LUTONIX® 035 DCB

Drug Coated Balloon PTA Catheter

Meeting of the Circulatory System Devices Panel
Regarding Paclitaxel-Coated Products Indicated
for Peripheral Arterial Disease (PAD)

June 19-20, 2019

BD

BD-Lutonix

Presenters and Additional Speakers

- **JD Meler**, MD, VP Medical & Clinical Affairs, BD-Interventional
- **Kenneth Ouriel**, MD, President & CEO, Syntactx
- **John DeFord**, PhD, EVP & Chief Technology Officer, BD
- **George Papandreou**, PhD, VP & Site Lead, Lutonix, BD
- **Roseann White**, Statistical Consultant, Syntactx

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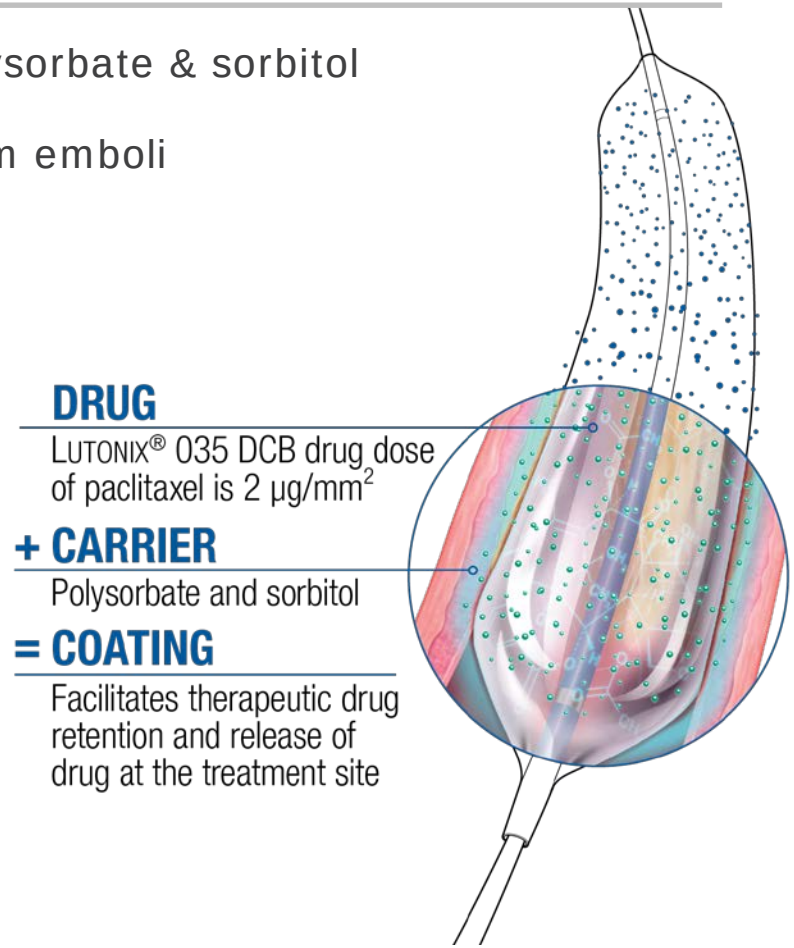
Agenda

- Overview of LUTONIX® 035 DCB Data
- Methods of Analysis
- Key Findings
- Conclusions and Next Steps

LUTONIX® DCB
Development Program

- **DCB drug dose -** 2µg/mm^2 paclitaxel with commonly used excipients polysorbate & sorbitol
- **GLP porcine studies -** No systemic toxicity/No ischemia from downstream emboli
- **LEVANT 2 pharmacokinetics -** Serum paclitaxel <3 ng/mL @ 1 hr. / Mean elimination half-life = 6.88 hr.
- **Over 400,000 patients treated worldwide** (~3,400 in clinical trials)
  - First DCB approved, subject to Advisory Panel review
  - Over 1,000 patients treated under the LEVANT 2 IDE protocol (1,029 DCB [316 RCT, 713 CA/RI] & 160 PTA)
  - Largest IDE cohort with 5-year follow-up
- **Demonstrated benefit**
  - Approximately 30% relative improvement in primary endpoint (patency) at 12 months* in LEVANT 2 RCT (DCB 73.5% / PTA 56.8%, p<0.001)
  - Global SFA Real-World Registry TLR-free 90.3% at 24 months*
- **Clinical trials conducted** in multiple vascular beds: SFA, AV and BTK



* Kaplan-Meier Analysis

LUTONIX® 035 DCB
Clinical Program (studies to be reviewed today)

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

- First in class – over 1,000 subjects total as part of FDA approval
- Pivotal clinical study was LEVANT 2 RCT with roll-ins (RI)
- LEVANT 2 Continued Access (CA)
  - Single-arm (DCB) continuation of the RCT
  - Same inclusion/exclusion criteria, same follow-up timeframes and assessments
- Two other RCTs for de novo/restenotic lesions (LEVANT 1 and LEVANT Japan)

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LUTONIX® DCB
Full Clinical Program

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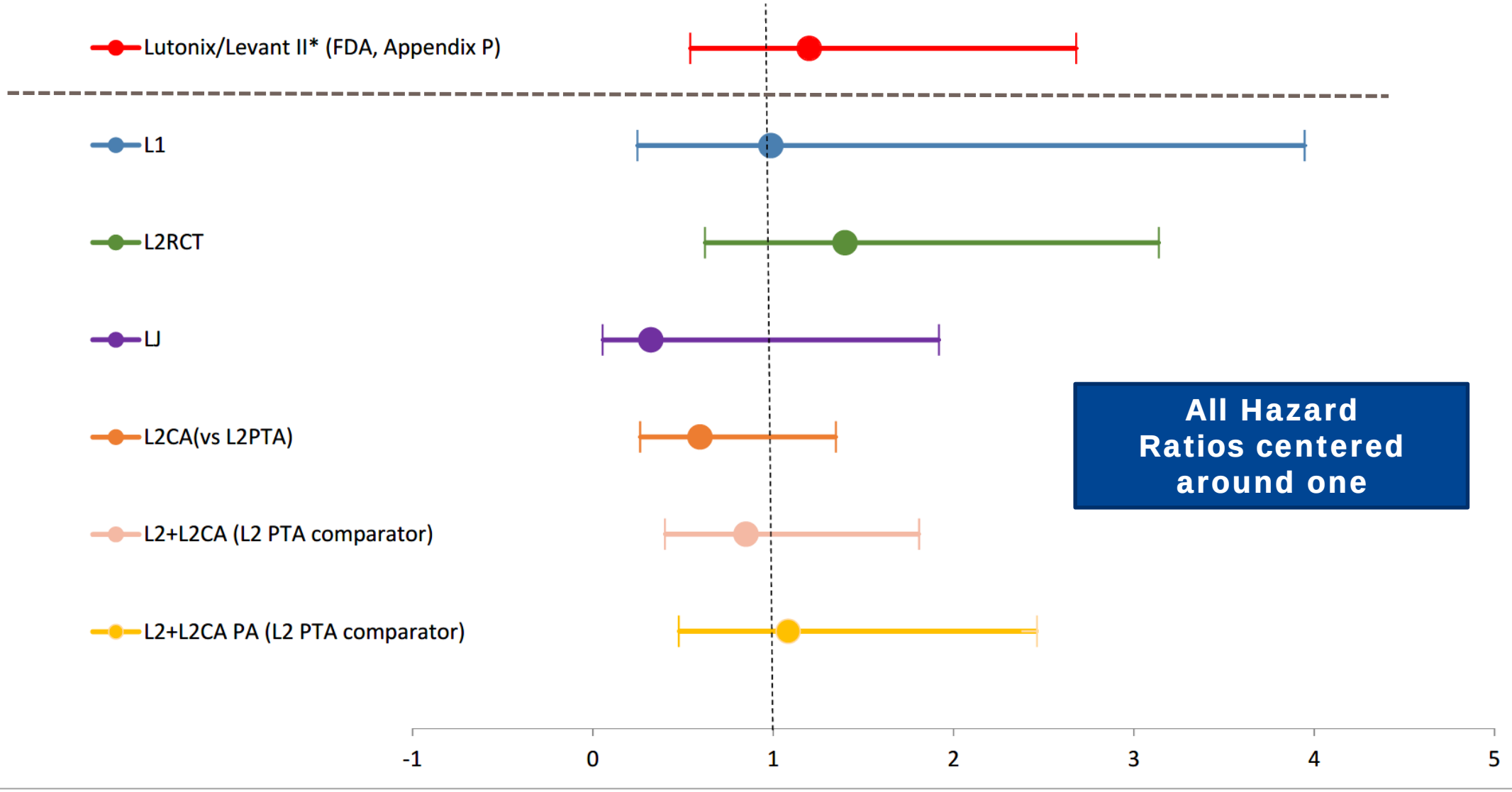
LEVANT Japan	RCT	109 (71:38)	Japan	24 months
ISR	RCT	73 (50:23)	US	36 Months
Long Lesion	Registry	118	Europe	36 Months
Global Registry	Registry	691	Europe	24 Months
SAFE-DCB	Registry	1005	US	36 Months
BTK	RCT	442 (287:155)	US, Europe, Japan	36 months
AVF	RCT	285 (141:144)	US	24 months
Total		**3,441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

Analysis of Risk Across Studies

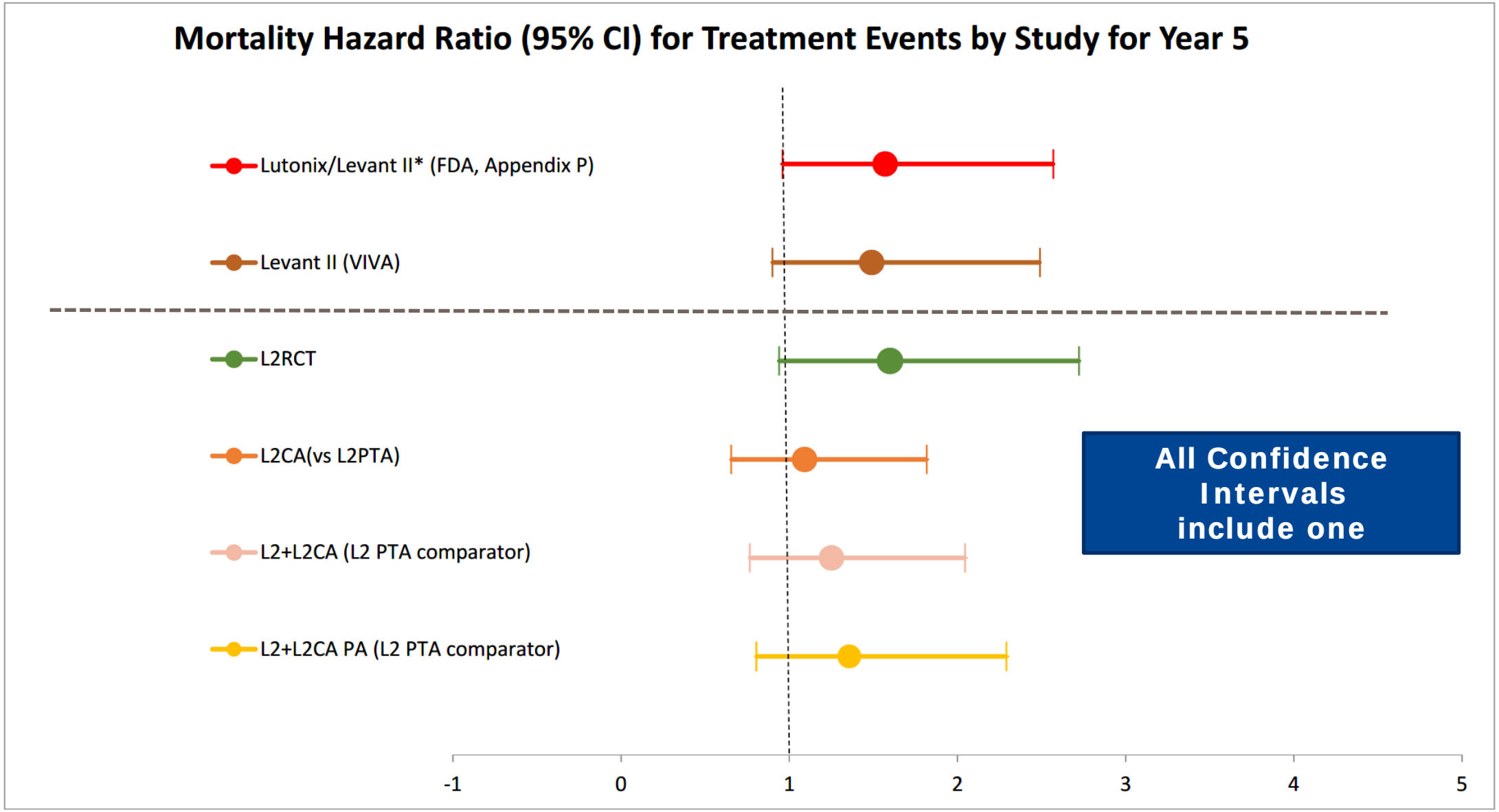
LEVANT 2 Program
Analysis Differences

	Katsanos	FDA	VIVA	BD-Lutonix
Analysis population (denominator)				
Total enrollment			✓	✓
Subjects who completed follow-up	✓	✓		✓
Addition of lost to follow-up subjects		✓	✓	✓
Patient-level data		✓	✓	✓
Study populations				
LEVANT 2 RCT	✓	✓	✓	✓
LEVANT 2 Continued Access		✓		✓
LEVANT 2 Combined				✓
Propensity adjustment				✓
Time dependent analyses, including subsequent intervention				✓
Multivariate analyses				✓

Mortality Hazard Ratio (95% CI) for Treatment Events by Study for Year 2



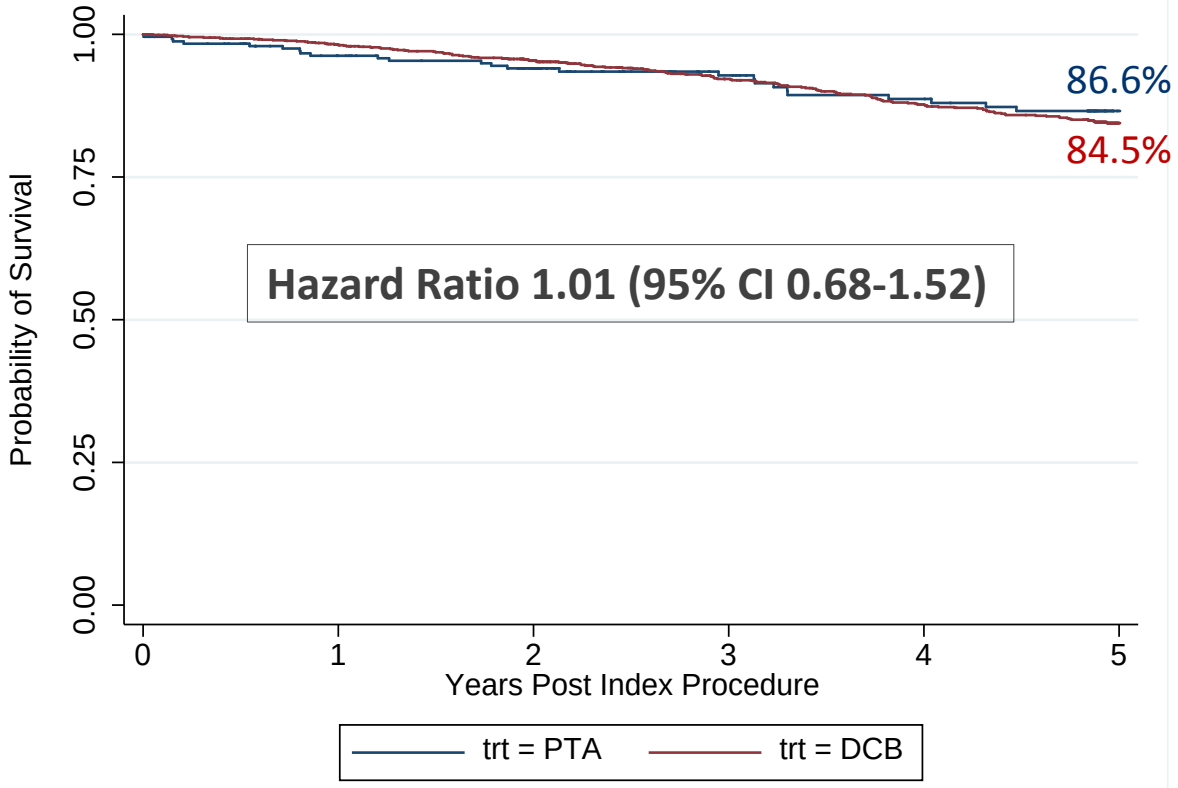
*Risk ratio for L2RCT only
PA = propensity adjusted



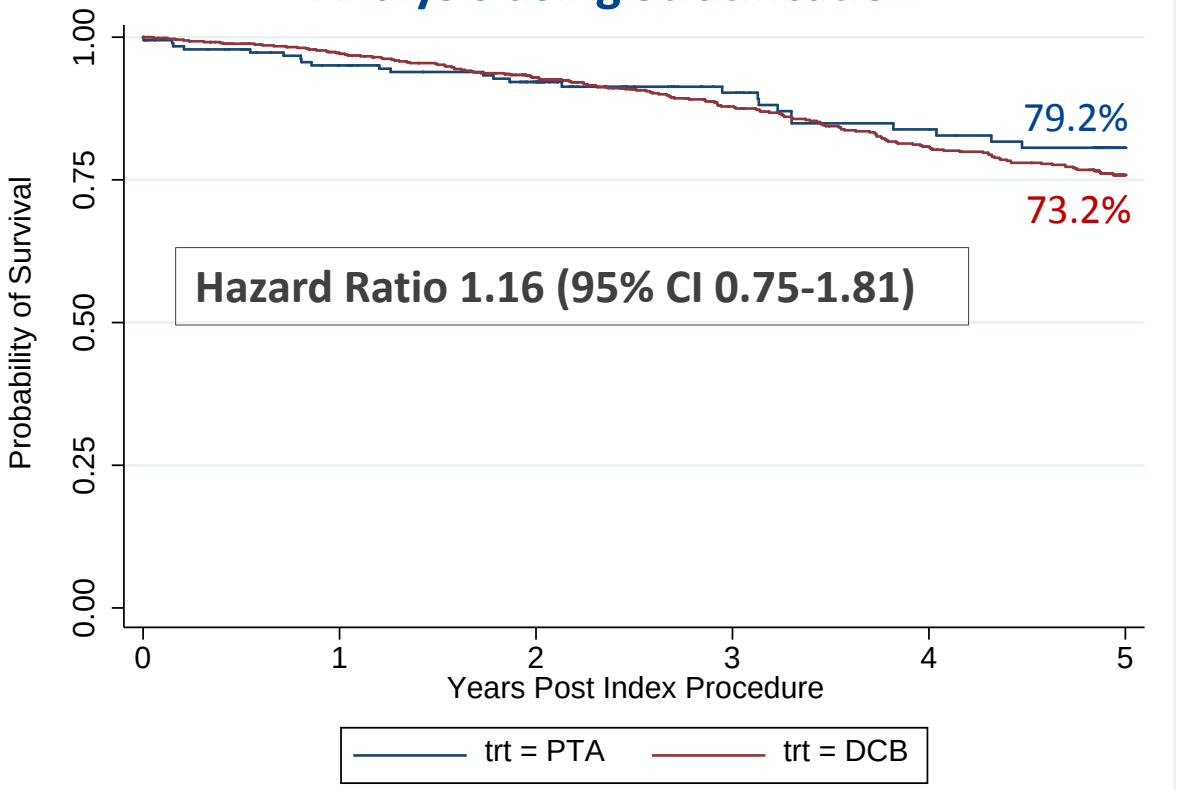
*Risk ratio for L2RCT only
PA = propensity adjusted

Mortality Risk Is Reduced As More Patients Are Added (LEVANT 1, L2RCT, L2CA, LEVANT Japan)

No Adjustment



Propensity (DCB vs. PTA) Adjusted Analysis using Stratification



N =1093 DCB, 250 PTA

Kenneth Ouriel, MD

President & CEO

Syntactx

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 MOA?	**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?]

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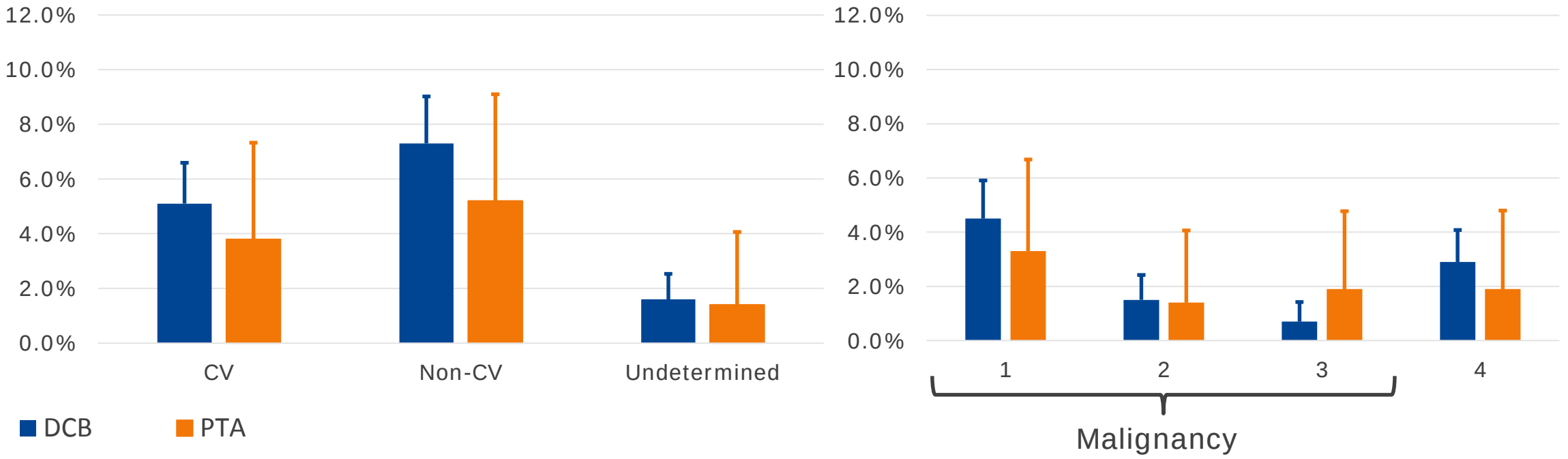
No Clustering by Cause of Death
LEVANT 1, L2 Combined



	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

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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

Treatment (DCB vs. PTA) was not a significant predictor

(HR = 1.37, p=0.23)

* p<0.05

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	

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

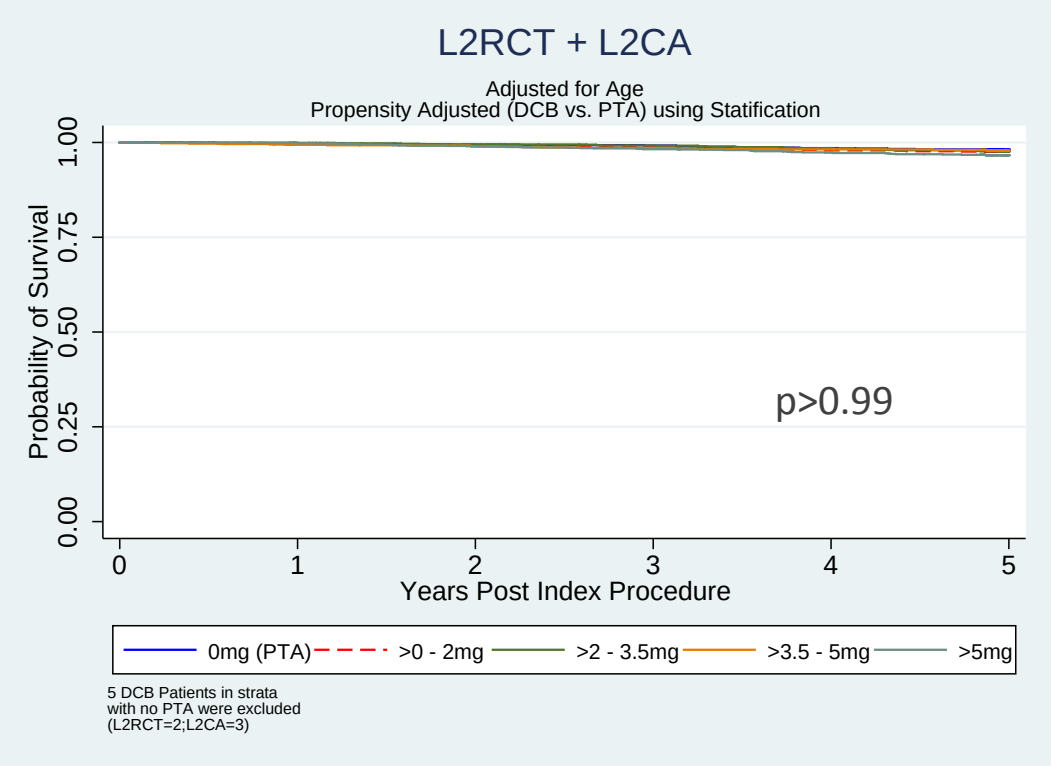
There was no significant dose-response relationship identified

Dose Response
LEVANT 2 RCT + LEVANT 2 CA Propensity and Age Adjusted

Significant Predictors of Mortality (both treatment groups)

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

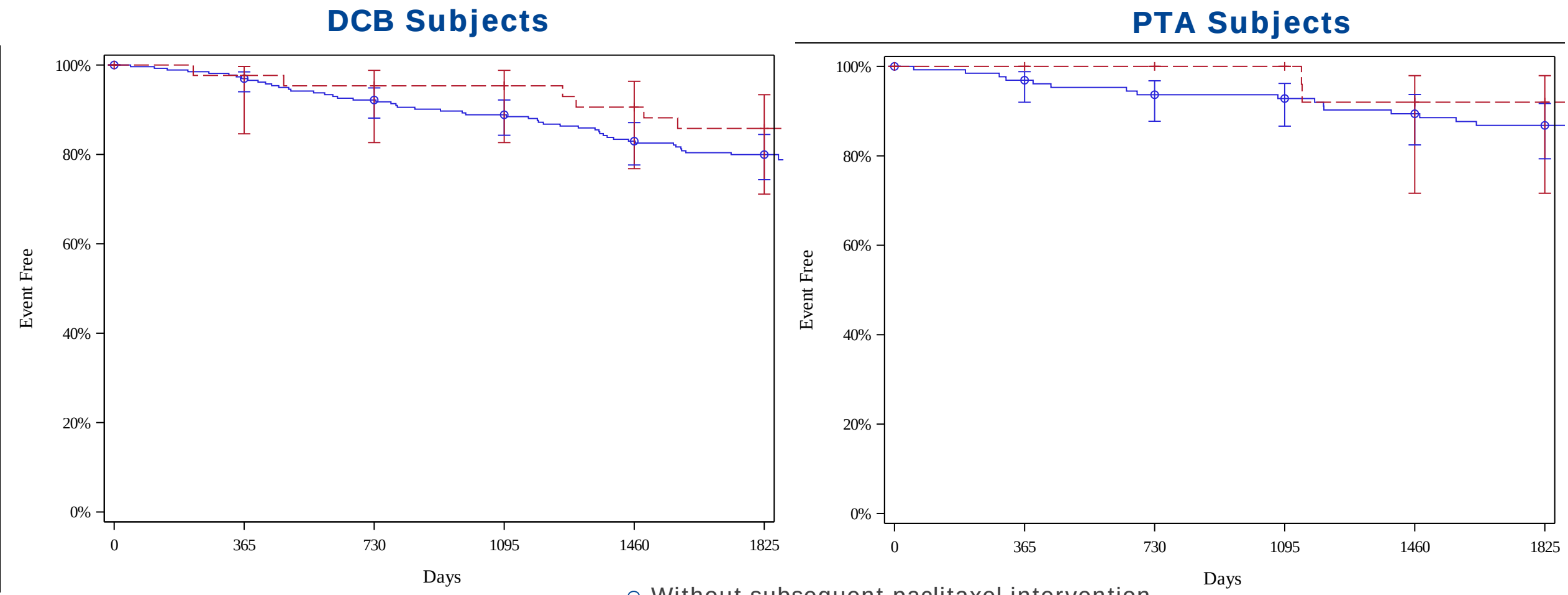
After Adjusting for Age



No dose-response relationship was identified after adjusting for age

Subsequent Paclitaxel Interventions Did Not Increase Mortality

Freedom from All-Cause Mortality (LEVANT 2RCT)



Potential Reason for an Association
The Effect of Clinical Management

- Subjects in clinical trials may do better with additional clinical management
  - Mortality in both the PTA and DCB groups in the LEVANT 2 RCT was lower than the PAD population
  - ~25% mortality in intermittent claudicants at 5 years in the Swedevasc registry (Sartipy et. al 2018)

- Subjects in both groups who underwent any subsequent intervention also had higher 5-year survival rates than those that did not
  - Subsequent intervention involves additional interactions with health care providers
    - PTA arm had 29% more subsequent lower limb interventions than DCB arm in the LEVANT 2 RCT
  - Health care provider interactions - medication management, lifestyle change recommendations, earlier identification of other conditions

Reducing subsequent interventions is beneficial for patients, but also reduces additional "touch points" with health care providers

Association vs. Causation

The Bradford Hill Criteria

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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

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 MOA? 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

* Virmani et al

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
- Appropriate analyses should include propensity adjustment across studies, account for time dependent variables, and include multivariate analysis
- LUTONIX® 035 DCB **continues to offer meaningful benefit** relative to risk in patients with PAD

Next Steps

- BD is committed to ensuring patient safety and minimizing risks, and will **continue to monitor safety data**
- BD plans to **incorporate additional analyses into labeling in coordination with FDA** to inform physicians and patients of all risk information
- Analysis of large data sets that are appropriately structured to evaluate overall patient health will **enable additional investigation of association**

Thank You