer to enable different concentrations of drug in a preclinical model was also a critical aspect in the polymer system selection. In addition to drug release and biocompatibility considerations, the ideal polymer coating would withstand the extreme mechanical forces of the femoropopliteal segment and not require additional forces for deployment. Researchers at Boston Scientific evaluated multiple biostable and biodegradable polymers and determined that PVDF-HFP performed within desired parameters in tests of drug release and deployment forces, and the coating demonstrated durability during deployment and fatigue testing. Given that restenosis incidence following stenting of the SFA peaks at about 12 months – later than occurs following coronary stenting – and that the underlying restenotic cascade has a multiphase time course, an elution profile to overlap disease progression through at least 12 months was targeted. The

pharmacokinetic profile of the selected dose through 6 months has been described by Hou et al. (shown below)



CLINICAL DATA

In the IMPERIAL randomized pivotal clinical trial ELUVIA has demonstrated superior Clinically Driven Target Lesion Revascularization outcomes at 2 years. ELUVIA's reintervention rates were 1/3 lower than the Zilver PTX drug coated stent studied in this trial and 1/2 the rate of percutaneous transluminal angioplasty (PTA), as noted by the FDA during their June 2019 Panel meeting.

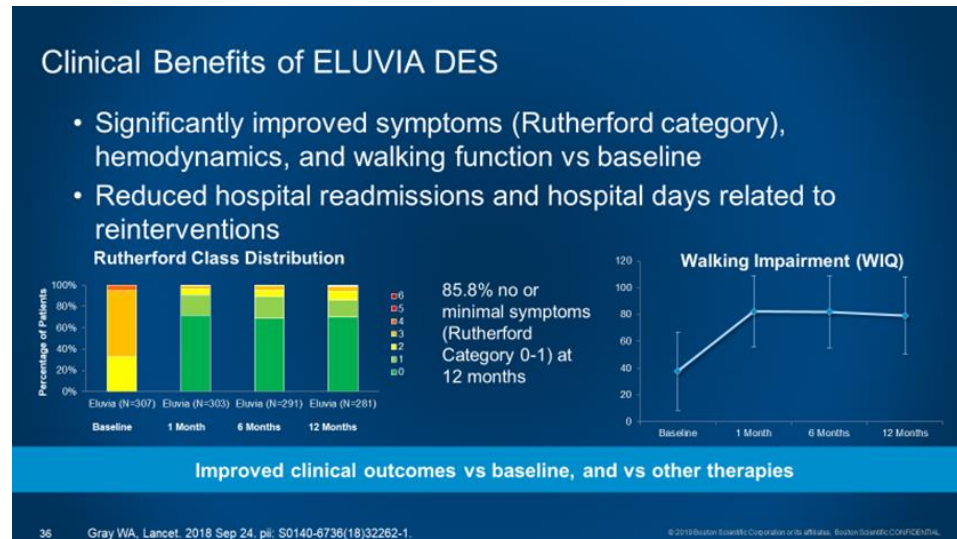


ELUVIA's statistically significant reduction in TLR represents a benefit to the healthcare system. When the healthcare system utilizes ELUVIA, they are recognized for doing right by the hospital, physicians, and patients because patients stay out of the hospital longer and keep walking longer without pain, while the hospital utilizes the newest technology in procedures. Payers benefit from the lowest reintervention rate for devices indicated to treat restenosis in the SFA; physicians' benefit from offering superior technology to their patients; hospitals, physicians and patients benefit from faster procedure times; overall, ELUVIA is successfully reducing the burden on the health system today.

Patient Benefits:

Patients experiencing lifestyle limiting claudication (leg pain) and lower extremity peripheral artery disease are increasing in prevalence because of the ageing population and rise in number of patients with diabetes. Prior to endovascular options, patients typically had surgical bypass or in severe cases, amputation. Both options required significant hospital stays, multiple follow-up appointments and altered lifestyles for most patients.

ELUVIA is a same day procedure with patients able to return home and resume their lifestyles. ELUVIA has demonstrated the best in class lowest Clinically Driven Target Revascularization Rate among SFA treatment options (Lancet reference) to date. It is important to note that there are potential risks associated with repeat interventions such as contrast exposure, surgical risks, etc. Patients treated with ELUVIA have significantly improved symptoms, hemodynamics and walking function compared to their condition prior to being treated with ELUVIA. Additionally, patients benefit from faster procedure times as Eluvia does not require adjunctive therapies during the procedure to achieve the superior outcomes observed in the IMPERIAL trial.



In recognition of the differentiated technology, statistically superior clinical data, and the price premium it commands vs. competitive devices; in 2020, the Centers for Medicare and Medicaid Services (CMS) announced that it will provide an add-on payment exclusively for the use of Eluvia of up to \$3,646.50 per qualifying Medicare inpatient hospitalization admission. This payment is not applicable to any other peripheral device, only to Eluvia.

Key peer-reviewed papers encompassing Eluvia preclinical development and IMPERIAL pivotal study are listed below.

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