



**Advisory Committee Panel Pack**  
**ELUVIA Paclitaxel-Eluting Stent System**

Submitted by:  
Melissa Young

Boston Scientific Corporation  
Maple Grove, MN

15-May-2019

**Table of Contents**

|   |           |
|---|-----------|
| <b>1. Executive Summary .....</b>   | <b>3</b>  |
| <b>2. Paclitaxel-Eluting Stent Clinical Experience: TAXUS .....</b>                                   | <b>4</b>  |
| <b>3. ELUVIA Device Description and Differentiation .....</b>   | <b>7</b>  |
| 3.1 ELUVIA Drug-Eluting Vascular Stent.....   | 7         |
| 3.2 ELUVIA is Fundamentally Different from Non-polymeric Peripheral<br>Paclitaxel-coated Devices..... | 8         |
| 3.2.1 Paclitaxel Dose.....  | 9         |
| 3.2.2 Targeted Delivery and Systemic Exposure .....   | 10        |
| 3.2.3 Particulate Loss.....   | 12        |
| <b>4. Paclitaxel-Eluting Stent Clinical Experience: ELUVIA .....</b>                                  | <b>14</b> |
| 4.1 PAD Mortality .....   | 14        |
| 4.2 ELUVIA Mortality .....  | 14        |
| 4.3 ELUVIA Benefit-Risk Profile .....   | 15        |
| <b>5. Presence of a Signal and Causality .....</b>  | <b>17</b> |
| 5.1 Mortality Analyses of Paclitaxel-containing Devices .....   | 17        |
| 5.2 No Causal Link between Paclitaxel and All-Cause Mortality .....                                   | 17        |
| <b>6. Next Steps.....</b>   | <b>18</b> |
| <b>7. Conclusion.....</b>   | <b>18</b> |
| <b>8. References.....</b>   | <b>19</b> |

**1. Executive Summary**

At Boston Scientific (“BSC”), patient safety is paramount. BSC reaffirms our commitment to patient safety with our continued desire to assist global regulatory agencies and physician organizations such as VIVA Physicians in interpreting the observed mortality signal for peripheral paclitaxel devices reported in the meta-analysis by Katsanos et al.<sup>6</sup>

BSC’s ELUVIA drug-eluting stent for use in the peripheral vasculature was not included in the Katsanos study, and is substantially different from the devices in the meta-analysis, including FDA-approved paclitaxel-coated peripheral devices (i.e., Cook Zilver PTX, Medtronic IN.PACT, BD Lutonix, Phillips Stellarex), with regard to the drug release mechanism, formulation of the drug, initial dose and dose over time.

ELUVIA has a demonstrated safety profile, which is supplemented with data from patients treated with BSC’s TAXUS coronary paclitaxel-eluting stents in the coronary and peripheral vasculature. The ELUVIA peripheral stent and TAXUS coronary stent are similar in design and have the same mechanism of action. They deliver the same drug via a polymer-matrix elution mechanism, albeit with a different polymer. Both yield sustained, targeted paclitaxel delivery directly to the vascular lesion. BSC’s TAXUS polymer matrix-based drug-eluting stents have a well-established, strong safety profile with data on more than 4000 patients followed out to 5 years.<sup>2,4,5,7-9</sup> Furthermore, no link between paclitaxel and all-cause mortality is present in comparative data between TAXUS and uncoated therapies out to 5 years.<sup>10,11</sup> Any effect of paclitaxel exposure via polymer-matrix drug-eluting stents on mortality would have been observed with coronary and infrapopliteal use; however, no mortality signal was identified in these studies. Paclitaxel eluted through a polymer matrix has a long and well-established safety profile which has been demonstrated through rigorous clinical evidence from the coronary vasculature.

Unlike other paclitaxel-coated devices, the ELUVIA stent is designed with a polymer matrix layer which allows for controlled, localized, low-dose amorphous paclitaxel delivery to lesions in peripheral vessels over time, with minimal systemic distribution or particulate loss. This design feature of ELUVIA presents significant differences in drug dose, in both the immediate- and long-term, and drug distribution compared to the other FDA-approved devices, which utilize paclitaxel coatings that result in a high initial bolus release.

ELUVIA has demonstrated significant clinical benefit in treatment of peripheral arterial lesions in terms of providing a high patency rate and avoiding target lesion reintervention, with no overt all-cause mortality risk in the short- to mid-term.<sup>1,12</sup> In addition, patients had improved symptoms, health-related quality of life, and walking function compared with baseline.<sup>1</sup> Long-term follow-up from clinical studies of ELUVIA including more than 1000 paclitaxel-treated patients is ongoing.

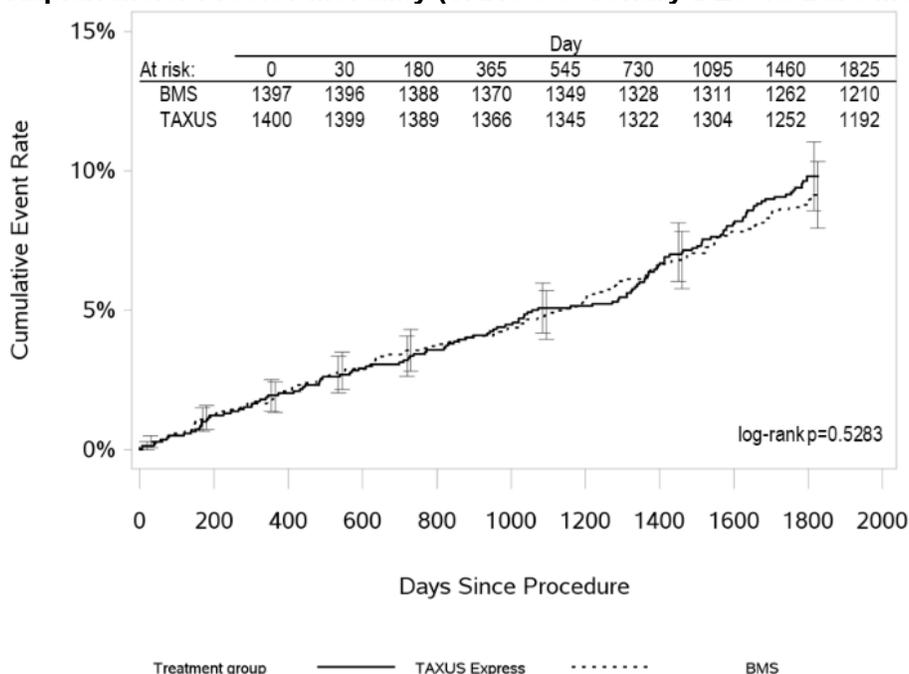
In light of the differences between ELUVIA and peripheral paclitaxel-coated products, attribution of any observed mortality signal with the devices in the Katsanos et al., meta-analysis<sup>6</sup> and other similar analyses to ELUVIA is unsubstantiated. There is no evidence in the data on any of BSC’s polymer-based paclitaxel eluting devices of an increased mortality risk. BSC urges FDA and the Panel to consider the differences in the devices so that the products are not inappropriately grouped together as a class given their potentially disparate safety and efficacy profiles.

## 2. Paclitaxel-Eluting Stent Clinical Experience: TAXUS

ELUVIA is a paclitaxel-eluting stent that employs a polymer-based elution mechanism to treat lesions in the femoropopliteal arteries, as described in **Section 3**. The ELUVIA peripheral drug-eluting stent and TAXUS coronary drug-eluting stent are similar in design intent and mechanism of action. With the same drug and comparable low-dose controlled drug elution profiles achieved via a polymer matrix, the ELUVIA peripheral stent bears greater similarity to the TAXUS coronary stent than to any peripheral paclitaxel-coated balloon or non-polymeric paclitaxel-coated stent with respect to design features and drug release kinetics. Signals for any potential long-term systemic effects of targeted paclitaxel eluted from a stent polymer matrix would be apparent in patients treated with TAXUS. Therefore, data on the controlled, localized and low dose paclitaxel elution by TAXUS in the coronary or infrapopliteal vasculature can be used to gauge potential systemic effects of paclitaxel eluted from ELUVIA.

TAXUS stent use has been extensively studied with more than 14 years of commercial experience and clinical trial data out to 10 years in patients with coronary<sup>2,7,8,10</sup> implants and 5 years for those with infrapopliteal<sup>11</sup> implants. Newer generation coronary drug-eluting stents have improved upon the TAXUS design to use a more thromboresistant PVDF-HFP polymer (the one used on ELUVIA), and now typically utilize limus drugs, which were found to have improved efficacy in the coronary vessels. However, in the femoropopliteal segment, limus-based stents have failed to show benefit over bare metal as evidenced in the SIROCCO and STRIDES clinical studies, making paclitaxel the proven drug of choice for devices used in the peripheral vasculature.<sup>13,14</sup> Although BSC discontinued distribution of TAXUS stents, this was based on physician perceived disadvantage of higher late lumen loss, and not due to any safety concern.

In the TAXUS stent family series of coronary studies, paclitaxel-based treatment did not differentially affect long-term all-cause mortality as compared to bare stent treatment. Stone et al.<sup>10</sup> report 5-year patient-level pooled results from nearly 2800 patients in randomized studies showing that all-cause mortality for patients treated with TAXUS was similar to that of patients treated with the bare metal platform (9.8% vs 9.1%, p=0.53). Kaplan-Meier event rate analysis of mortality through 5 years for patients treated with TAXUS (n=1400) compared to patients treated with the bare metal platform (n=1397) is shown in **Figure 1** (log-rank p=0.5283). These analyses represent approximately triple the sample size of the studies with >2 year data included in the Katsanos meta-analysis<sup>6</sup> and in FDA's analysis of 5-year data from paclitaxel-coated devices.<sup>15</sup> In addition, long-term data from more than 4,000 patients who received coronary TAXUS in randomized<sup>2,4,5,8,9</sup> and nonrandomized<sup>7</sup> studies show mortality rates consistent with those expected for this patient population.<sup>16,17</sup>

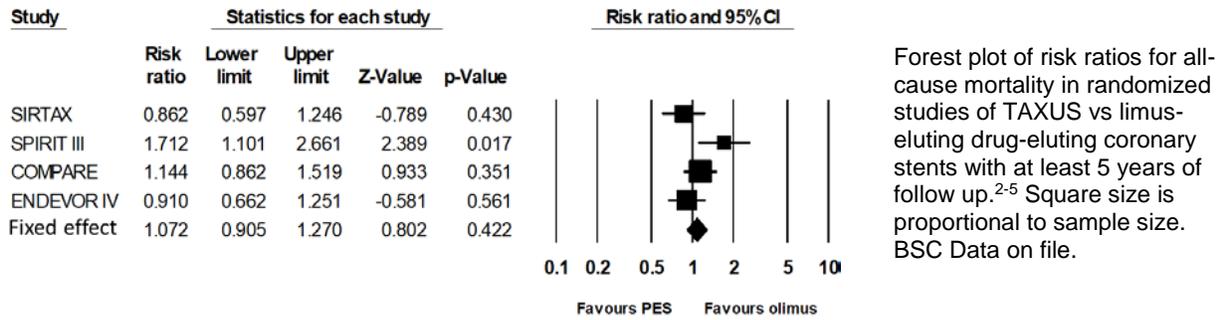
**Figure 1. Kaplan-Meier Plot for Mortality (TAXUS Coronary DES vs Bare Metal Stent)**

Five-year all-cause mortality for patients treated with TAXUS was similar to that of patients treated with the bare metal platform (log-rank p=0.5283). BSC Data on file.

Consistent with the similar all-cause mortality rates observed between paclitaxel-eluting and bare metal stents in the coronary vasculature, in the periphery, infrapopliteal artery treatment with TAXUS in the randomized PADI study of 137 patients with critical limb ischemia revealed similar mortality rates for paclitaxel-eluting vs uncoated device treatments (5-year mortality 62.3% vs 63.0%, log-rank test p=0.45).<sup>11</sup> The overall low survival rates in the study highlight the high mortality of patients with critical limb ischemia.<sup>11</sup>

TAXUS use has also been compared with newer generation limus-eluting coronary stents with follow-up to 5<sup>3-5</sup> and 10 years,<sup>2</sup> with all-cause mortality rates consistent with those expected for patients treated for coronary artery disease. Although some smaller individual studies have shown statistically significant differences in long-term mortality between paclitaxel-eluting and limus-eluting stents, taken together, results from these studies suggest no difference in mortality risk for coronary artery patients treated with paclitaxel-eluting vs. limus-eluting stents (**Figure 2**). An additional meta-analysis of coronary-treated patients demonstrated similar long-term mortality risk for those with drug-eluting or bare-metal stents.<sup>18</sup>

**Figure 2. All-cause Mortality Risk in Randomized Studies of TAXUS vs Limus-eluting Coronary Stents**



Although mortality rates for patients treated for PAD are not directly comparable to rates for patients with coronary artery or infrapopliteal disease due to appreciable differences in baseline risk, an additive effect due to low dose paclitaxel elution over time; if it exists, would have been observed in patients receiving treatment in these vessel beds; however, no mortality signal was identified in any of these studies.

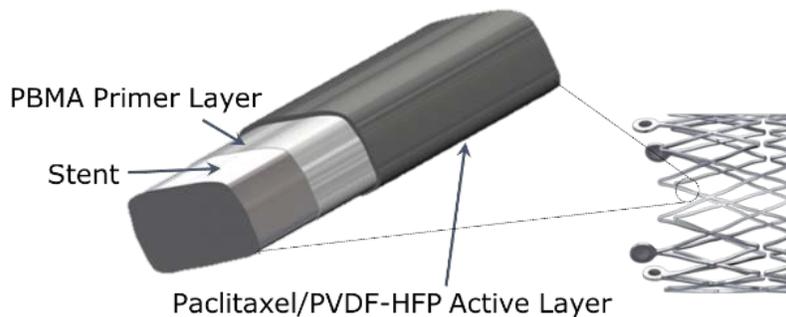
**3. ELUVIA Device Description and Differentiation**

**3.1 ELUVIA Drug-Eluting Vascular Stent**

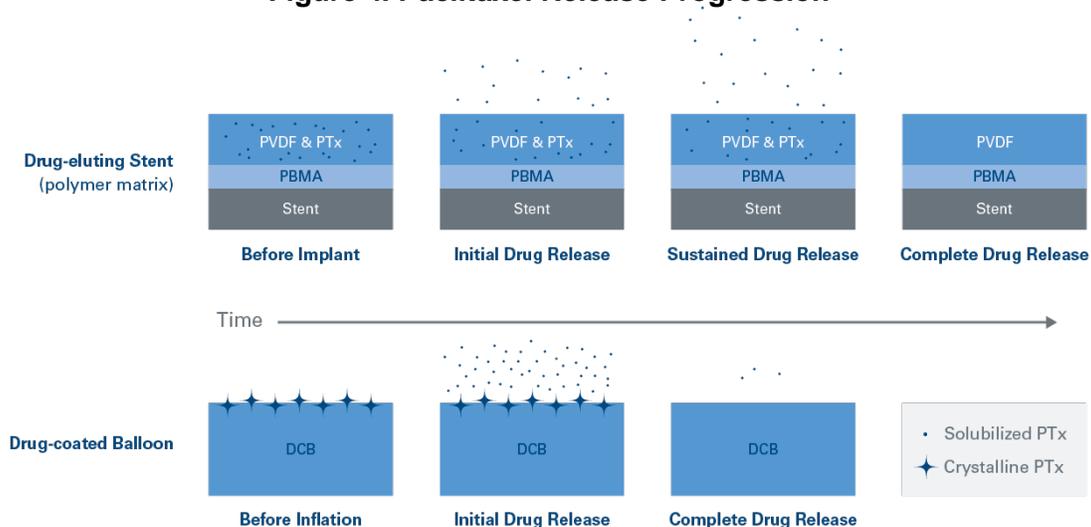
The ELUVIA drug-eluting stent is indicated for improving luminal diameter in the treatment of symptomatic de-novo or restenotic lesions in the native superficial femoral artery (SFA) and/or proximal popliteal artery with reference vessel diameters ranging from 4.0 - 6.0 mm and total lesion lengths up to 190 mm. The ELUVIA drug-eluting stent is designed to elute paclitaxel directly to the vessel lesion in a low dose sustained over time. ELUVIA utilizes low-dose paclitaxel (drug density on the stent is 0.167 µg/mm<sup>2</sup>) in the same amorphous form as is used in the BSC TAXUS family of coronary stents.

The self-expanding nitinol stent has a dual layer coating; a primer layer to enhance adhesion of the polymer matrix layer and an active drug/polymer matrix layer as illustrated in **Figure 3**. Paclitaxel release from drug-eluting stents (ELUVIA, TAXUS, PROMUS/XIENCE) occurs in two phases: an initial release of surface paclitaxel followed by a sustained slow release phase resulting from the dissolution and diffusion of paclitaxel through the drug/polymer matrix. An illustration of this mechanism, which is substantially similar to that of TAXUS and PROMUS/XIENCE stents, is shown in **Figure 4**.

**Figure 3. ELUVIA Dual Layer Coating Design**



**Figure 4. Paclitaxel Release Progression**



Diffusion-controlled elution mechanism of drug-eluting stents (top) and dissolution of crystalline drug from coated devices (bottom).

The ELUVIA primer and copolymer layers are the same as those used on the FDA-approved PROMUS/XIENCE coronary stents. The polymer matrix layer plays an essential role in drug-eluting stent safety and performance impacting biocompatibility, ability to control the drug release, coating integrity, stability and processability. The fluorinated polymer PVDF-HFP (poly(vinylidene fluoride-co-hexafluoropropylene) used in ELUVIA to control the release of paclitaxel directly to the vessel wall is highly vascular- and hemo-compatible and its fluorine-rich composition leads to low surface tension and high lubricity. More importantly, the fluorine-rich surfaces adsorb higher ratios of albumin to fibrinogen which passivates the drug coating surface,<sup>19,20</sup> resulting in significant reductions in platelet adhesion and activation and increased thromboresistance. The PVDF-HFP polymer for ELUVIA is utilized with the PROMUS/XIENCE stents, which have been implanted in more than 20 million vessels and studied in more than 100,000 patients in clinical trials.<sup>21,22</sup> ELUVIA design characteristics are compared with TAXUS and PROMUS/XIENCE in **Table 1**.

**Table 1. Comparison Between ELUVIA Peripheral Drug-eluting Stent and Coronary Drug-eluting Stents**

|                            | ELUVIA<br>(P180011)                                     | TAXUS Express <sup>2</sup><br>(P030025) | TAXUS Liberté<br>(P060008) | PROMUS/XIENCE<br>(P110010/P070015) |
|----------------------------|---|---|----------------------------|------------------------------------|
| Drug                       | PTx   | PTx                                     | PTx                        | Everolimus                         |
| Coating Morphology         | Amorphous   |   |                            |                                    |
| Polymer                    | PVDF-HFP  | SIBS                                    | SIBS                       | PVDF-HFP                           |
| Drug : Polymer Ratio (w/w) | 1:9   | 1:10.4                                  | 1:10.4                     | 1:4.9                              |
| Drug Dose Density          | 0.167 µg/mm <sup>2</sup>                                | 1.0 µg/mm <sup>2</sup>                  | 1.0 µg/mm <sup>2</sup>     | 1.0 µg/mm <sup>2</sup>             |
| Total Dose                 | 135 µg<br>(6.0 mm x 40 mm)                              | 282 µg<br>(4.0 mm x 38 mm)              | 273 µg<br>(4.0 mm x 38 mm) | 242 µg<br>(4.0 mm x 38 mm)         |
| Drug Delivery Mechanism    | Controlled release via diffusion through polymer matrix |   |                            |                                    |
| Coating Placement          | Conformal   |   |                            |                                    |

Abbreviations: PTx, paclitaxel; PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene), SIBS, poly(styrene-block-isobutylene-block-styrene).

### 3.2 ELUVIA is Fundamentally Different from Non-polymeric Peripheral Paclitaxel-coated Devices

ELUVIA is different from peripheral paclitaxel-coated devices due to its targeted, controlled, low-dose paclitaxel elution with minimal systemic loss and particulate loss. While each of the FDA-approved devices deliver paclitaxel to the vessel wall, there are significant differences in the device designs which impact drug dose, release mechanism and kinetics as summarized in **Table 2**.

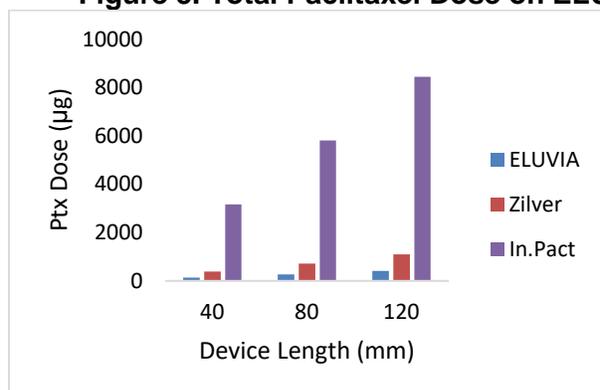
**Table 2. Comparison of ELUVIA Drug-eluting Stent to FDA-approved Drug-coated Peripheral Products**

|   | Paclitaxel-Eluting               | Paclitaxel-Coated         |                                 |                       |                     |
|---|----------------------------------|---------------------------|---------------------------------|-----------------------|---------------------|
|   | ELUVIA DES                       | Zilver PTX                | DCB                             |                       |                     |
|   |                                  |                           | IN.PACT                         | Lutonix               | Stellarex           |
| Drug  | PTx                              | PTx                       | PTx                             | PTx                   | PTx                 |
| Polymer   | PVDF-HFP                         | N/A                       |                                 |                       |                     |
| Excipient                                       | N/A                              | N/A                       | Urea                            | Polysorbate, Sorbitol | Polyethylene Glycol |
| Coating Morphology                              | Amorphous                        | Amorphous                 | Crystalline                     |                       |                     |
| Drug Dose Density ( $\mu\text{g}/\text{mm}^2$ ) | 0.167                            | 3                         | 3.5                             | 2                     | 2                   |
| Total Dose (6 mm x 120 mm)                      | 409 $\mu\text{g}$                | 1103 $\mu\text{g}$        | 8448 $\mu\text{g}$              | 4500 $\mu\text{g}$    | 4721 $\mu\text{g}$  |
| Control Drug Delivery Mechanism                 | Diffusion through polymer matrix | Dissolution of solid drug | Dissolution of crystalline drug |                       |                     |

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; N/A, not applicable; PTx, paclitaxel; PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene).

### 3.2.1 Paclitaxel Dose

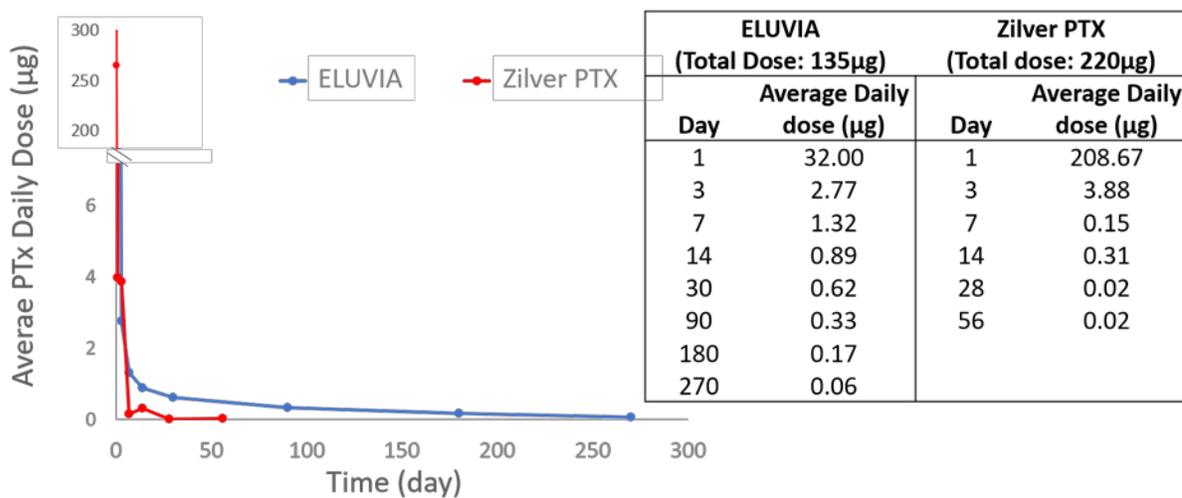
ELUVIA is the only paclitaxel-containing product for the treatment of PAD that uses a polymer to attain targeted and controlled drug release. As a result, ELUVIA utilizes the lowest therapeutic paclitaxel dose to achieve efficacy, as demonstrated by clinical data.<sup>1,12</sup> As shown in **Figure 5**, the total paclitaxel dose on ELUVIA compared with equivalent-length paclitaxel-coated devices is approximately 3 times less than Zilver PTX and more than 20 times less than IN.PACT.

**Figure 5. Total Paclitaxel Dose on ELUVIA, Zilver PTX and IN.PACT Devices**

Total paclitaxel dose on ELUVIA is approximately 3 times less than Zilver PTX and >20 times less than IN.PACT (equivalent-length devices). Data from the respective IFUs.

In addition to dose on the device, it is also important to consider the drug release kinetics. As shown in **Figure 6**, ELUVIA delivers a lower initial dose to achieve therapeutic drug concentration and thereafter paclitaxel is eluted through a diffusion-controlled mechanism. In contrast, paclitaxel is released from Zilver PTX in a high initial burst dose, then rapidly declines, similar to the release profile of drug-coated balloons (DCB), which inherently only have a high dose bolus release as these devices are not implanted in the vessel. Zilver PTX coating has no polymer or excipient and thus the release mechanism is solely based on paclitaxel dissolution, rather than a controlled elution.

**Figure 6. Daily Paclitaxel Dose for ELUVIA and Zilver PTX**



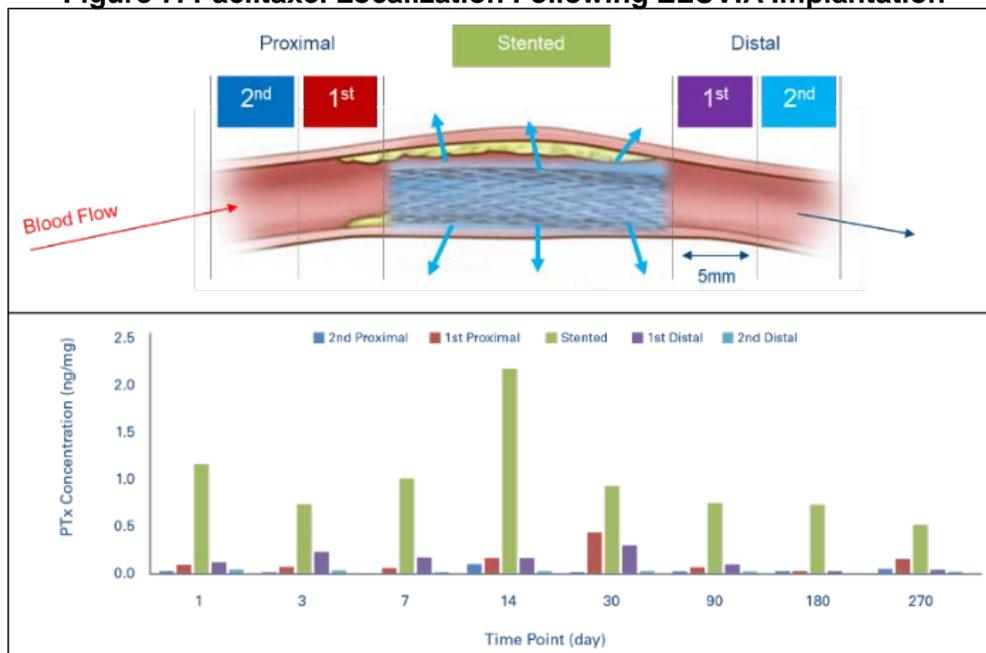
The daily dose of paclitaxel released calculated from the preclinical in vivo release curves. ELUVIA: P180011. Zilver PTX: Dake et. al.<sup>23</sup>

### 3.2.2 Targeted Delivery and Systemic Exposure

Of the FDA-approved peripheral paclitaxel devices, only ELUVIA utilizes a polymer matrix to modulate paclitaxel release over time and ensure delivery of paclitaxel directly to the vessel wall with minimal systemic loss. With an excipient rather than polymer matrix, the DCBs utilize paclitaxel in a crystalline form. Crystalline paclitaxel exhibits lower solubility than the amorphous form utilized in polymer-matrix based drug-eluting stents and drug-coated stents, and a majority of the crystalline paclitaxel is lost to the systemic circulation and end organs while less than 10% of the crystalline paclitaxel coating is transferred at the intended lesion site.<sup>24-27</sup>

The localization of paclitaxel eluted from ELUVIA in treated arterial tissue is demonstrated by the preclinical GLP pharmacokinetic (PK) study. As shown in **Figure 7**, drug transferred to the tissue is localized in the stented vessel area. At 14 days post-implant (i.e., the time of maximum tissue concentration), the first 5 mm of tissue proximal and distal to the stented region had paclitaxel tissue concentrations of less than 10% of the concentration within the stented region. Similar paclitaxel localization in the stented segment was observed across all study time points.

**Figure 7. Paclitaxel Localization Following ELUVIA Implantation**

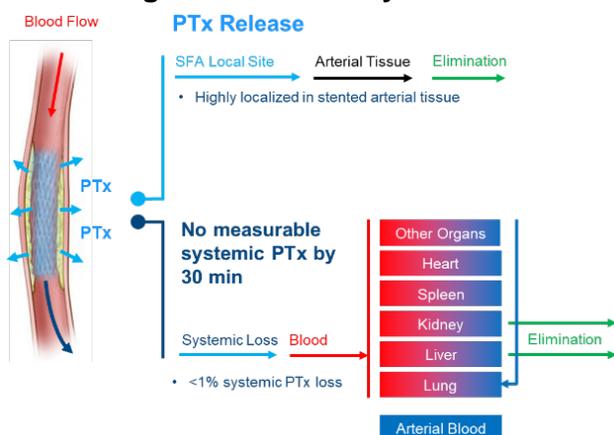


**Top panel:** Paclitaxel concentrations were analyzed in tissue samples from the arterial region directly contacting the stent (green), and in segments 5 mm and 10 mm proximal to and distal to the stent in swine arteries that had been implanted with ELUVIA.

**Bottom panel:** At each timepoint, paclitaxel tissue concentration is highly localized in the stented area, with concentrations greatest in the samples directly contacting the stent and decreasing with distance from the stent.

Preclinical PK GLP study results show that paclitaxel is undetectable in plasma 24 hours after stent implantation and remains undetectable for all later measured time points. Therefore, the major systemic loss of paclitaxel occurs immediately following implantation with a total systemic loss of less than 1% of the total drug (**Figure 8**). Clinical results were consistent with the preclinical findings: systemic paclitaxel was below detectable levels 30 minutes following ELUVIA implantation in the IMPERIAL Pharmacokinetics Sub-study.<sup>1</sup>

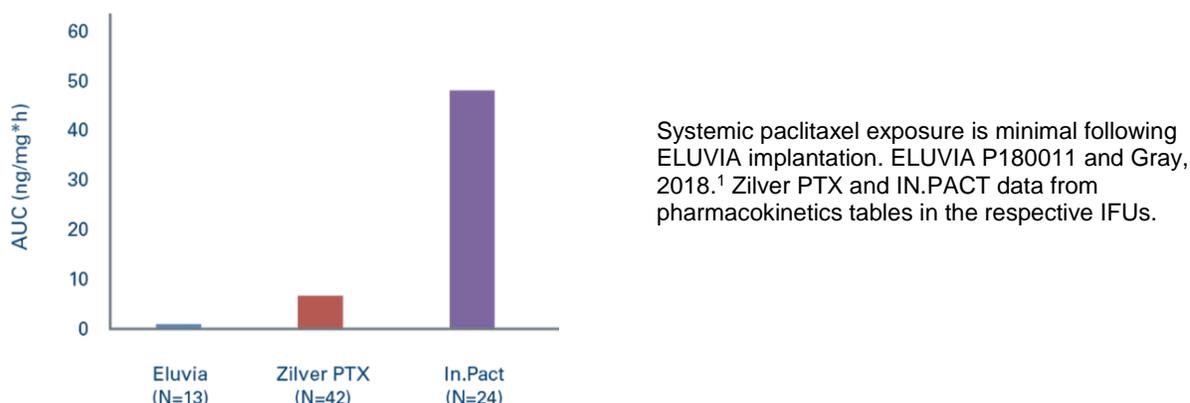
**Figure 8. Minimal Systemic Loss of Paclitaxel Released from ELUVIA**



Paclitaxel released from ELUVIA remains localized in the stented arterial tissue, with <1% total systemic loss of the total drug.

Systemic paclitaxel exposure following ELUVIA implantation can be estimated from the area under the curve (AUC) from the IMPERIAL Pharmacokinetics Sub-study. **Figure 9** compares the systemic paclitaxel exposure from ELUVIA with Zilver PTX and IN.PACT DCB (i.e., the two FDA-approved paclitaxel-coated devices with data >2 years implicated in the meta-analysis by Katsanos et al.<sup>6</sup>). The greatest systemic paclitaxel exposure was found for IN.PACT DCB, which has the highest paclitaxel dose and no polymer or other mechanism to protect the drug coating from systemic release during delivery to the target lesion. In contrast, ELUVIA's localized low-dose drug delivery with minimal systemic loss meets BSC's design intent of maximizing effectiveness and minimizing potential systemic side effects, as described above.

**Figure 9. Human Systemic Paclitaxel Exposure Following ELUVIA, Zilver PTX, or IN.PACT Implantation**



### 3.2.3 Particulate Loss

Quantification of the size and numbers of downstream particulates has been required by regulatory agencies for both quality control and safety purposes. BSC has conducted particulates testing per FDA guidance for ELUVIA, and also for commercially available paclitaxel-coated peripheral devices. Particulate counts from simulated use testing (**Table 3** and **Table 4**) show that ELUVIA has the lowest particulate burden among these devices by orders of magnitude, and therefore the lowest downstream embolic risk. As shown in **Table 3**, ELUVIA counts typically approach or are below the lower limit of quantification in the large particulate bins (25-50 $\mu$ m and >50 $\mu$ m). In addition, particulate counts for ELUVIA were similar to those of EverFlex Entrust, an FDA-approved non-coated bare metal stent with wide commercial utilization. These low particulate counts for ELUVIA are expected due to the fundamentally different polymer-based coating design, which encapsulates the amorphous form of the drug within the polymer matrix.

**Table 3. Particulate Counts for FDA-Approved SFA Stents**

| Particulate Size     | Bare Metal Stent | Paclitaxel-Eluting | Paclitaxel-Coated |
|----------------------|------------------|--------------------|-------------------|
|                      | EverFlex Entrust | ELUVIA DES         | Zilver PTX        |
| $\geq 10\mu\text{m}$ | 1,524            | 1,308              | 10,771            |
| $\geq 25\mu\text{m}$ | 56*              | 63                 | 1,106             |
| $\geq 50\mu\text{m}$ | 16*              | 10*                | 51                |

Testing of 6mmx120mm devices in a simulated use in a tortuous vessel model under clinically relevant flow conditions. \*Limit of Quantification is 360 particle count for  $\geq 10\mu\text{m}$ , 60 particle count for  $\geq 25\mu\text{m}$ ; and 30 particle count for  $\geq 50\mu\text{m}$ . BSC Data on file

**Table 4. Particulate Counts for FDA-Approved SFA Paclitaxel-Coated Balloons**

| Particulate Size | IN.PACT | Lutonix | Stellarex |
|------------------|---------|---------|-----------|
| 10-25 $\mu$ m    | 510,223 | 158,853 | 165,288   |
| 25-50 $\mu$ m    | 51,424  | 32,009  | 22,617    |
| >50 $\mu$ m      | 5,785   | 19,458  | 6,063     |

Testing of 6mmx80mm devices in a simulated use in a tortuous vessel model under clinically relevant flow conditions.

\*Limit of Quantification = 360 particle count for 10-25 $\mu$ m; 60 particle count for 25-50 $\mu$ m; and 30 particle count for  $\geq$ 50 $\mu$ m. BSC Data on file.

The results from BSC's extensive bench, preclinical, and clinical studies demonstrate that ELUVIA has a targeted local paclitaxel delivery, the lowest systemic and end organ paclitaxel exposure, and minimal downstream particulate counts. These differentiating characteristics form the mechanistic basis for ELUVIA's efficacy and safety profile.

#### 4. Paclitaxel-Eluting Stent Clinical Experience: ELUVIA

##### 4.1 PAD Mortality

Patients with PAD have elevated mortality risk relative to individuals without PAD, with rates of 15%-30% reported at 5 years.<sup>28-30</sup> Mortality risk increases depending on the PAD stage, and can vary greatly even within symptomatic cohorts.<sup>29-31</sup> Those who receive interventional treatment represent higher-risk subsets of PAD patients, with risk factors such as average age >65 years, comorbid coronary artery disease, diabetes, hypertension, and hyperlipidemia highly prevalent within clinical populations.<sup>29-31</sup> Mortality risk also increases with time, with an inflection point for increased risk approximately 2-3 years after presentation which is especially pronounced among patients with more severe PAD.<sup>30</sup> Although mortality rates for patients with PAD are high relative to a healthy population, death remains a relatively low frequency occurrence as reflected in the clinical literature.

##### 4.2 ELUVIA Mortality

The ELUVIA paclitaxel-eluting stent has been prospectively studied in two trials with complete follow-up through defined time points: MAJESTIC and IMPERIAL. The MAJESTIC first-in-human single-arm study followed 57 patients enrolled at 13 centers in Europe, Australia, and New Zealand and is complete with follow-up through 3 years. IMPERIAL enrolled 369 patients treated with ELUVIA across 3 cohorts: a randomized study (n=310) of ELUVIA vs. the paclitaxel-coated Zilver PTX stent, a single-arm study of patients with long lesions (ELUVIA only n=50), and a single-arm study of paclitaxel pharmacokinetics (ELUVIA only; n= 13; 4 patients were enrolled in both the long lesion and pharmacokinetics sub-studies). IMPERIAL was conducted at 65 centers in the United States, Austria, Belgium, Canada, Germany, Japan, and New Zealand. Two-year follow-up is complete in the IMPERIAL study, and long-term follow-up planned to 5 years. Additionally, ELUVIA is being compared with bare metal stents in the currently enrolling EMINENT RCT (N=500 ELUVIA, 250 bare metal stent), which is being conducted in Europe.

As treated mortality data from these ELUVIA clinical studies are shown in **Table 5** and **Table 6**. Pooled analysis of patients in MAJESTIC and IMPERIAL yielded a 2-year mortality rate of 6.5% (26/398). This rate aligns with cumulative incidence estimates (5-11% 2 years after presentation) for PAD patients meeting criteria for symptomatic PAD.<sup>30</sup> No additional deaths occurred among patients in MAJESTIC from 2 to 3 years of follow-up. The currently-available data from EMINENT show similar mortality rates between the ELUVIA and bare metal study arms (**Table 6**).

**Table 5. Cumulative Mortality Rates in MAJESTIC and IMPERIAL**

|                   | Complete Follow-up <sup>a</sup> |  |  |
|-------------------|---------------------------------|--|--|
|                   | MAJESTIC (N=57)                 | IMPERIAL ELUVIA RCT, LL, PK (N=369) <sup>b</sup> | Total MAJESTIC + IMPERIAL (N=426) <sup>b</sup> |
| 1 year            | 0.0% (0/56)                     | 1.7% (6/359)                                     | 1.4% (6/415)                                   |
| Cardiovascular    | 0.0% (0/56)                     | 0.8% (3/359)                                     | 0.7% (3/415)                                   |
| Noncardiovascular | 0.0% (0/56)                     | 0.8% (3/359)                                     | 0.7% (3/415)                                   |
| 2 year            | 3.6% (2/56)                     | 7.0% (24/342)                                    | 6.5% (26/398)                                  |
| Cardiovascular    | 1.8% (1/56)                     | 4.1% (14/342)                                    | 3.8% (15/398)                                  |
| Noncardiovascular | 1.8% (1/56)                     | 2.9% (10/342)                                    | 2.8% (11/398)                                  |
| 3 year            | 3.6% (2/55)                     | NA   | NA   |
| Cardiovascular    | 1.8% (1/55)                     | NA   | NA   |
| Noncardiovascular | 1.8% (1/55)                     | NA   | NA   |

Abbreviations: RCT, randomized controlled trial; LL, long lesion; PK, pharmacokinetics. <sup>a</sup>MAJESTIC follow-up is final at 3 years. IMPERIAL follow-up is complete through 2 years and ongoing through 5 years. <sup>b</sup>As treated.

**Table 6. Mortality in EMINENT**

|                   | Incomplete Follow-up <sup>a</sup>   |                                  |
|-------------------|-------------------------------------|----------------------------------|
|                   | EMINENT ELUVIA (N=332) <sup>b</sup> | EMINENT BMS (N=184) <sup>b</sup> |
| 1 year            | 2.1% (3/145)                        | 1.4% (1/72)                      |
| Cardiovascular    | 1.4% (2/145)                        | 0.0% (0/72)                      |
| Noncardiovascular | 0.7% (1/145)                        | 1.4% (1/72)                      |

Abbreviations: BMS, bare metal stent <sup>a</sup>EMINENT enrollment is ongoing. Crude rate calculated based on total deaths per number of patients at 1 year post-procedure; data lock 27 Mar 2019. <sup>b</sup>As treated.

### 4.3 ELUVIA Benefit-Risk Profile

Patients with symptomatic lower limb PAD have pain, impaired mobility and diminished quality of life and are at risk for progression to critical limb ischemia and amputation. Treatment with uncoated balloons or stents may improve patency in the short term, but lesions frequently restenose in a relatively short time frame necessitating repeat interventions, which are not without risk to the patient and cost to the healthcare system.<sup>32,33</sup> For example, reported 1-year target lesion revascularization rates following bare metal stenting in the femoropopliteal arterial segment are typically about 13%-14%,<sup>34-42</sup> and uncoated balloon angioplasty yields rates of about 27%-29%.<sup>43,44</sup> Patients with diabetes or lesions that are long, occluded, or severely calcified are generally considered to be at increased risk for restenosis. These characteristics were highly prevalent among patients treated with ELUVIA in clinical studies (**Table 7**).

**Table 7. Target Lesion Revascularization in Studies of the ELUVIA Drug-eluting Stent**

|           | IMPERIAL (N=368)                               |                                     |                               |                                |                               | MAJESTIC (N=57)  |
|-----------|--|-------------------------------------|-------------------------------|--------------------------------|-------------------------------|--|
|           | RCT (N=309)                                    | RCT Diabetic Subgroup (n=116)       | RCT CTO Subgroup (n=96)       | RCT Moderate/severe Ca (n=193) | Long Lesions Sub-study (N=50) |  |
| TLR       |  |                                     |                               |                                |                               |  |
| 1 year    | 4.5% (13/292)                                  | 3.7% (4/108)                        | 7.9% (7/89)                   | 2.8% (5/181)                   | 6.5% (3/46)                   | 3.6% (2/56)  |
| 2 years   | NA   | NA                                  | NA                            | NA                             | NA                            | 7.1% (4/56)  |
| 3 years   | NA   | NA                                  | NA                            | NA                             | NA                            | 14.5% (8/55)   |
| Reference | P180011_R001 and Gray et al, 2018 <sup>1</sup> | Müller-Hülsbeck, 2019 <sup>45</sup> | Vermassen, 2019 <sup>46</sup> | Vermassen, 2019 <sup>46</sup>  | Gray, 2018 <sup>47</sup>      | BSC data on file and Müller-Hülsbeck et al <sup>12</sup> |

Abbreviations: CTO, chronic total occlusion; RCT, randomized controlled trial; TLR, target lesion revascularization.

Paclitaxel has been shown to be an effective antirestenotic agent when applied to balloons or stents.<sup>48-51</sup> ELUVIA is the only peripheral device featuring targeted, controlled drug elution via a polymer matrix and the efficacy of its low dose and sustained elution has been verified clinically. Trial results have confirmed some of the highest patency rates and among the lowest target lesion revascularization rates attributed to endovascular treatments for symptomatic femoropopliteal PAD. Specifically, the single-arm first-in-human MAJESTIC study yielded a low TLR rate through 3 years (**Table 7**),<sup>12</sup> and in the IMPERIAL RCT, ELUVIA demonstrated a significantly improved patency rate through 1 year compared to the higher-dose, non-polymeric,

paclitaxel-coated comparator Zilver PTX.<sup>1</sup> In addition, patients treated with ELUVIA had a TLR rate of 4.5%.<sup>1</sup> This low TLR rate corresponded with a low hospital readmission rate, with ELUVIA-treated patients readmitted about half as often as patients treated with Zilver PTX over 12 months (3.9% vs 7.1%) and fewer hospital days.<sup>1</sup> In addition, patients in both arms of the study had improved symptoms, health-related quality of life, and walking function compared with baseline.<sup>1</sup> These benefits, specifically, low reintervention rates together with improved patient outcomes, were consistently observed even across patient subgroups typically at increased risk for restenosis at 1 year, including those with long lesions,<sup>47</sup> diabetes,<sup>45</sup> baseline occluded lesions or moderate/severe calcification (**Table 7**).<sup>46</sup>

In its March 15 Letter, FDA referred to the need to assess benefit-risk profile for individual patients stating that: “For some individual patients at particularly high risk for restenosis, clinicians may determine that the benefits of using a paclitaxel-coated product may outweigh the risks.”<sup>15</sup> Importantly, ELUVIA has demonstrated significant benefits across the entire spectrum of restenosis risk without evidence of significant safety or mortality tradeoffs.

## **5. Presence of a Signal and Causality**

### **5.1 Mortality Analyses of Paclitaxel-containing Devices**

It remains questionable and unproven that the root cause of the observed higher mortality in certain retrospective meta-analyses has a direct relationship to the presence of paclitaxel in the evaluated devices. In the March 15 Letter To Health Care Providers,<sup>15</sup> the FDA observed, “These data should be interpreted with caution for several reasons. First, there is large variability in the risk estimate of mortality due to the limited amount of long-term data. Second, these studies were not originally designed to be pooled, introducing greater uncertainty in the results. Third, the specific cause and mechanism of the increased mortality is unknown.”

Notably, the number of studies, patients, and devices contributing to the mortality calculations significantly decreased with the longer follow-up time frames. In addition, understanding possible effects of paclitaxel exposure is not possible without complete analysis of uniformly re-adjudicated patient level data, particularly with treatment arm crossover and previous interventions or subsequent reinterventions with paclitaxel-coated devices, which occurred in the analyzed studies.

Explanations unrelated to drug exposure may account for the signal observed in the meta-analysis by Katsanos et al. These include preferential follow-up for control-arm patients (i.e., more physician visits, closer monitoring, enhanced comorbidity management), which may improve survival in these arms. Not adjusting for between-arm imbalance of predisposing conditions or comorbidities associated with increased mortality risk in the cohort-level analysis could also contribute to a false signal.

Many flaws have been pointed out with the meta-analysis by Katsanos et al, yet the meta-analysis ultimately does not apply to polymer matrix-based paclitaxel eluting devices, such as ELUVIA, which were not included.<sup>6</sup> The forthcoming VIVA analysis will also not include ELUVIA due to the paclitaxel-coated randomized control arm instead of an uncoated device control arm, and lack of data beyond two years in IMPERIAL. Beyond not being directly represented in these analyses, ELUVIA presents substantial differences compared with the products addressed in these analyses with regard to drug delivery, initial dose and dose over time, and formulation of the drug, that limit generalizability of the results to ELUVIA. Therefore, concluding that any observed mortality signal in the Katsanos meta-analysis or other analyses of paclitaxel-coated products would also be applicable to ELUVIA and is inappropriate.

No evidence to date suggests increased all-cause mortality risk for patients treated with ELUVIA or with TAXUS, a polymer-matrix paclitaxel-eluting stent with a comparable mechanism of action. Longer-term results from IMPERIAL, as well as results from the currently enrolling EMINENT RCT, which includes ELUVIA and bare metal stent arms, will help to provide direct evidence regarding long-term all-cause mortality in patients treated with ELUVIA. However, as with the other studies underlying the Katsanos meta-analysis, long-term mortality was not a powered endpoint in these studies.

### **5.2 No Causal Link between Paclitaxel and All-Cause Mortality**

Currently, no plausible mechanistic link between paclitaxel and death has been postulated or established. To the contrary, systemic paclitaxel infusions are known to improve survival among cancer patients.<sup>52,53</sup> The periodically-repeated systemic doses of paclitaxel for chemotherapy are multiple orders of magnitude greater<sup>54</sup> than the doses following treatment with either paclitaxel-coated devices<sup>23,27,55,56</sup> or ELUVIA.<sup>1,57</sup> It is extremely unlikely that localized micro-doses associated with peripheral device use would have a negative effect on long-term survival.

As no local vascular-based causes of mortality have been identified, any paclitaxel effect on mortality would occur via a systemic or non-vascular mechanism and would be apparent following paclitaxel exposure regardless of the administration route or implant location. No such effect on mortality was seen among thousands of patients who received a TAXUS paclitaxel-eluting coronary stent with a design very similar to that of ELUVIA, and no systemic effect should be expected with peripheral application.

## 6. Next Steps

Maintaining patient access to beneficial treatment options where benefit outweighs potential risk is critical. BSC will continue to work with the FDA, industry partners, health care professionals, and patients to provide safe devices and to communicate information appropriately as more is learned through additional analyses.

BSC intends to continue enrollment; to the extent possible, and diligent follow-up for studies of ELUVIA, as shown in **Table 8**, and continue post-market surveillance through MDR reporting.

**Table 8: ELUVIA Clinical Studies**

| Study Name | Design                          | Status              | Total Enrollment                   | Number of ELUVIA Subjects            | Follow-up |
|------------|---------------------------------|---------------------|------------------------------------|--------------------------------------|-----------|
| IMPERIAL   | RCT 2:1 – ELUVIA vs. Zilver PTX | Long-term follow up | 465 RCT<br>50 long lesion<br>13 PK | 309 RCT<br>50* long lesion<br>13 PK* | 5 years   |
| EMINENT    | RCT 2:1 – ELUVIA vs. BMS        | Enrolling           | 750                                | 500                                  | 3 years   |
| REGAL      | Registry                        | Enrolling           | 500                                | 500                                  | 2 years   |

\*4 patients are included in both the long lesion and PK sub-studies

BSC will work with relevant groups on potential next steps such as guideline enhancements, the design and conduct of future PAD studies, and assessment of larger data sets which could potentially be used to investigate causality.

## 7. Conclusion

BSC is committed to patient safety. No causal link with paclitaxel and mortality has been established. The totality of clinical evidence from BSC's TAXUS coronary drug-eluting stents (DES) and ELUVIA has demonstrated that no mortality signal exists for polymer matrix-based drug-eluting stents. Furthermore, ELUVIA clinical data did not contribute to the signal in the original Katsanos analysis or in any subsequent meta-analyses completed to date.

BSC strongly recommends that the FDA and panel not group ELUVIA in the class of devices included in the various meta-analyses given the design differences reasonably justify that this unique device should be considered separately from paclitaxel-coated peripheral devices.

**8. References**

1. Gray WA, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet*. 2018;392(10157):1541-1551.
2. Yamaji K, Raber L, Zanchin T, et al. Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial. *Eur Heart J*. 2016;37(45):3386-3395.
3. Gada H, Kirtane AJ, Newman W, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv*. 2013;6(12):1263-1266.
4. Smits PC, Vlachojannis GJ, McFadden EP, et al. Final 5-Year Follow-Up of a Randomized Controlled Trial of Everolimus- and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice: The COMPARE Trial (A Trial of Everolimus-Eluting Stents and Paclitaxel Stents for Coronary Revascularization in Daily Practice). *JACC Cardiovasc Interv*. 2015;8(9):1157-1165.
5. Kirtane AJ, Leon MB, Ball MW, et al. The "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. *JACC Cardiovasc Interv*. 2013;6(4):325-333.
6. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. 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(24):e011245.
7. Ormiston JA, Charles O, Mann T, et al. Final 5-year results of the TAXUS ATLAS, TAXUS ATLAS Small Vessel, and TAXUS ATLAS Long Lesion clinical trials of the TAXUS Liberte paclitaxel-eluting stent in de-novo coronary artery lesions. *Coron Artery Dis*. 2013;24(1):61-68.
8. Kereiakes DJ, Cannon LA, Dauber I, et al. Long-term follow-up of the platinum chromium TAXUS Element (ION) stent: The PERSEUS Workhorse and Small Vessel trial five-year results. *Catheter Cardiovasc Interv*. 2015;86(6):994-1001.
9. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381(9867):629-638.
10. Stone GW, Ellis SG, Colombo A, et al. Long-term safety and efficacy of paclitaxel-eluting stents final 5-year analysis from the TAXUS Clinical Trial Program. *JACC Cardiovasc Interv*. 2011;4(5):530-542.
11. Spreen MI, Martens JM, Knippenberg B, et al. Long-Term Follow-up of the PADI Trial: Percutaneous Transluminal Angioplasty Versus Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. *J Am Heart Assoc*. 2017;6(4).
12. Müller-Hülsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cardelle J. Long-Term Results from the MAJESTIC Trial of the Eluvia Paclitaxel-Eluting Stent for Femoropopliteal Treatment: 3-Year Follow-up. *Cardiovasc Interv Ther*. 2017;40(12):1832-1838.
13. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther*. 2006;13(6):701-710.
14. Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. *J Vasc Surg*. 2011;54(2):394-401.
15. UPDATE: Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers. 2019; <https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm633614.htm>. Accessed April 15, 2019, 2019.
16. Shishehbor MH, Goel SS, Kapadia SR, et al. Long-term impact of drug-eluting stents versus bare-metal stents on all-cause mortality. *J Am Coll Cardiol*. 2008;52(13):1041-1048.
17. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. *Ann Intern Med*. 2007;147(10):703-716.
18. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370(9591):937-948.

19. Hasebe T, Yohena S, Kamijo A, et al. Fluorine doping into diamond-like carbon coatings inhibits protein adsorption and platelet activation. *J Biomed Mater Res A*. 2007;83(4):1192-1199.
20. Hasebe T, Ishimaru T, Kamijo A. Effects of surface roughness on anti-thrombogenicity of diamond-like carbon films. *Diamond & Related Mater*. 2007;16(N4-7):1343-1348.
21. Data on file at Boston Scientific. Represents total global sales of the PROMUS (Boston Scientific) and XIENCE (Abbott) stents since 2007.
22. Data on file at Boston Scientific. Represents total population of patients studied in the PROMUS and XIENCE series of clinical trials.
23. Dake MD, Van Alstine WG, Zhou Q, Ragheb AO. Polymer-free paclitaxel-coated Zilver PTX Stents--evaluation of pharmacokinetics and comparative safety in porcine arteries. *J Vasc Interv Radiol*. 2011;22(5):603-610.
24. Boitet A, Grassin-Delyle S, Louedec L, et al. An Experimental Study of Paclitaxel Embolisation During Drug Coated Balloon Angioplasty. *Eur J Vasc Endovasc Surg*. 2019.
25. Kolodgie FD, Pacheco E, Yahagi K, Mori H, Ladich E, Virmani R. Comparison of Particulate Embolization after Femoral Artery Treatment with IN.PACT Admiral versus Lutonix 035 Paclitaxel-Coated Balloons in Healthy Swine. *J Vasc Interv Radiol*. 2016;27(11):1676-1685 e1672.
26. Torii S, Yahagi K, Mori H, et al. Biologic Drug Effect and Particulate Embolization of Drug-Eluting Stents versus Drug-Coated Balloons in Healthy Swine Femoropopliteal Arteries. *J Vasc Interv Radiol*. 2018;29(7):1041-1049 e1043.
27. Speck U, Cremers B, Kelsch B, et al. Do pharmacokinetics explain persistent restenosis inhibition by a single dose of paclitaxel? *Circ Cardiovasc Interv*. 2012;5(3):392-400.
28. Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*. 2006;113(11):e463-654.
29. Sigvant B, Lundin F, Wahlberg E. The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg*. 2016;51(3):395-403.
30. Sartipy F, Sigvant B, Lundin F, Wahlberg E. Ten Year Mortality in Different Peripheral Arterial Disease Stages: A Population Based Observational Study on Outcome. *Eur J Vasc Endovasc Surg*. 2018;55(4):529-536.
31. Feringa HH, Bax JJ, Hoeks S, et al. A prognostic risk index for long-term mortality in patients with peripheral arterial disease. *Arch Intern Med*. 2007;167(22):2482-2489.
32. Secemsky EA, Schermerhorn M, Carroll BJ, et al. Readmissions After Revascularization Procedures for Peripheral Arterial Disease: A Nationwide Cohort Study. *Ann Intern Med*. 2018;168(2):93-99.
33. Mahoney EM, Wang K, Keo HH, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes*. 2010;3(6):642-651.
34. Garcia L, Jaff MR, Metzger C, et al. Wire-Interwoven Nitinol Stent Outcome in the Superficial Femoral and Proximal Popliteal Arteries: Twelve-Month Results of the SUPERB Trial. *Circ Cardiovasc Interv*. 2015;8(5).
35. Bosiers M, Deloose K, Callaert J, et al. 4-French-compatible endovascular material is safe and effective in the treatment of femoropopliteal occlusive disease: results of the 4-EVER trial. *J Endovasc Ther*. 2013;20(6):746-756.
36. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation vs. balloon angioplasty for lesions in the superficial femoral and proximal popliteal arteries of patients with claudication: three-year follow-up from the RESILIENT randomized trial. *J Endovasc Ther*. 2012;19(1):1-9.
37. Laird JR, Jain A, Zeller T, et al. Nitinol stent implantation in the superficial femoral artery and proximal popliteal artery: twelve-month results from the Complete SE multicenter trial. *J Endovasc Ther*. 2014;21(2):202-212.
38. Cordis. SMART CONTROL SSED (STROLL). 2012.  
[http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/P120002b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120002b.pdf). Accessed 20 April 2016.

39. Matsumura JS, Yamanouchi D, Goldstein JA, et al. The United States Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal By using the Protege Everflex Nitinol Stent System II (DURABILITY II). *J Vasc Surg.* 2013;58(1):73-83 e71.
40. Powell RJ, Jaff MR, Schroe H, Benko A, Diaz-Cardelle J, Muller-Hulsbeck S. Stent placement in the superficial femoral and proximal popliteal arteries with the innova self-expanding bare metal stent system. *Catheter Cardiovasc Interv.* 2017;89(6):1069-1077.
41. Schillinger M, Sabeti S, Loewe C, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Engl J Med.* 2006;354(18):1879-1888.
42. Jeon-Slaughter H, Khalili H, Tsai S, et al. Comparative Effectiveness Study of Drug-Eluting and Bare-Metal Peripheral Artery Stents in Endovascular Femoropopliteal Artery Revascularization. *J Invasive Cardiol.* 2018;30(10):373-379.
43. Jongsma H, Bekken JA, de Vries JP, Verhagen HJ, Fioole B. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty in patients with femoropopliteal arterial occlusive disease. *J Vasc Surg.* 2016;64(5):1503-1514.
44. Jaff MR, Nelson T, Ferko N, Martinson M, Anderson LH, Hollmann S. Endovascular Interventions for Femoropopliteal Peripheral Artery Disease: A Network Meta-Analysis of Current Technologies. *J Vasc Interv Radiol.* 2017;28(12):1617-1627 e1611.
45. Müller-Hülsbeck S. Diabetic Patients Treated in the IMPERIAL Randomized Trial Comparing Eluvia and Zilver PTX Stents [Abstract]. *LINC, Leipzig.* 2019.
46. Vermassen F. Challenging Baseline Lesion Characteristics: Subgroup Analysis of Patients Treated in the IMPERIAL Randomized Trial [Abstract]. *Charing Cross Symposium, London.* 2019.
47. Gray WA. 1-Year Outcomes for Eluvia in Long Lesions: IMPERIAL Long Lesion Sub-study [Abstract]. *VIVA, Las Vegas.* 2018.
48. Tepe G, Laird J, Schneider P, et al. Drug-Coated Balloon versus Standard Percutaneous Transluminal Angioplasty for the Treatment of Superficial Femoral and/or Popliteal Peripheral Artery Disease: 12-Month Results from the IN.PACT SFA Randomized Trial. *Circulation.* 2015;131(5):495-502.
49. Krishnan P, Faries P, Niazi K, et al. Stellarex Drug-Coated Balloon for Treatment of Femoropopliteal Disease: 12-Month Outcomes from the Randomized ILLUMENATE Pivotal and Pharmacokinetic Studies. *Circulation.* 2017;136(12):1102-1113.
50. Rosenfield K, Jaff MR, White CJ, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. *N Engl J Med.* 2015;373(2):145-153.
51. Dake MD, Ansel GM, Jaff MR, et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. *Circulation.* 2016;133(15):1472-1483.
52. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev.* 2007(4):CD004421.
53. Ghersi D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev.* 2015(6):CD003366.
54. Stage TB, Bergmann TK, Kroetz DL. Clinical Pharmacokinetics of Paclitaxel Monotherapy: An Updated Literature Review. *Clin Pharmacokinet.* 2018;57(1):7-19.
55. Yazdani SK, Pacheco E, Nakano M, et al. Vascular, downstream, and pharmacokinetic responses to treatment with a low dose drug-coated balloon in a swine femoral artery model. *Catheter Cardiovasc Interv.* 2014;83(1):132-140.
56. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. *JACC Cardiovasc Interv.* 2014;7(1):10-19.
57. Hou D, Huibregtse BA, Eppihimer M, et al. Fluorocopolymer-coated nitinol self-expanding paclitaxel-eluting stent: pharmacokinetics and vascular biology responses in a porcine iliofemoral model. *EuroIntervention.* 2016;12(6):790-797.