Paclitaxel-Coated Drug Coated Balloon and Drug-Eluting Stent Late Mortality Panel

Circulatory System Devices Panel Meeting
General Issues Meeting:
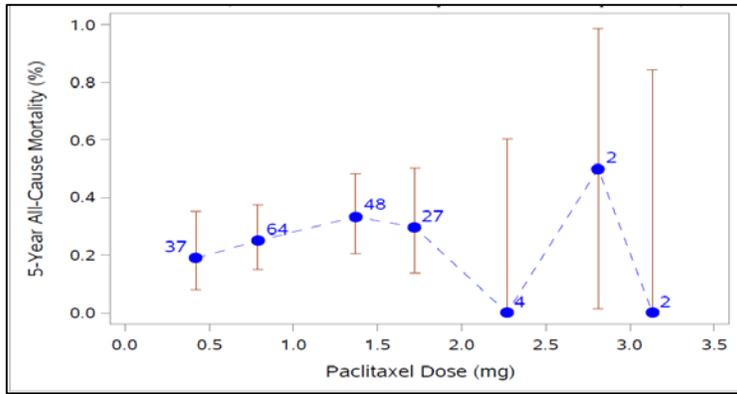
Day Two Questions
June 20, 2019
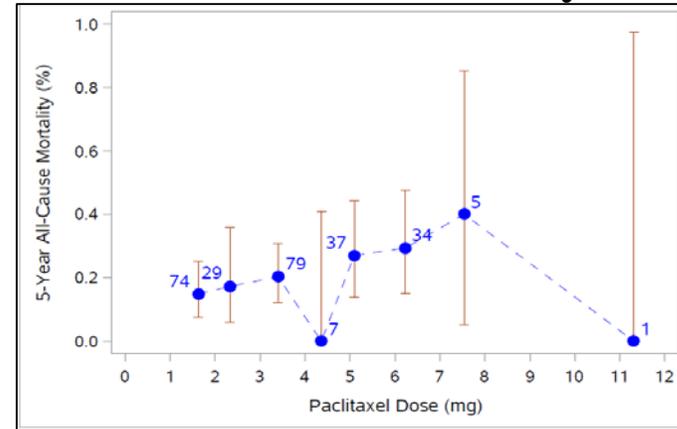
Question 6: Paclitaxel Dose/Mortality Relationship

Please discuss the relationship between paclitaxel dose and mortality.

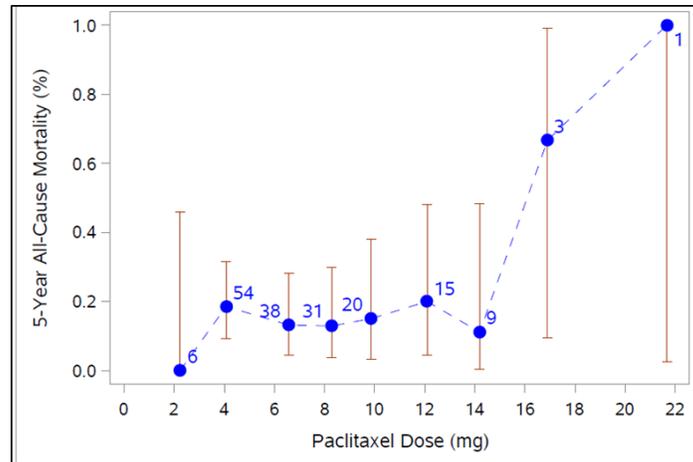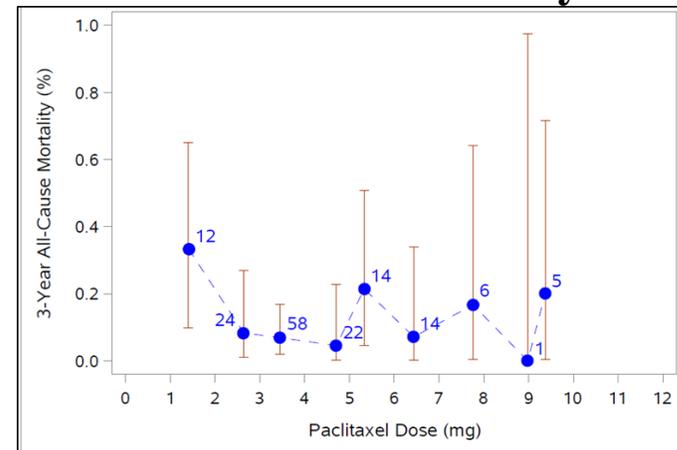**All-Cause Mortality Rate for Paclitaxel Dose (AT Population):**
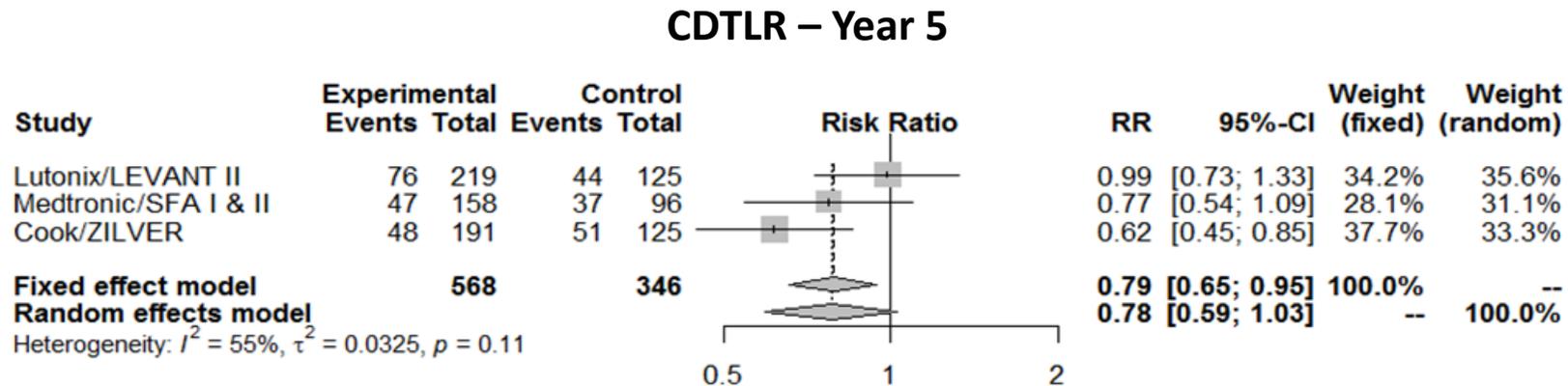
Question 7: Pre-clinical Studies

FDA re-evaluated the pre-clinical animal studies that were previously conducted for approved devices in order to determine if any data were available, including safety and PK evaluations, to associate a potential cause for the increase in mortality. From this review, no conclusive evidence was available to FDA to attribute causality. Drug related changes in downstream tissues for treated hind limbs were noted at low levels in acute, 30 day, and 90-day timepoints, sometimes containing crystalline drug material. However, no skeletal muscle lesions were large enough to produce clinical symptoms in the animals. There was no evidence of device-related bone marrow suppression, hepatic, or renal toxicity. There were no reports of malignancy or unusual gross findings in any of the reviewed animal studies. Extremely low animal mortality and relatively low morbidity rates were observed. However, the animal studies were relatively shortly in duration and were not designed to specifically evaluate for late effects of the drug. Please comment on whether any of the pre-clinical animal data provide mechanistic insights into the late mortality signal and discuss and describe what new animal studies, if any, may be helpful.

Question 8: Benefit-Risk Profile

Please discuss benefit-risk considerations related to paclitaxel-coated DCB and DES

CDTLR – Year 5

Study	Experimental Events	Total	Control Events	Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Lutonix/LEVANT II	76	219	44	125		0.99	[0.73; 1.33]	34.2%	35.6%
Medtronic/SFA I & II	47	158	37	96		0.77	[0.54; 1.09]	28.1%	31.1%
Cook/ZILVER	48	191	51	125		0.62	[0.45; 0.85]	37.7%	33.3%
Fixed effect model		568		346		0.79	[0.65; 0.95]	100.0%	--
Random effects model						0.78	[0.59; 1.03]	--	100.0%

Heterogeneity: $I^2 = 55\%$, $\tau^2 = 0.0325$, $p = 0.11$

$NNT_{(5\ YEARS)}$ avoid clinically driven TLR = 13 pts
$NNH_{(5\ YEARS)}$ experience mortality event = 14 pts

Question 9: Post Market Studies/Surveillance

If you conclude that the totality of the available data shows that the benefits outweigh the risks for paclitaxel-coated devices, but the potential late mortality signal is not fully understood, please discuss whether post-approval studies or post-market surveillance assessments are recommended. Please discuss the objectives of new post-market data collections, what information should be collected, study endpoints, and study design. In addition, please comment on the feasibility of conducting new studies of paclitaxel-coated devices in patients with symptomatic SFA/PPA disease.

Question 10: Labeling

Based on your conclusions regarding the presence and potential cause of a late mortality signal, please discuss modifications, if any, should be made to the labeling of all approved paclitaxel-coated devices for PAD, as well as devices being studied in clinical trials, in order to convey appropriate safety information.

Question 11: Changes to Study Design

Please discuss any study design recommendations to better evaluate these devices for PAD.

a. Is a primary safety endpoint at 12-month is sufficient?

b. Can the death adjudication process can be improved to help determine potential causes for late mortality?

c. What information should be included in the informed consent document?

d. Comments on study design, control population, statistical analysis plan, and efforts to minimize missing data.

Question 12: Other Indications

Please comment on whether you believe any of your above recommendations are applicable to paclitaxel-coated devices with other indications for use. Please also discuss whether you believe benefit-risk considerations for these indications (e.g., AVF, CLI) are likely to be different than for SFA/PPA disease.