FDA Circulatory System Devices Panel
Advisory Committee Meeting on
Paclitaxel-Coated DCB and DES Late Mortality

June 19 & 20, 2019

FDA Panel Questions- Day 1

Question 1: Presence of Signal

An FDA meta-analysis of the pivotal randomized controlled trials (RCTs) of US approved paclitaxel-coated products used to treat peripheral arterial disease in the femoropopliteal arteries presented a trend of increased late mortality starting at 2 years (data from 4 trials) through 5 years (data from 3 trials) when compared to non-paclitaxel-coated devices. At 2 years, fixed and random effects models showed mortality RR estimates >1 (RR = 1.42 for a fixed effects model and RR = 1.29 for a random effects model), but the corresponding 95% confidence intervals (CIs) that included one. At three years, RR = 1.46 for a fixed effects model and RR=1.41for a random effects model, and at four years, RR= 1.53 for both fixed and random effects model. At five years, RR =1.57 with the lower limit of the 95% CI >1 for both fixed and random effects models. Note that these results should be interpreted with caution, due to limited number of studies with long-term follow-up data and the potential impact of missing data on the results. Based on your interpretation of this data, please discuss the potential presence and magnitude of a late mortality signal associated with paclitaxel-coated devices.

Question 2: Class Effect

Data from individual pivotal RCTs (Medtronic IN.PACT, Cook Zilver PTX and Lutonix LEVANT 2) showed a trend of increased late mortality risk associated with paclitaxel-coated devices starting at 2 years (and subsequent timepoints) when compared to non-coated devices. The RR estimates were >1, for the three individuals RCTs with follow-up data up to 5 years. The Philips ILLUMENATE RCT had a RR estimate of 2.02 at 1 year, 0.95 at 2 years, and 0.84 at 3 years. The 3-year crude mortality rate for the paclitaxel-coated device group observed in the Philips ILLUMENATE RCT (10.9%) is comparable to the 3-year mortality outcomes seen in the other 3 pivotal RCTs (10.6%, 11.5% and 9.9%). However, the percent mortality rate in the Philips ILLUMENATE RCT control group (13.0%) is higher than the other three studies (2.8%, 8.8%, 6.3%). Based on available co-variates, the ILLUMENATE control patients were not at higher risk for mortality at baseline compared to the other RCTs. Given these results and considering the limitations in the data, please discuss the strength of the evidence supporting a late mortality risk class effect among all US-approved paclitaxel-coated devices used to treat femoropopliteal arterial disease regardless of dose, platform (i.e., balloon versus stent), and drug formulation.

Question 3: Impact of Missing Data

In the initial analyses, the pivotal trials had approximately 14.4-38.3% missing data at 5 years with as much or more missing data noted in the OUS RCTs and registries at 3 years and beyond. Sponsors attempted to gain additional information on patients lost to follow-up, resulting in approximately 2.7-26.0% missing data at 5 years for the pivotal RCTs. Missing data was generally comparable in the paclitaxel-coated device arm compared to the control for these trials. The amount of missing data up to 5

years introduces some uncertainty regarding the long-term mortality signal. A sensitivity analysis was performed to evaluate the potential impact of missing data on the meta-analysis results. However, the full impact of missing data on the meta-analysis results remains unclear, especially when one considers the impact of uncollected information (e.g., concomitant medications that may affect mortality, repeat paclitaxel exposure). Please discuss how missing data influence your interpretation of the meta-analysis results with regard to a potential late mortality signal associated with paclitaxel-coated devices used to treat femoropopliteal arterial disease.

Question 4: Subgroup Analyses

Subgroup analyses were conducted to assess heterogeneity in treatment effects across region (US/OUS) and gender (Male/Female). No clear trends were observed based on region or gender. In addition, baseline characteristics were compared between patients that died and patients remaining alive at the end of available follow-up period for the pivotal studies. In general, patients who died were older with more co-morbidities and had longer lesion lengths compared to surviving subjects. However, no consistent pattern was determined. Please discuss whether these analyses help identify specific patient subgroups that are at increased (or reduced) risk of late mortality following treatment with paclitaxel-coated devices.

Question 5: Cause of Death

FDA evaluated the pivotal trial death narratives for trends in the potential causes of death and made the following observations:

- Among non-cardiovascular death subtypes, the most common causes of death categorized by the sponsor (in descending order of frequency) were malignancy, unknown, pulmonary, infection, gastrointestinal and renal. Except for the category of infection, numerically higher mortality rates were seen in all aforementioned categories in patients treated with paclitaxel-coated devices compared to the uncoated control devices. Lung cancer was the most frequent malignancy in both groups.
- Among cardiovascular mortality subtypes, the most common causes of death categorized by the sponsor (in descending order of frequency) were other, heart failure, sudden death, unknown, myocardial infarction, and stroke. Higher rates were seen in all aforementioned categories in patients treated with paclitaxel-coated devices compared to the uncoated control devices. (Note that descriptions of "other" are included in Table 13 for the pivotal studies and Appendix I for all studies.)

Please discuss whether the cause of death data supports the presence of a late mortality signal associated with paclitaxel-coated device treatment and whether the data suggests a mechanism for this signal.