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Dear Valued Customer,

We wanted to share with you Boston Scientific's perspective on the recent news about paclitaxel-coated peripheral artery endovascular devices. We have worked diligently over the years to deliver meaningful innovations for your patients supported by Level 1 evidence. We believe paclitaxel is safe and will work transparently with all stakeholders to continue to move the field forward.

Paclitaxel-based endovascular devices have represented a significant advancement in treatment options for patients with peripheral artery disease. These devices have significantly reduced restenosis rates by up to 50% compared to non-coated devices and have helped hundreds of thousands of patients avoid costly and potentially hazardous reinterventions. We continue to believe in both the safety and efficacy of Boston Scientific's paclitaxel devices, the Eluvia Drug-Eluting Stent and the Ranger Drug-Coated Balloon. Based on all available clinical data specific to Boston Scientific paclitaxel devices out to 3 years, we have not observed any safety signal in all-cause mortality rates.

On March 15, the FDA published a letter to US Health Care Providers following an initial review of all available paclitaxel-coated devices. As always, patient safety remains our top priority and we are working with the FDA in a very transparent manner to help answer questions about the safety of these devices.

The FDA letter made the following points:

- The FDA stated that there are known benefits to paclitaxel-coated devices. However, the *preliminary* analysis of three trials with 5-year follow-up data has identified a potentially concerning signal of increased all-cause mortality at the 5-year interval. *It is important to note that the IMPERIAL trial, a large, global randomized trial evaluating Boston Scientific's Eluvia stent, was not one of these trials, nor part of the Katsanos, et al. meta-analysis*[1].
- The FDA acknowledged that the exact mechanism of action linking paclitaxel to late all-cause mortality is unclear, and these data should be interpreted with caution.
- The FDA announced they will be holding a panel meeting in the coming months to evaluate all available data and will attempt to identify the cause of the signal.
- The FDA recommended that physicians discuss and weigh the risks and benefits with patients prior to using a paclitaxel device. The FDA said that alternative treatment options should generally be used until the panel has further information. In their recommendations, the FDA indicated that clinicians may determine that the benefits of using a paclitaxel device may outweigh the risks for some patients at high risk for restenosis. The FDA statement can be found here.
  https://www.fda.gov/MedicalDevices/Safety/LetterstoHealthCareProviders/ucm633614.htm

While the FDA panel may have further recommendations, a paper published in the *Journal of Vascular Surgery* has identified those factors that may put a patient at high risk of restenosis. These factors include diabetes, long lesions (greater than 150 mm), critical limb ischemia (CLI), dialysis, poor runoff and female gender. For full reference, please see the manuscript listed at the end of this letter[2].

The Eluvia stent was purposely designed to deliver the best clinical results with the lowest paclitaxel dose density of *any* product on the market:

- The Eluvia drug dose density is 12 to 20 times less than other paclitaxel-coated devices on the market.
- Eluvia is the only paclitaxel-based device that utilizes a thrombo-resistant polymer, allowing it to deliver drug to the lesion in a highly controlled manner with the majority of drug transferred into the lesion instead of downstream.
- The Pharmacokinetic sub-study conducted in the IMPERIAL trial showed that paclitaxel from Eluvia is undetectable in plasma after 10 minutes.

As you evaluate your patients who may be at higher risk for restenosis, we wanted to share the most recently presented data for the Eluvia stent:

- The IMPERIAL Long Lesion sub-study reported an 87.9% 12-month primary patency rate (Kaplan-Meier) in lesions with an average length of 163 mm.
- The IMPERIAL Diabetic Subgroup demonstrated an 87.4% 12-month primary patency rate (Kaplan-Meier).
- The Münster All-comers Eluvia Registry, which had an average lesion length of 200 mm, and in which nearly half of the patients had CLI and 79% had total occlusions, reported a 12-month primary patency rate of 87%.

All safety events in Boston Scientific clinical trials of Eluvia were carefully reviewed by an independent clinical events committee. In the IMPERIAL trial, Eluvia demonstrated an excellent safety profile with a TLR rate of 4.5% at 1 year. The MAJESTIC trial reported a 15% TLR rate at 3 years with Eluvia. In perspective, TLR rates for uncoated stents and uncoated PTA reported at 3 years are 31.3%[3] and 34.0%[4], respectively. TLR is not a benign event and any peripheral artery intervention carries potential complications.

With respect to mortality, the IMPERIAL trial reported a 2.0% all-cause mortality rate at 1 year in the Eluvia arm. This rate is not greater than rates observed with contemporary non-coated devices. Of the six patients who died, three of the deaths were related to cardiac problems, and three were non-cardiovascular related. Eluvia demonstrated a 3.6% all-cause mortality rate at 3 years in the MAJESTIC trial, which is not higher than rates reported with non-coated devices. Of the two patients who died, one death was due to cardiac problems and the other was related to complications from metastatic squamous cell carcinoma.

The Ranger DCB was purposely designed with a low drug dose density (2µg/mm^2) and a proprietary excipient for efficient, local drug delivery. The Ranger DCB has been shown to produce the lowest amount of downstream particulates when compared to other DCBs[5].

In the Ranger SFA Trial (2:1 randomization), there was no statistically significant difference between Ranger DCB and uncoated balloons (PTA) for all-cause mortality at 3 years (Ranger: 13.8%, n=9/65; PTA: 10.7%, n=3/28). Of the 9 patients who died in the Ranger arm, 3 of the deaths were related to cardiac problems and 6 were non-cardiovascular related. 12-month all-cause mortality results were included in the Katsanos et al meta-analysis which also showed no difference between Ranger DCB and PTA. Patients enrolled in the global RANGER II SFA Trial will be followed out to 5 years. The pharmacokinetic sub-study within the Ranger II SFA Trial has just completed enrollment and the results of this analysis will be available in late 2019.

At BSC we are firmly committed to being transparent with the totality of our data, providing truthful and complete analyses, as this is the only way to further advance the field and better serve patients and the scientific community. We hope this summary is helpful to you as you make decisions on what is best for your patients.

Best regards,

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[1]Katsanos K, et al. J Am Heart Assoc. 2018;7(24):e011245. doi: 10.1161/JAHA.118.011245.
[2]Soga Y, et al. J Vasc Surg. 2011;54(4):1058-66. doi: 10.1016/j.jvs.2011.03.286.
[3]Rocha-Singh KJ, et al. Catheter Cardiovasc Interv. 2015;86(1):164-70. doi: 10.1002/ccd.25895.
[4]Schneider PA, et al. Circ Cardiovasc Interv. 2018;11(1):e005891. doi: 10.1161
[5]Scheinert D, LINC 2019.