In Depth Independent Safety Analysis by Syntactx (CRO) of the Lutonix SFA DCB

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Disclosures

Kenneth Ouriel:

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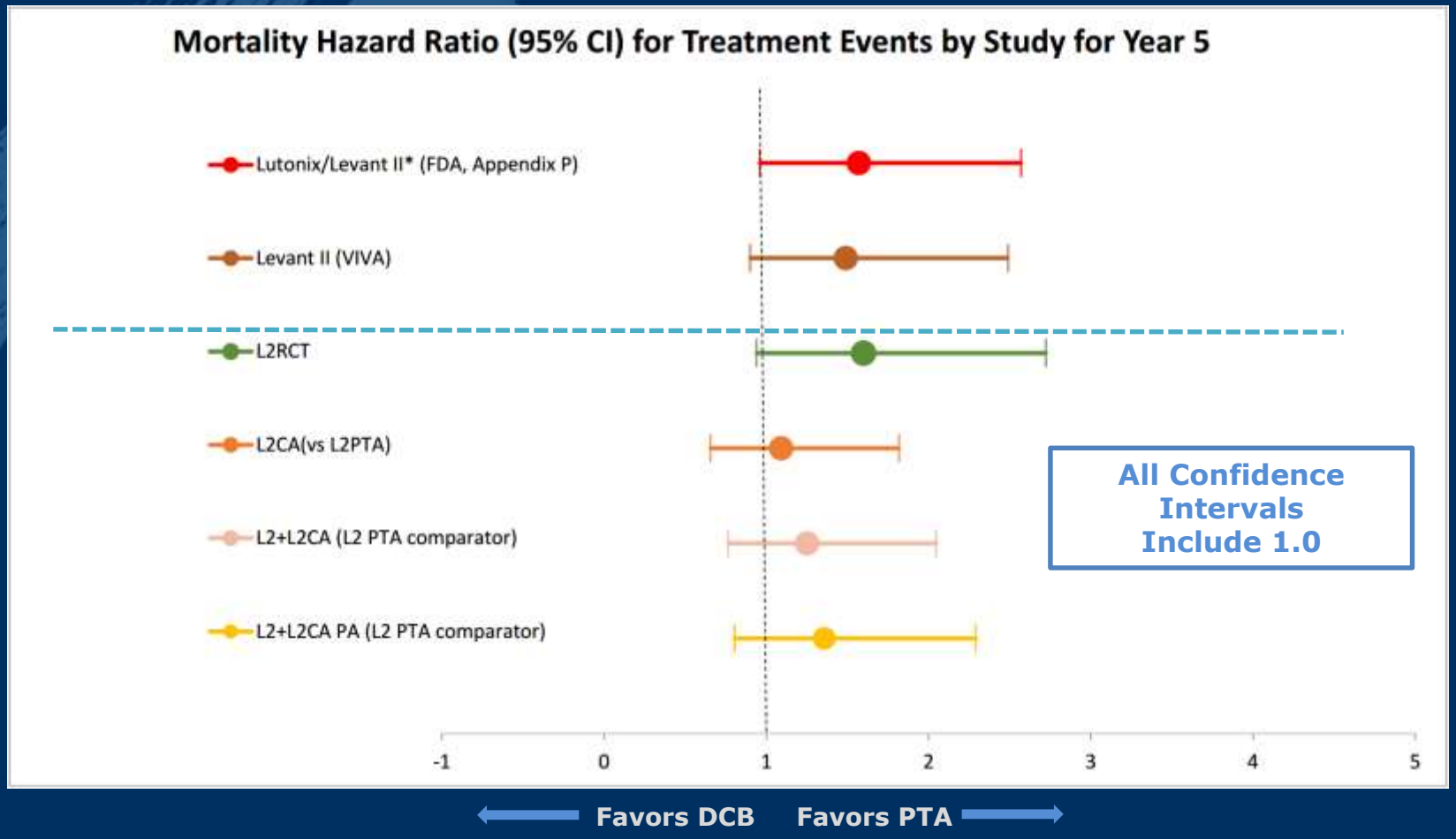
I have the following potential conflicts of interest to report:

Employment in industry- Dr Ouriel is an equity holder and receives a salary from Syntactx. Syntactx recieved funding from Becton Dickinson, the manufacturer of the Lutonix products.

LUTONIX® DCB
Full Clinical Program

Study	Study Design	Subjects (DCB : PTA)	Geography	Follow-Up
LEVANT 1	RCT	101 (49:52)	Europe	24 months
LEVANT 2	RCT with Roll-Ins	532 (316:160) randomized 56 DCB roll-in	US, Europe	60 months
	Continued Access	657	US, Europe	60 months
LEVANT Japan	RCT	109 (71:38)	Japan	24 months
ISR	RCT	73 (50:23)	US	36 Months
Long Lesion	Registry	118	Europe	36 Months
Global Registry	Registry	691	Europe	24 Months
SAFE-DCB	Registry	1005	US	36 Months
BTK	RCT	442 (287:155)	US, Europe, Japan	36 months
AVF	RCT	285 (141:144)	US	24 months
Total		3,441 : 572	US, Europe, Japan	24-60 months

Mortality Hazard Ratios
All Confidence Intervals Overlap 1.0

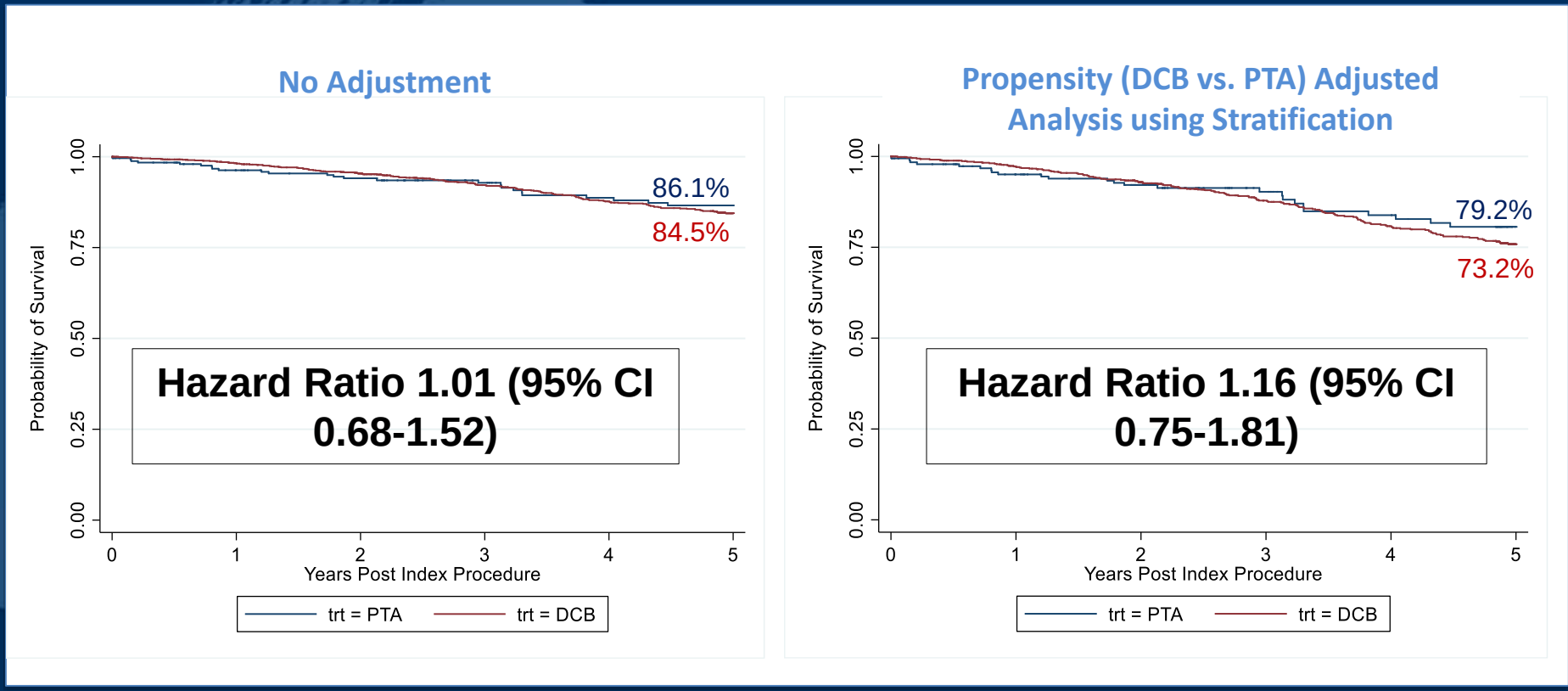


*Risk ratio for L2RCT only

PA = propensity adjusted

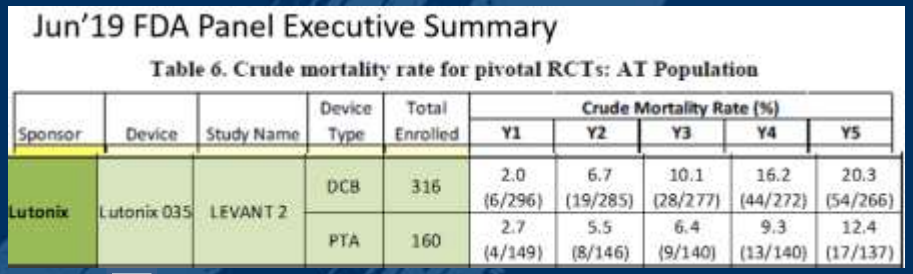
Mortality Risk Is Reduced As More Patients Are Added

LEVANT 1, L2RCT, L2CA, LEVANT Japan



N =1093 DCB, 250 PTA

Jan 2020 Lutonix Mortality Data



Jun'19 FDA Panel Executive Summary

Table 6. Crude mortality rate for pivotal RCTs: AT Population

Sponsor	Device	Study Name	Device Type	Total Enrolled	Crude Mortality Rate (%) Y1	Y2	Y3	Y4	Y5
Lutonix	Lutonix 035	LEVANT 2	DCB	316	2.0 (6/296)	6.7 (19/285)	10.1 (28/277)	16.2 (44/272)	20.3 (54/266)
			PTA	160	2.7 (4/149)	5.5 (8/146)	6.4 (9/140)	9.3 (13/140)	12.4 (17/137)

Jun 2019 FDA Panel Executive Summary

Jan 2020 Updated Mortality Rate

Strict Annual Timepoints	DCB RCT Cumulative Deaths (Numerator For Year)	DCB RCT Crude Mortality Rate (numerator/denominator)	PTA RCT Cumulative Deaths (Numerator For Year)	PTA RCT Crude Mortality Rate (numerator/denominator)	p-value (Fisher's exact test)	DCB RCT + CA Cumulative Deaths (Numerator For Year)	DCB RCT + CA Crude Mortality Rate (numerator/denominator)	p-value*** (Fisher's exact test)
1 year (day 0-365)	7	2.2508039	5	3.205128	0.546	18	1.7664377	0.216
2 years (day 366-730)	22	7.0967742	10	6.493506	1	48	4.729064	0.323
3 years (day 731-1095)	32	10.38961	12	7.792208	0.406	86	8.5487078	0.877
4 years (day 1096-1460)	50	16.286645	18	11.68831	0.212	135	13.5	0.611
5 years (day 1461-1825)	61	20.065789	22	14.37908	0.158	168	16.901408	0.484

Added Deaths	Original analysis (May' 19)	Updated analysis (Jan'20)
PTA	17	22
RCT DCB	54	61
RCT + CA DCB	146	168

Due to overall low mortality, a small increase in deaths (5 subjects in the PTA arm) significantly impacted the results.

Bradford Hill Criteria
Association vs. Causality

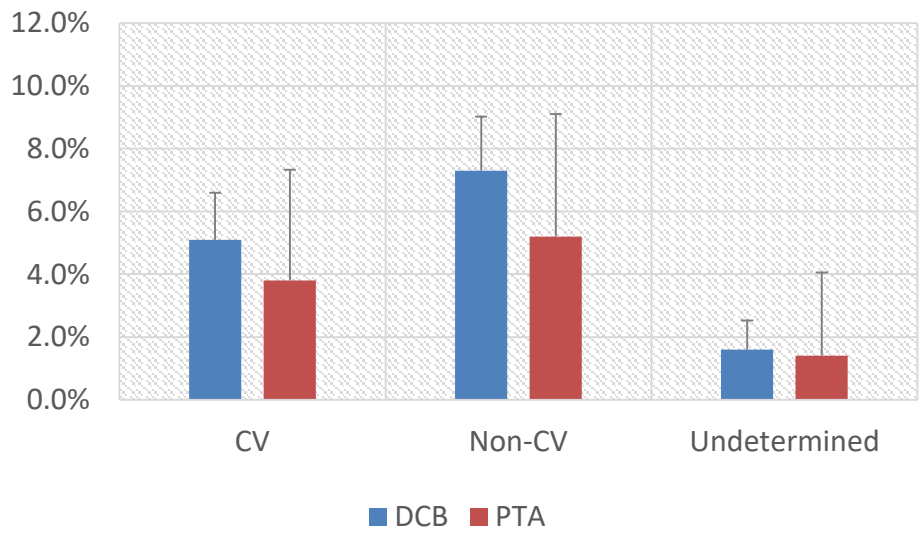
Consistency: Were paclitaxel safety concerns identified in the animal studies?	Biological Gradient: Is there a dose response?
Strength: Was the effect shown for all studies?	Coherence: Do other findings support the mortality concern?
Specificity: Was mortality paclitaxel related?	Temporality: Does mortality increase following index procedure?
Plausibility: Was there a Mechanism of Action?	Analogy: Could the effects be due to immunogenic particulates?
Coherence: Do other findings support the mortality concern?	

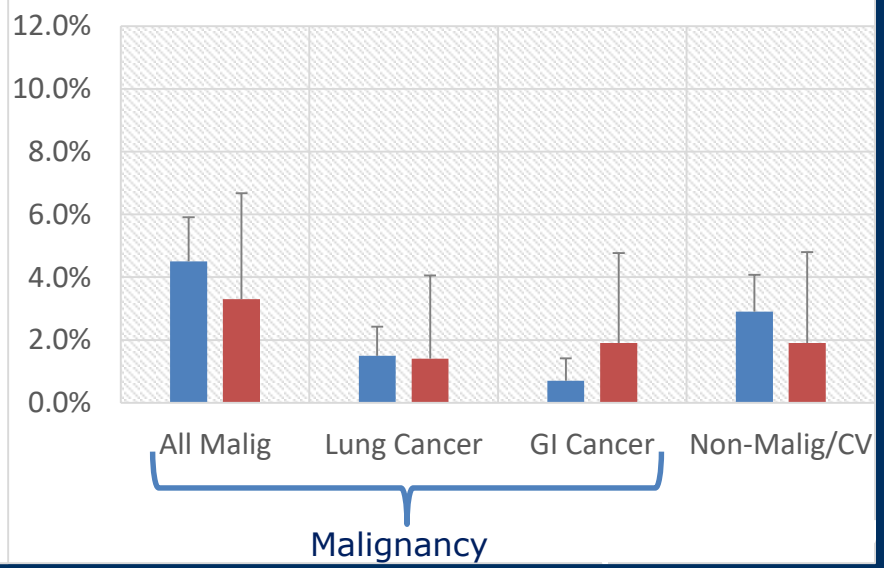
1. Is there a plausible mechanism for paclitaxel-associated mortality?

[If so, is there clustering of causes of death which suggest a common mechanism?]

Independently Adjudicated

No Clustering by Cause of Death (LEVANT 1, L2 Combined)





	CV	Non-CV	Undetermined
DCB (N=1078)	55 (5.1%)	79 (7.3%)	17 (1.6%)
PTA (N=212)	8 (3.8%)	11 (5.2%)	3 (1.4%)

	All Malig	Lung CA	GI Cancer	Non-Malig/CV
DCB (N=1078)	48 (4.5%)	16 (1.5%)	8 (0.7%)	31 (2.9%)
PTA (N=212)	7 (3.3%)	3 (1.4%)	4 (1.9%)	4 (1.9%)

Balanced Rates of SAEs, AEs Between Groups LEVANT 2RCT

Event Type	Serious Adverse Events			All Adverse Events (Serious and Non-Serious)		
	DCB	PTA	P Value	DCB	PTA	P Value
Cardiovascular	18.0% (57/316)	18.1% (29/160)	>0.99	45.6% (144/316)	50.0% (80/160)	0.38
Bleeding	4.1% (13/316)	3.1% (5/160)	0.80	13.9% (44/316)	12.5% (20/160)	0.78
Infection	8.9% (28/316)	7.5% (12/160)	0.73	32.0% (101/316)	30.6% (49/160)	0.83
Malignancy	6.3% (20/316)	4.4% (7/160)	0.53	12.3% (39/316)	8.8% (14/160)	0.28
Any Type	30.4% (96/316)	27.5% (44/160)	0.53	62.7% (198/316)	66.9% (107/160)	0.42

Subjects with ≥1 event of the specified type

2. Are there patient or treatment-related variables associated with increased risk?

[If so, what are the variables and do they relate to paclitaxel?]

Multivariable Analysis of Mortality (5 years)

- Performed a propensity-adjusted multivariable analysis of mortality in LEVANT 2 RCT and LEVANT 2 CA
- Variables identified as significant* predictors of mortality irrespective of treatment group (DCB or PTA):

Variable	HR	P-value
Age (per year)	1.03	<0.0001
Rutherford Category	1.7	0.003
Left limb	1.6	0.005
Arrhythmia	1.8	0.011
Angiotensin II Receptor Blockers	0.6	0.02
Diabetes	1.4	0.028
Anticoagulant	2.1	0.029
Prior treatment	1.6	0.03

* $p<0.05$

Treatment (DCB vs. PTA) was not a significant predictor (HR = 1.37, p=0.23)

3. Is there a relationship between additional exposure to paclitaxel and risk of mortality?

[If drug is implicated, there should be a dose-response relationship and additional exposure should increase mortality.]

Dose Response: LEVANT 2 RCT + CA

Changes in 5-Year KM Survival Rate with Dose

Dose	L2RCT		L2CA	
	N	5-Year Survival Rate	N	5-Year Survival Rate
>0 & <=2mg	88	0.87	185	0.86
>2mg & <= 3.5 mg	91	0.76	197	0.90
>3.5mg & <= 5 mg	47	0.9	108	0.85
>5mg	90	0.73	167	0.83
Test for Trend* P-value	0.092		0.341	

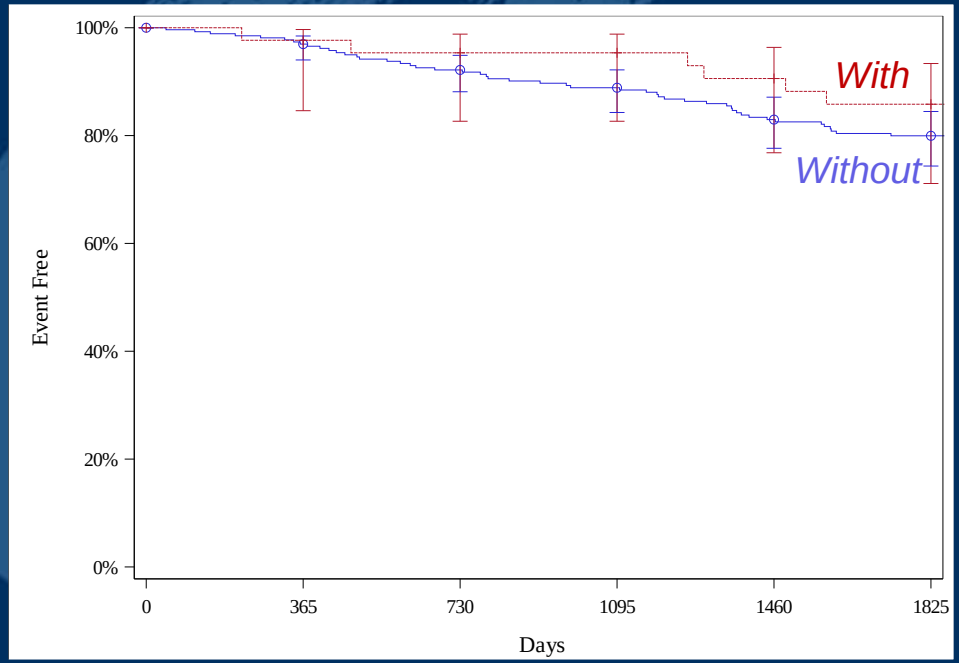
There was no significant dose-response relationship identified

*Log rank Chi-square test for trend of the survivor function across three or more ordered groups.

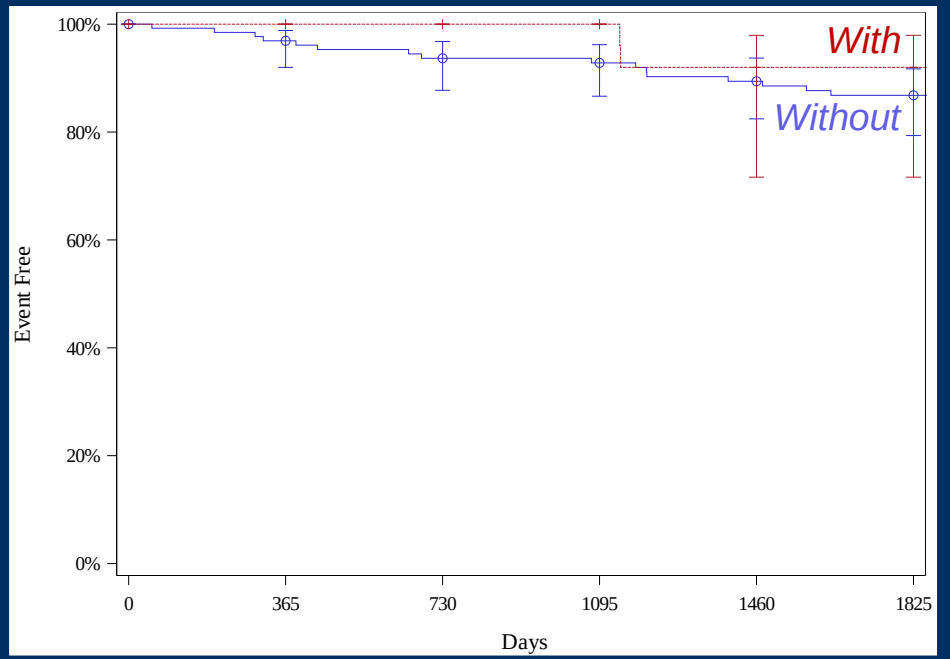
Subsequent Paclitaxel Interventions Did Not Increase Mortality

Freedom from All-Cause Mortality (LEVANT 2RCT)

DCB Subjects



PTA Subjects



- Without subsequent paclitaxel intervention
- With subsequent paclitaxel intervention

Association vs. Causation
The Bradford Hill Criteria

Bradford Hill Criteria
Association vs. Causality

No safety issues identified in animal studies*

Effect not shown in all studies

No significant difference between groups and no clustering of cause of death

Treatment not a significant predictor of mortality or AEs

Virmani et al.

Consistency: Were paclitaxel safety concerns identified in the animal studies? X	**Biological Gradient:** Is there a dose response? X
Strength: Was the effect shown for all studies? X	**Coherence:** Do other findings support the mortality concern? X
Specificity: Was the mortality paclitaxel related? X	**Temporality:** Does mortality increase following index procedure?
Plausibility: Was there a Mechanism of Action? X	**Analogy:** Could the effects be due to immunogenic particulates?
Coherence: Do other findings support the mortality concern? X	

No increase in mortality with increased dose, subsequent intervention with paclitaxel-coated device was protective

Temporality is present

Particulates have been implicated in other situations

Conclusions

- There is no significant increase in the hazard ratio for mortality in any analysis of LUTONIX® 035 DCB
- No plausible mechanism for mortality or evidence of paclitaxel causation
- There was no increase in mortality with additional exposure to paclitaxel in both cohorts (DCB/PTA)
- While reducing subsequent interventions is beneficial for patients, it also reduces additional visits with health care providers
- Addition of the newest data on patients formerly lost to follow-up further reduced the mortality differences to levels far from significance.

LUTONIX® 035 DCB **continues to offer meaningful benefit** relative to risk in patients with PAD

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