U.S. FOOD & DRUG ADMINISTRATION

Paclitaxel-Coated Drug-Coated Balloon (DCB) and Drug-Eluting Stent (DES) Late Mortality Panel

Circulatory System Devices Panel Meeting:
General Issues Meeting

Day Two (45 min)
June 20, 2019

FDA Presentation – Day Two

Section 1: Recap from Day One

Section 2: Pre-clinical Background

Section 3: Animal Safety Studies

Section 4: Dose Analysis

Section 5: Benefit/Risk – TLR

Section 6: Next Steps: PAS and Labeling

Section 7: Other Indications

Section 8: Day Two Summary

Day One Summary

- Presence of Signal
- Class Effect
- Impact of Missing Data
- Subgroup Analyses
- Cause of Death

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Paclitaxel Dosage for PAD

- 0.167 µg/mm^2 to 3.5 µg/mm^2 (dose per surface area)
- Maximum total drug load ranges from 0.1 mg to 17 mg
- The paclitaxel dose during DCB and DES treatment is orders of magnitude less than intravenous administration for cancer treatment
- Major differences in drug formulation and the route of administration may affect drug activity and metabolism

Pre-Clinical Animal Studies

- Over 30 animal studies were conducted for the 5 approved devices
- Safety (1X), Safety Margin (3X) dose, and Pharmacokinetic (PK) Studies were conducted separately for these devices
- Studies date back to early 2000s, so study design may be different than feedback FDA typically provides
- Limitations: Previous studies may not be consistent with current feedback (tissue and duration)

Paclitaxel Concentrations in Local Vessels and Plasma

- Local Vessel Concentration: Drug levels are detectable in the local vasculature (i.e., target lesion/artery wall) beyond 60 days with some studies demonstrating local arterial tissue levels above the level of quantitation at 180 and 270 days
- Plasma Concentration: Paclitaxel in plasma cleared rapidly from systemic circulation. Immediately post-procedure, detectable levels were low and generally declined to levels below quantitation between 6 to 24 hours

Paclitaxel Concentrations in Downstream Tissues and Organs

- Drug levels were evaluated in downstream tissues and organs of elimination
  - The downstream tissues evaluated for drug dosage was typically distal vasculature
  - Safety evaluations also included evaluations of the gluteus maximus, gracilis, semitendinosus, and semimembranosus muscles, and coronary bands (of the hooves)
  - Drug levels were also evaluated in organs of elimination such as kidneys, liver, lung, and spleen

Paclitaxel Concentrations in Downstream Tissues and Organs

- The detectable drug levels in these tissues and organs were assessed at acute and chronic time points
- Drug levels were detectable in the downstream tissues and organs of elimination beyond 90 days in most cases
- The highest drug levels for organs were in the lung, and were within the cytostatic potency range for paclitaxel for one device
- Levels were generally lower in the liver and kidneys and cleared more quickly

Adverse Effects Related to Paclitaxel

- The long-term effects of paclitaxel exposure in patients with PAD are largely unknown
- There are numerous adverse effects associated with paclitaxel use for cancer treatment, which can include:
  - neutropenia, hypersensitivity (e.g., skin reactions, dyspnea), cardiovascular effects (e.g., hypotension, bradycardia, hypertension), anaphylaxis, and nausea
- Based on literature reports, it has been reported that the effects of paclitaxel may be concentration-dependent
  - At high concentrations, paclitaxel is cytotoxic
  - At low concentrations paclitaxel is cytostatic, but may have other properties (i.e., pro-inflammatory and pro-angiogenic) which may result in other unintended effects
- Even though low doses of paclitaxel are used in DES and DCB, FDA does not believe there is evidence to suggest that no adverse effects can be experienced at this dose

Pre-clinical Conclusions for Paclitaxel Dosage and Concentration

- Regardless of low dose and single administration, paclitaxel was resident in local and downstream tissues for 60 days and beyond, and in some cases for as long as 270 days (last time point assessed).
- Though no relationship could be gleaned from paclitaxel concentration and local tissue effects, there is the potential that the drug could be having an effect on various tissue systems during its residence and thus allowing for chronic effects

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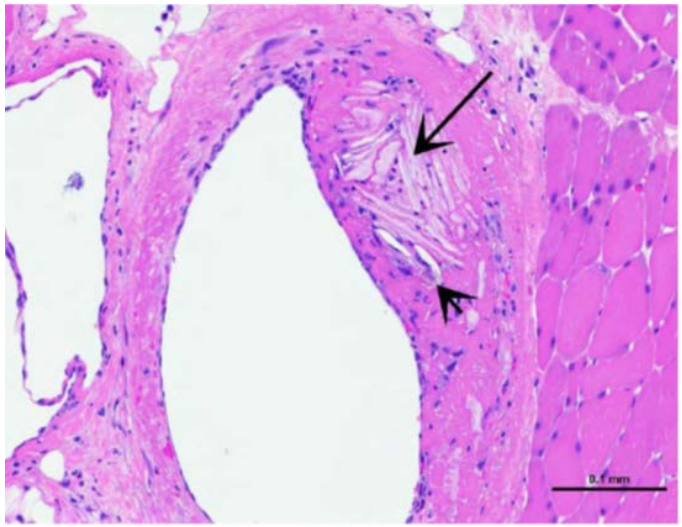
Preclinical Animal Vascular Safety Studies

- FDA review of all preclinical safety studies for PMA approved paclitaxel DCB and DES.
- 22 separate GLP vascular safety studies conducted between 2004 and 2018
- Naïve iliofemoral arteries of 512 non-diseased domestic or Yucatan mini-swine
- Nominal and 3X safety margin paclitaxel doses evaluated.

Preclinical Animal Safety Study Design

- Cohorts of 6-10 were exposed to the test and control devices

- 1-7 days, 30 days, 90 days, and 180 days prior to sacrifice (210 for one study)



- Study endpoints:
  - Acute device delivery and handling
  - General animal health
  - Angiographic imaging
  - Comprehensive gross pathology
  - Downstream and major systemic organ histopathology,
  - Arterial target tissue histomorphologic and histomorphometric analysis

Animal Safety Study Results

- Low animal mortality and low morbidity rates
- No evidence of device-related bone marrow suppression, hepatic or renal toxicity
- No reports of malignancy or unusual gross findings
- Medial smooth muscle loss with proteoglycan and collagen deposition was commonly reported
- Drug related changes in downstream skeletal muscle and coronary band arterioles noted in DCB treated hind limbs noted at low levels in acute, 30 day and 90-day timepoints, sometimes containing crystalline drug material.
- Downstream findings rare to absent with DES

Animal Safety Study Conclusions

- No systemic pathologic changes which appeared to be device or drug-related
- Reviewed data does not suggest a potential mechanism for increased late mortality observed in human study subjects.
- Chronic time-points for animal study data is still short term compared to the observed safety signal

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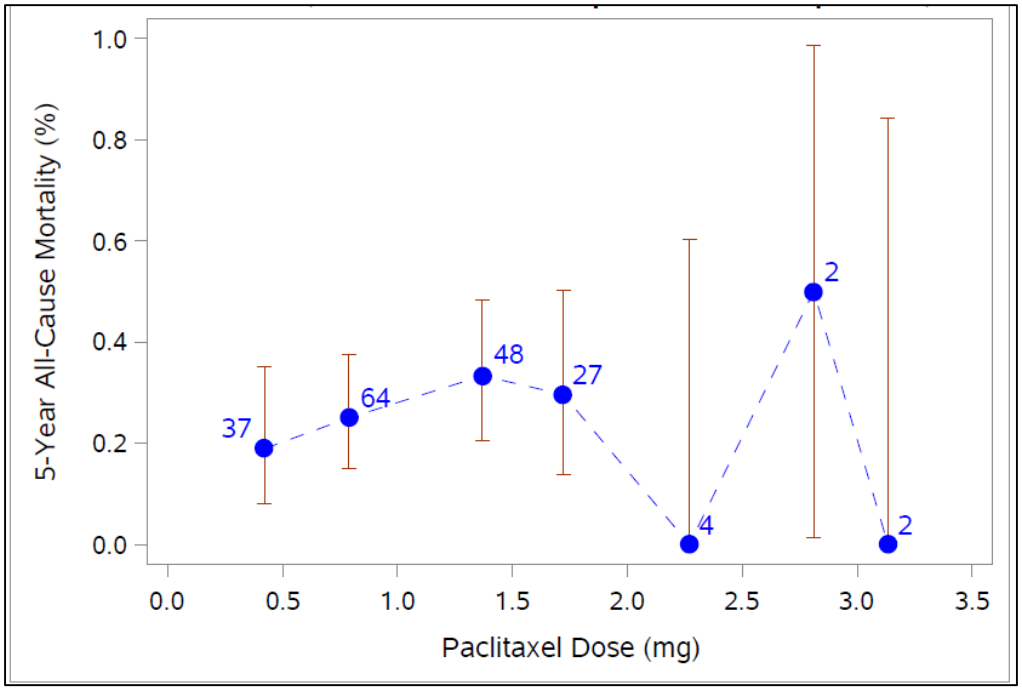
Dose Analysis

- Pivotal Trials (AT Population)
- Known 5-Year Mortality Separated Into Dose Groups
- Univariate Cox proportional hazard (PH) model



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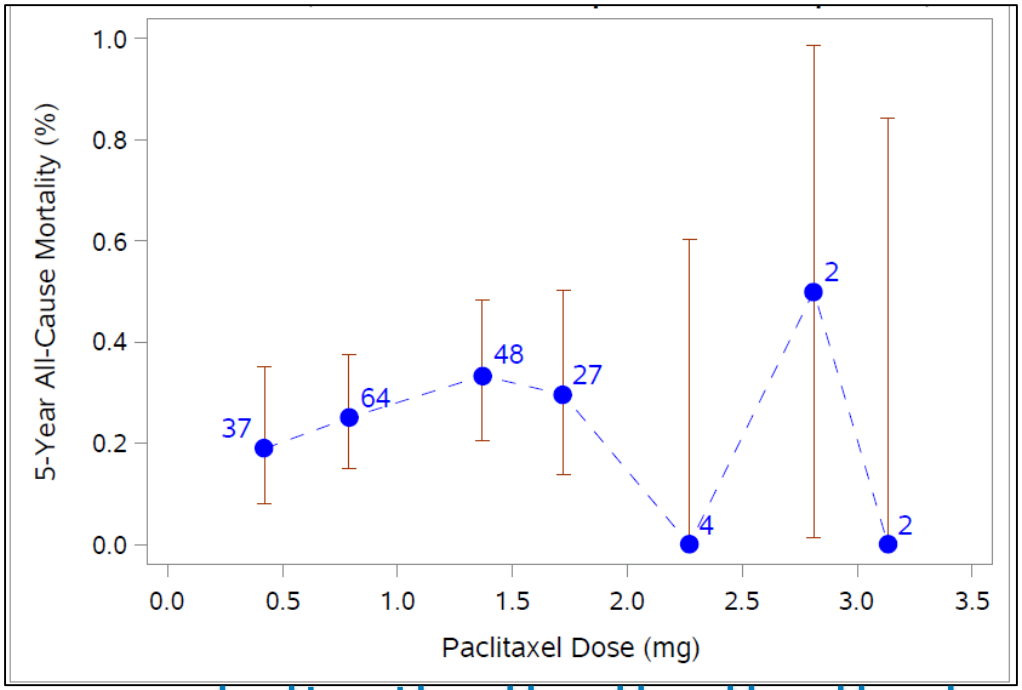

7-9 DOSE GROUPS

Dose Analysis

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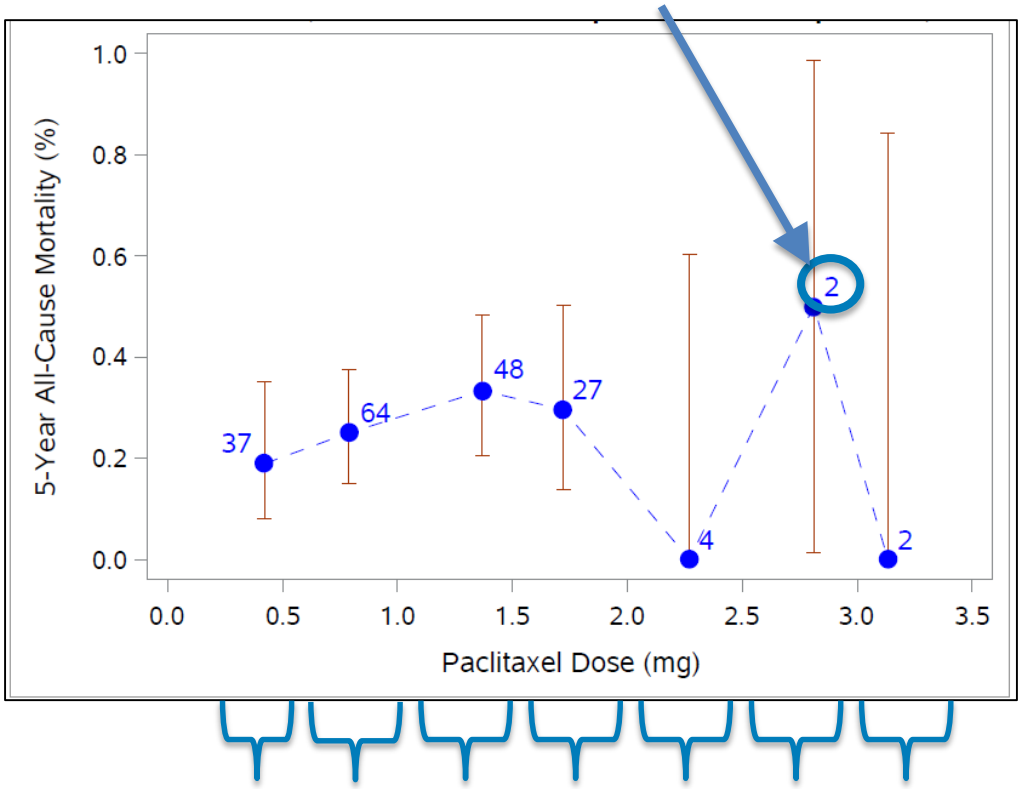
 # PTS IN EACH DOSE GROUP WITH KNOWN VITAL STATUS



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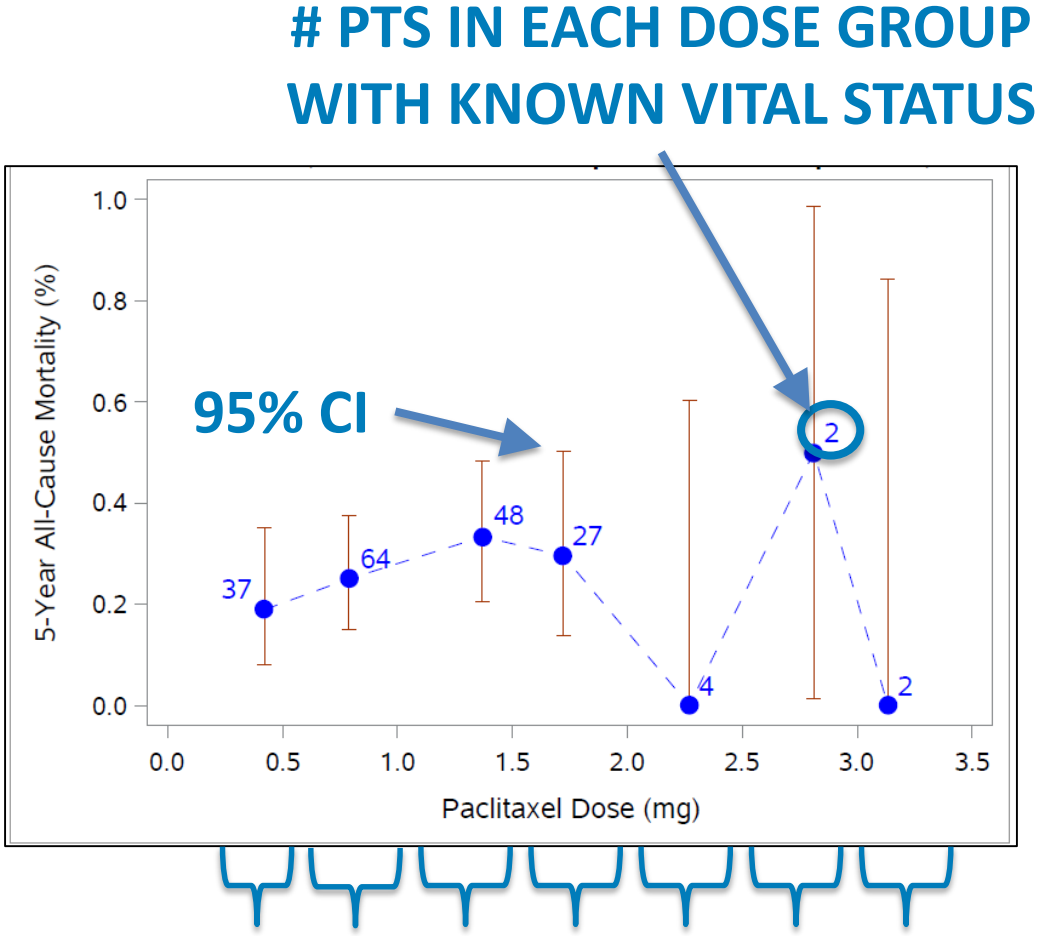
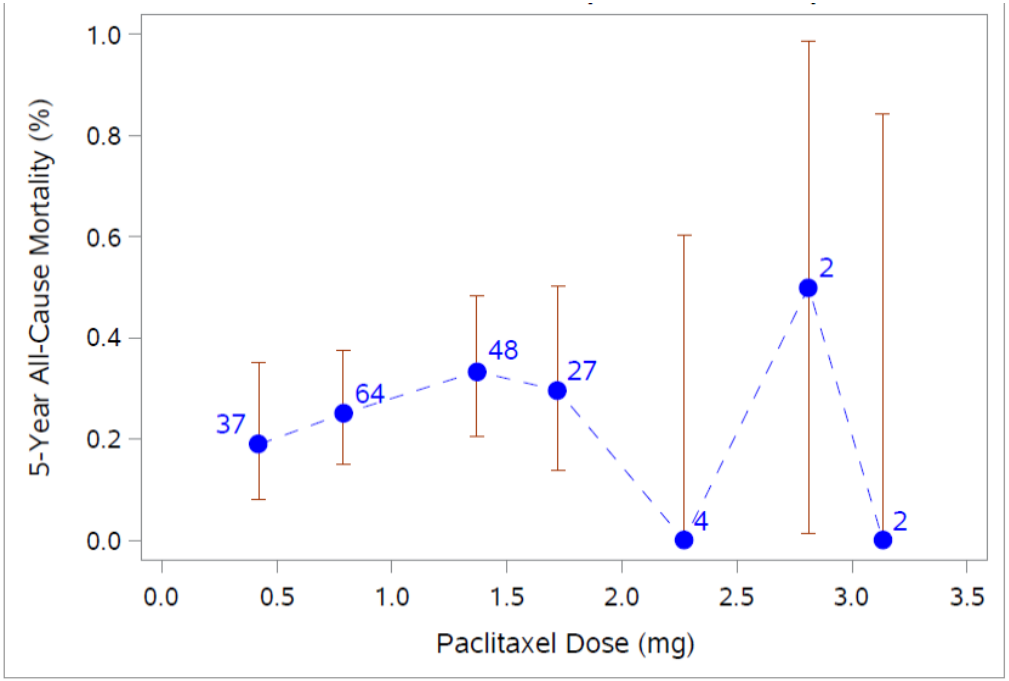


Dose Analysis – Zilver PTX DES

- Mean Dose = 1.1 ± 0.5 mg (range of 0.3-3.2 mg)
- No definitive dose trend
- P = 0.5

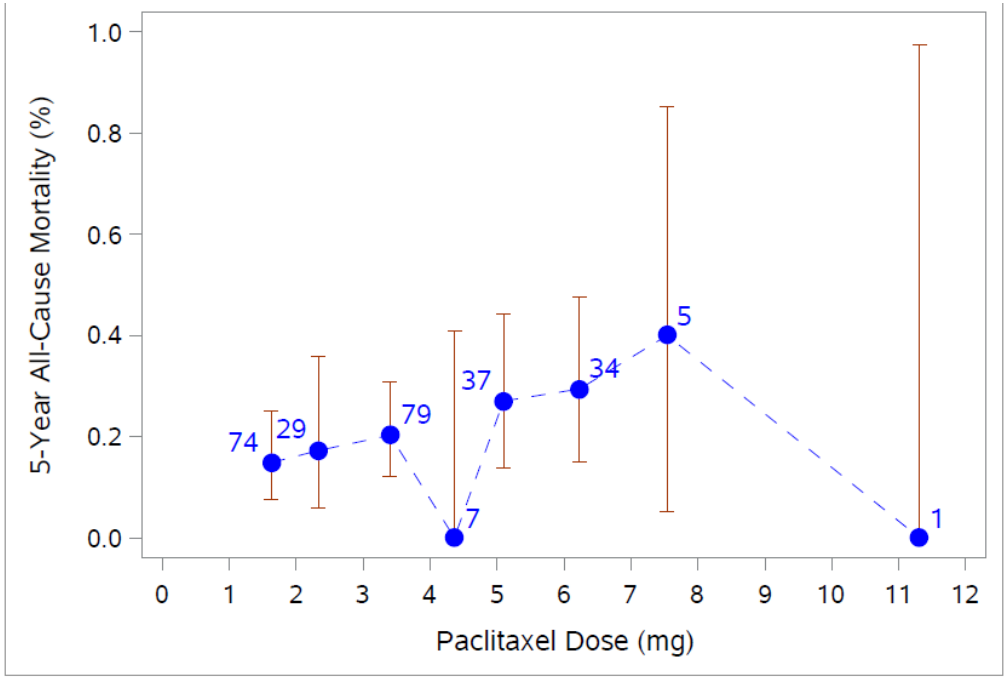
Five-Year All-Cause Mortality Rate for Paclitaxel Dose Groups: ZILVER PTX RCT (AT Population)



Dose Analysis – Lutonix DCB

- Mean Dose = 3.5 ± 1.8 mg (range 1.0-11.3 mg)
- Possible dose trend
- P = 0.04

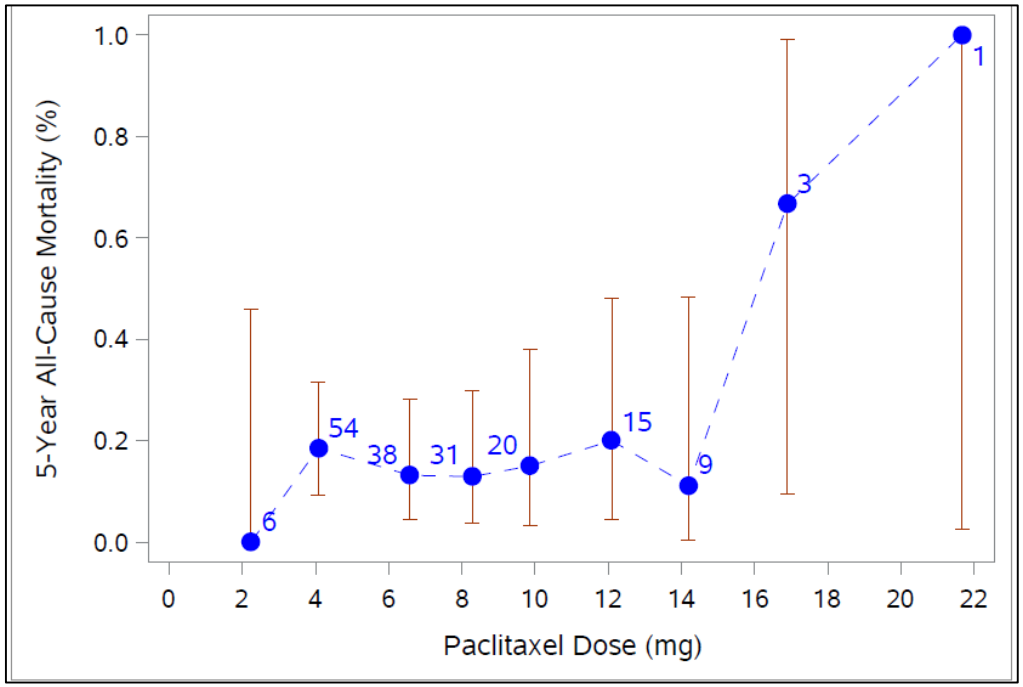
Five-Year All-Cause Mortality Rate for Paclitaxel Dose: LEVANT 2 RCT (AT Population)



Dose Analysis – In.Pact Admiral DCB

- Mean Dose = 7.5 ± 3.7 mg (range 1.9-21.7 mg)
- No definitive dose trend
- P = 0.09

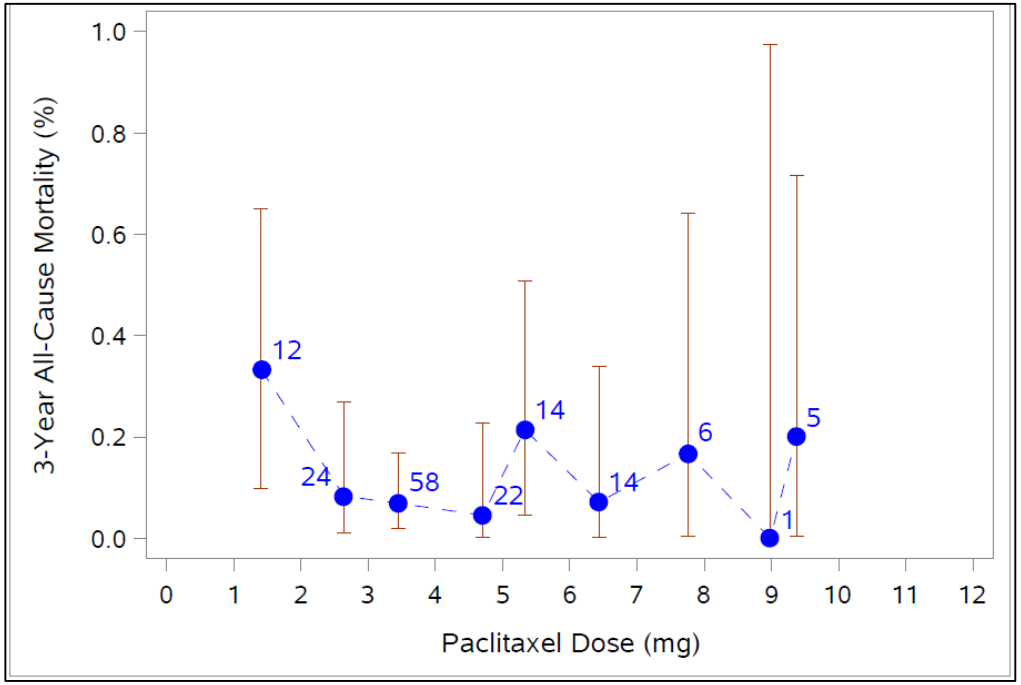
Five-Year All-Cause Mortality Rate for Paclitaxel Dose: IN.PACT SFA I & II (AT Population)



Dose Analysis – Stellarex DCB

- Mean Dose = 4.2 ± 1.8 mg (range 1.3-9.4 mg)
- No definitive dose trend
- P = 0.80

Three-Year All-Cause Mortality Rate for Paclitaxel Dose: ILLUMENATE RCT (AT Population))



Dose Analysis Conclusions

- ZILVER PTX RCT, IN.PACT SFA I & II and ILLUMENATE RCT - no clear relationship between dose and mortality
- LEVANT 2 RCT - possible trend of increased mortality with increased dose
- No consistent association between dose and mortality detected across studies

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Benefit/Risk – TLR Assessment

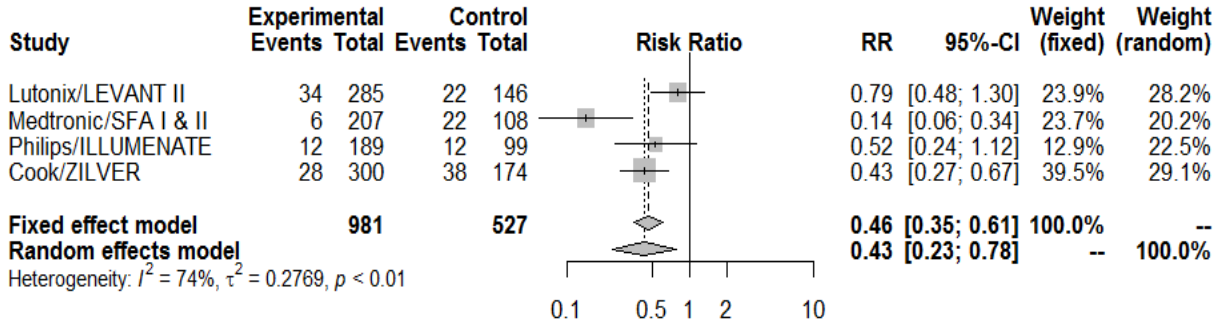
- Extent of the probable benefits and risk
  - Type
  - Magnitude/Severity
  - Probability
  - Duration
- Uncertainty
- Alternative Treatments
- Patient Perspectives
- Public Health Need

Benefit/Risk – TLR Assessment

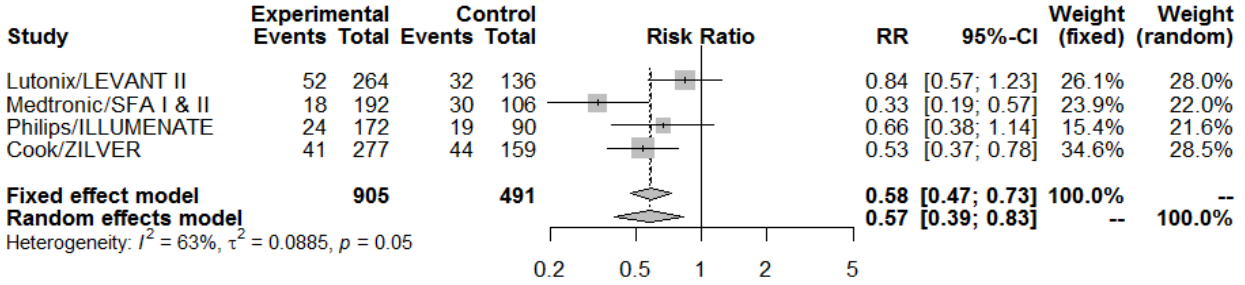
- Original PMA Approval
  - One-year follow-up for pivotal trials
  - Limited supplemental longer term data
  - Probable benefits outweighed the probable risks
  - No mortality/safety signal at the time of FDA approval

Clinically Driven TLR

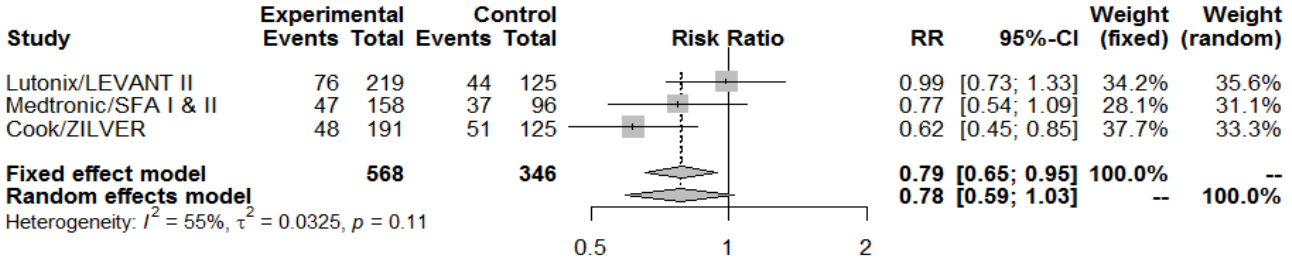
YEAR 1



YEAR 2



YEAR 5



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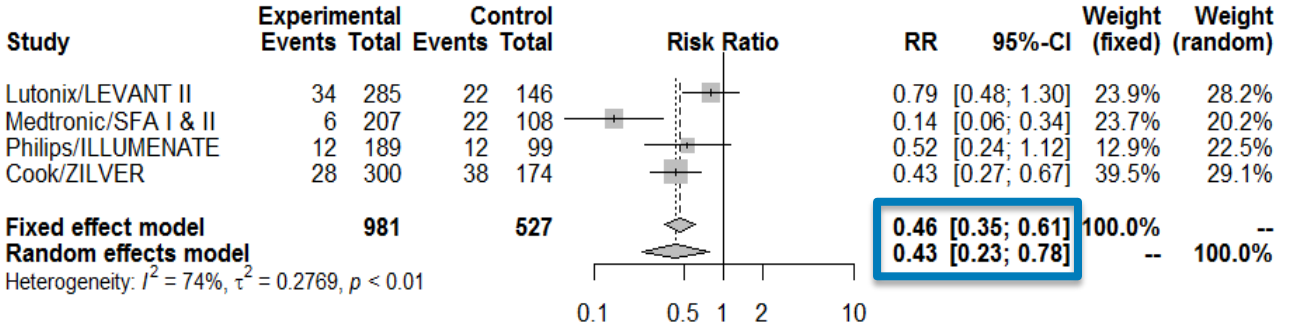

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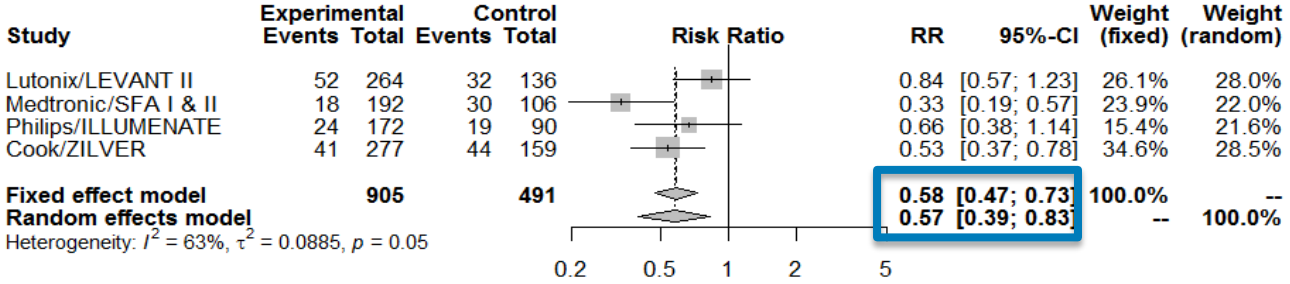

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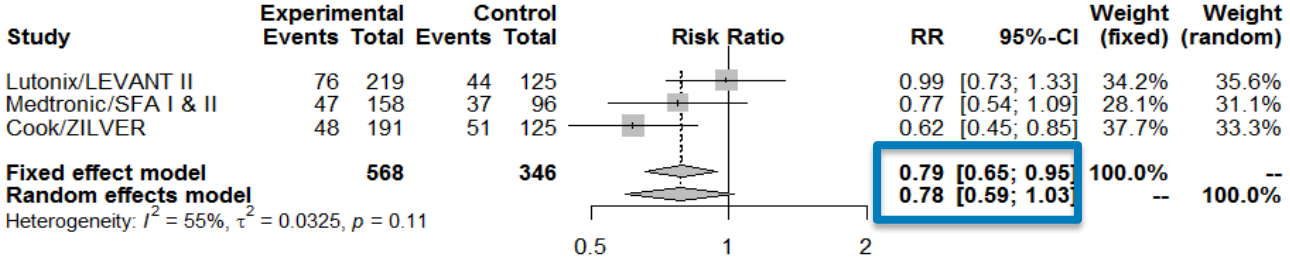

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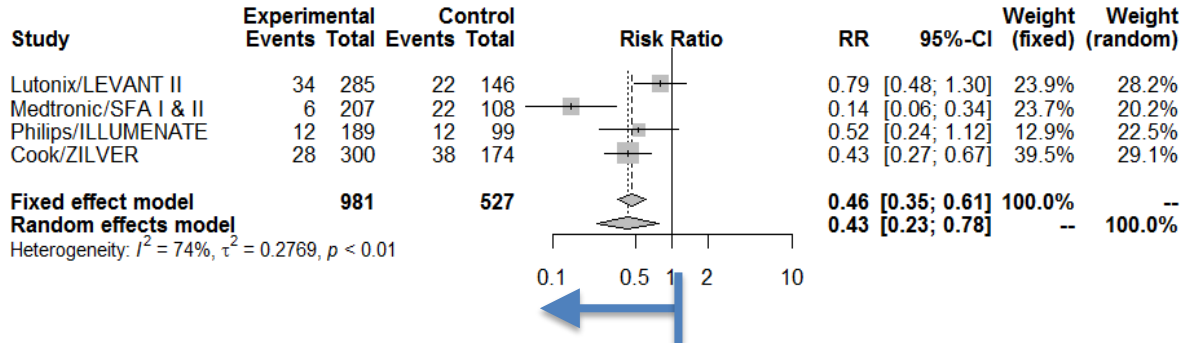

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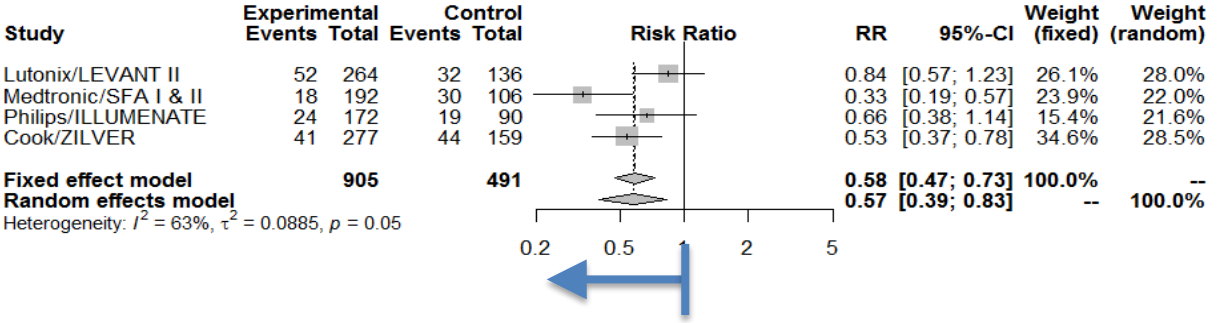

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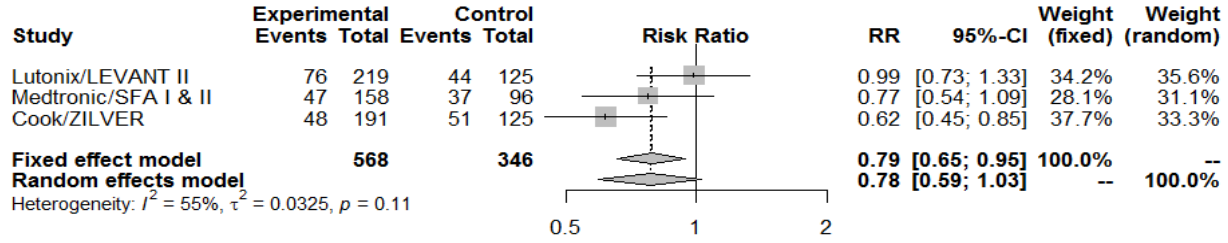

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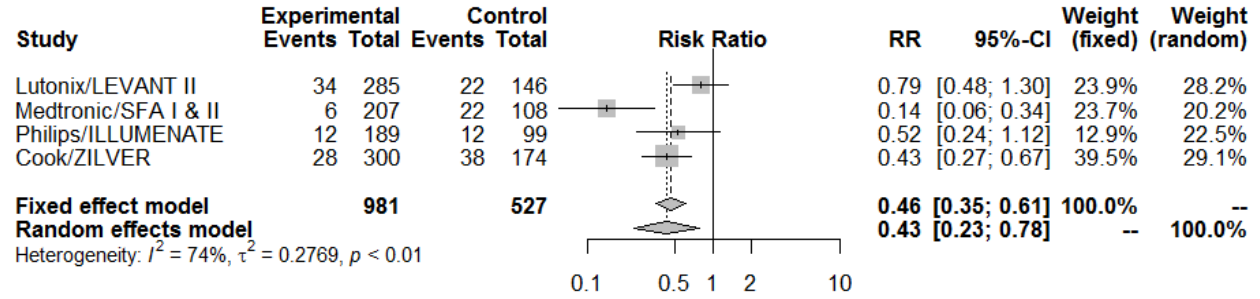

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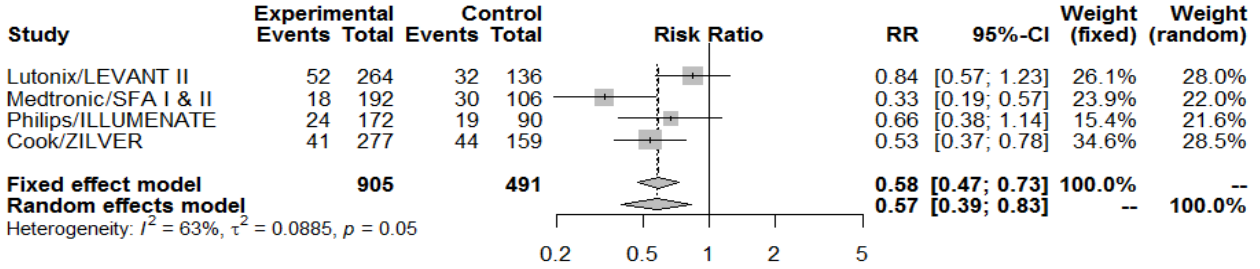

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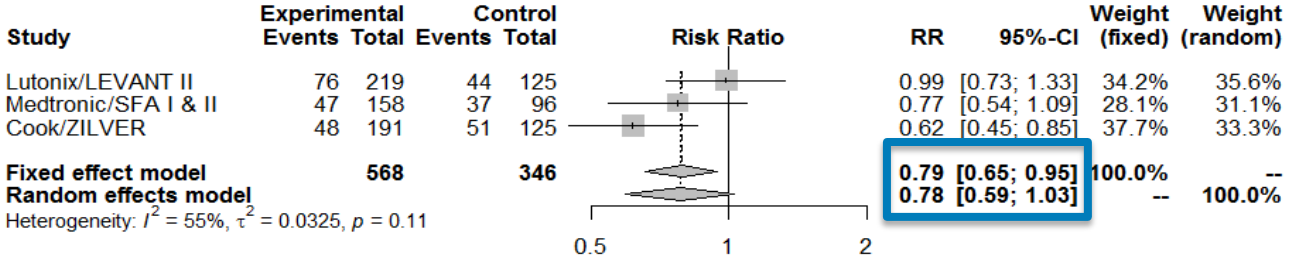

Number Needed to Treat (NNT)

- The number needed to treat (on average) to avoid one clinically driven TLR is defined as:

$$\frac{1}{\textbf{Absolute risk difference between treatment and the control group}}$$

- Absolute risk difference (RD) estimate is obtained from the meta-analysis

Year	Number of Studies	RD (treatment -control)	Absolute-RD	NNT
1	4	-0.10	0.10	10
2	4	-0.11	0.11	9
3	4	-0.10	0.10	10
4	3	-0.10	0.10	10
5	3	-0.08	0.08	13

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Number Needed to Harm (NNH)

- **NNH**: The number patients (on average) need to be exposed to the treatment to experience one adverse event (mortality). NNH is derived as:

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Year	Number of Studies	RD (treatment -control)	Absolute-RD	NNH
1	4	0.01	0.01	100
2	4	0.02	0.02	50
3	4	0.04	0.04	25
4	3	0.05	0.05	20
5	3	0.07	0.07	14

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Benefit/Risk – Considerations

- Class of PTX devices have shown consistent benefit in the reduction of reintervention to treat femoropopliteal disease
- $NNT_{(5\ YEARS)}$ avoid clinically driven TLR = 13 pts
- $NNH_{(5\ YEARS)}$ experience mortality event = 14 pts

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Limitations of Data & Analysis

- Availability of Long Term Data
  - <1,000 RCT pts with long term data
  - May not be sufficient to fully characterize presence, magnitude and causality of mortality signal

- Substantial Missing Data
  - 3-26% missing data at 5 years (14.8% pooled)
  - Reduces robustness of conclusions and introduces uncertainty

Limitations of Data & Analysis

- Additional Unknown Paclitaxel Treatments
  - Additional PTX exposure uncertain
  - PTX devices for PAD, other indications or IV use

- Cause of Death Adjudication
  - No adjudicated drug-related deaths
  - Detail of assessment
  - “Other” & “Unknown” categories

Mortality Signal Conclusions

- Primary Conclusions
  - Trend of increased mortality 3-5 years
  - Numerous limitations with data/analysis
  - Cause of late mortality signal is not evident

Post Approval Study (PAS) Data Collection

- New Post Approval Study (PAS) or a 522 Postmarket Surveillance Study
  - Individual manufacturer or industry consortium can proactively design a new study
  - Under Section 522, FDA can require data collection
- Collection of real-world evidence (RWE)
  - Wealth of available data
  - Limitations - sub-optimal data quality; reliability; lack of follow-up; lack of internal control; selection bias

PAS Considerations

- Sources of new data
  - Continued follow-up of ongoing pivotal trials that have not reached 5 years
  - Non-US RCTs
  - Non-randomized datasets
  - New RCT
- Important study elements
  - Clinically acceptable relative risk
  - Appropriate type I error rate
  - Feasible sample size
  - Optimal duration of follow-up to assess mortality rates
  - Data Safety Monitoring Board

PAS – Sample Size Estimates

Binary Outcome: Sample size of a 1:1 RCT, non-inferiority test based on Relative Risk (RR)*

H_0: RR ≥ RR_b vs. H_1: RR < RR_b

		alpha=0.025			alpha=0.05		
Year	Control Mortality Rate	RR_b 1.1	RR_b 1.2	RR_b 1.3	RR_b 1.1	RR_b 1.2	RR_b 1.3
3	0.074	43276	11846	5734	34094	9338	4524
5	0.128	23560	6450	3124	18562	5084	2464

*Farrington & Manning test, Power: 80%

Time-to-Event: Sample size of a 1:1 RCT, non-inferiority test based on Hazard Ratio (HR)*

H_0: HR ≥ HR_b vs. H_1: HR < HR_b

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5	7	0.0274	21832	5730	2666	17196	4512	2100

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Time to Event Assumptions

2-year study Enrollment Accrual Time, Constant hazard rate, Constant hazard ratio

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Time-to-Event: Sample size of a 1:1 RCT, non-inferiority test based on Hazard Ratio (HR)*

H_0: $HR \geq HR_b$ vs. H_1: $HR < HR_b$

			alpha=0.025			alpha=0.05		
Min. F-U Time	Study Time	Control Hazard Rate	HR_b 1.1	HR_b 1.2	HR_b 1.3	HR_b 1.1	HR_b 1.2	HR_b 1.3
3	5	0.0274	31854	8350	3880	25090	6576	3054
5	7	0.0274	21832	5730	2666	17196	4512	2100

*Log-rank test (Jung et al. 2005), Power: 80%

Time to Event Assumptions

2-year study Enrollment Accrual Time, Constant hazard rate, Constant hazard ratio

PAS – Sample Size Estimates

Binary Outcome: Sample size of a 1:1 RCT, non-inferiority test based on Relative Risk (RR)*

H_0: $RR \geq RR_b$ vs. H_1: $RR < RR_b$

		alpha=0.025			alpha=0.05		
Year	Control Mortality Rate	RR_b 1.1	RR_b 1.2	RR_b 1.3	RR_b 1.1	RR_b 1.2	RR_b 1.3
3	0.074	43276	11846	5734	34094	9338	4524
5	0.128	23560	6450	3124	18562	5084	2464

*Farrington & Manning test, Power: 80%

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Time to Event Assumptions

2-year study Enrollment Accrual Time, Constant hazard rate, Constant hazard ratio

Labeling

- Pivotal study subjects all planned for 5-year follow-up as a condition of PMA approval
- Labeling may be updated with required post market clinical data
- Labeling revisions to convey safety information

Other Indications

- FDA Approved or Under Study
  - Arteriovenous fistulae stenosis in renal patients
    - FDA approved - Lutonix DCB
  - Below-the-Knee PAD - Critical Limb Ischemia
    - No FDA approved devices
- FDA Approved, but not Marketed
  - Coronary disease
    - FDA approved – BSC TAXUS DES – no longer marketed

https://www.cms.gov/Medicare/Coverage/IDE/Approved-IDE-Studies.html

Day Two Summary

- FDA re-evaluated animal PK and safety studies, no potential mechanism for increased mortality
- No relationship between mortality and paclitaxel dosage was identified in the RCTs
- Paclitaxel coated devices demonstrate effectiveness/benefit as compared to uncoated devices; reduced TLR
- Impact on other indications