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FDA Advisory Committee

Philips Stellarex drug-coated balloon

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innovation you

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Executive summary

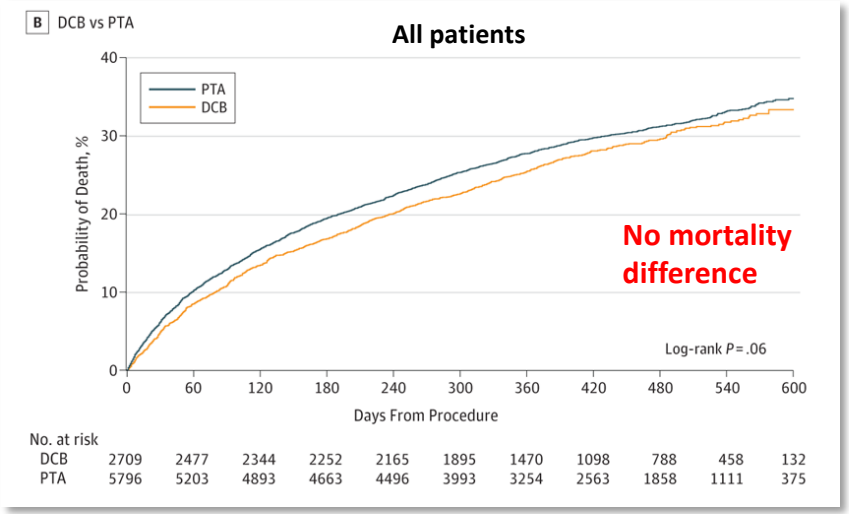
- Stellarex patient-level datasets and additional analyses address several of the deficiencies of recent meta-analyses
- Stellarex data analyses have confirmed its efficacy and safety
  - Continued benefits with durability in patency in all analyzed data sets
  - No mortality signal compared to standard of care (PTA)
  - No mortality effect of paclitaxel drug or dose
- Stellarex data analyses continue to support drug-coated balloons as the first-line treatment for PAD patients

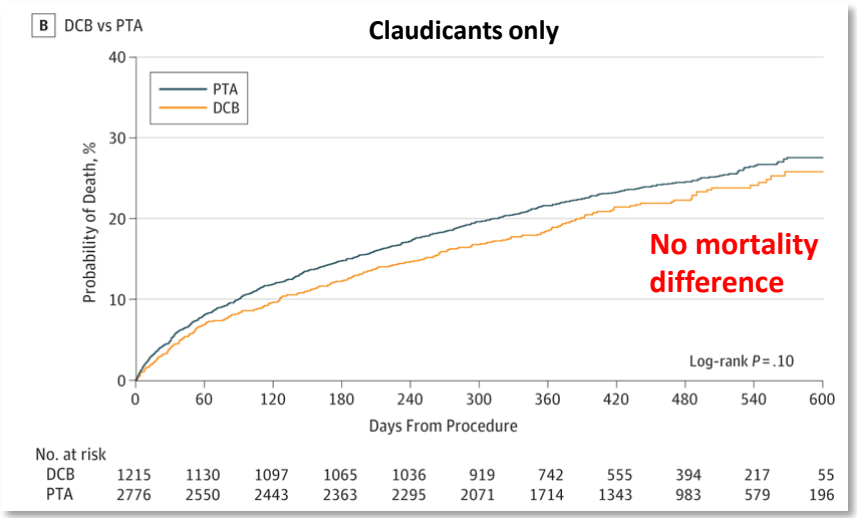
Paclitaxel DCB outcomes in existing published data

Results of analysis using large MEDPAR database of DCBs indicates no associated increased risk of mortality

Based on literature review of DCB ATK studies, Katsanos et al., 2018 is **only 1 of 16** demonstrating a significant increased risk of mortality with the use of DCBs

Analysis of 16,560 Medicare patients shows no evidence of increased all-cause mortality with DCBs/DES compared to PTA/BMS





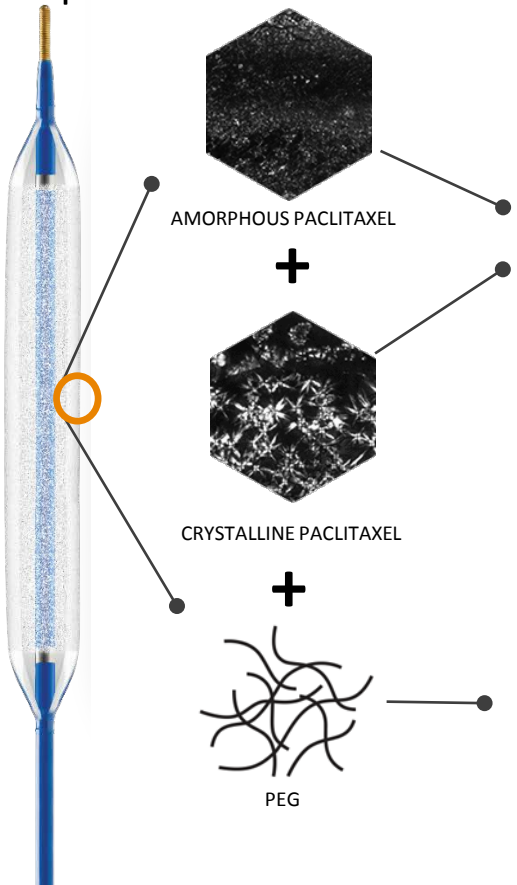
Long-term Survival Following Femoropopliteal Artery Revascularization With Drug-Coated Devices Compared With Non–Drug-Coated Devices Among Patients with and w/o Critical Limb Ischemia (Secemsky et al JAMA 2019)

What makes Stellarex unique?

Stellarex coating designed to maximize efficiency of paclitaxel delivery and clinical performance

DCB design goals

- Limited drug dose
- Limited drug loss
- High drug transfer
- High deliverability
- Clinical performance



- Prompt availability
- Optimized tissue residency with anti-proliferative effect

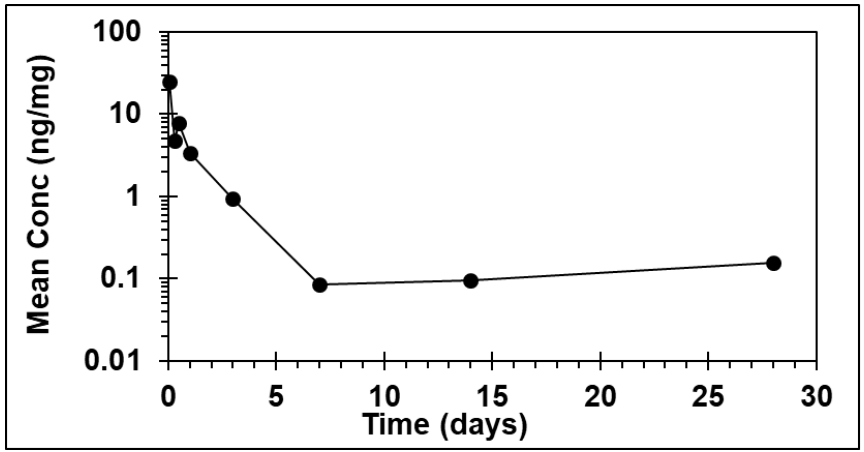
- More durability during handling, tracking, inflation
- Dissolves slowly to protect paclitaxel from loss prior to balloon inflation at target site
- Aids in keeping dose level low

1. Mark, J. et al. Physical Properties of Polymers – Cambridge University Press 3rd edition, 2004
2. Data on file at Philips

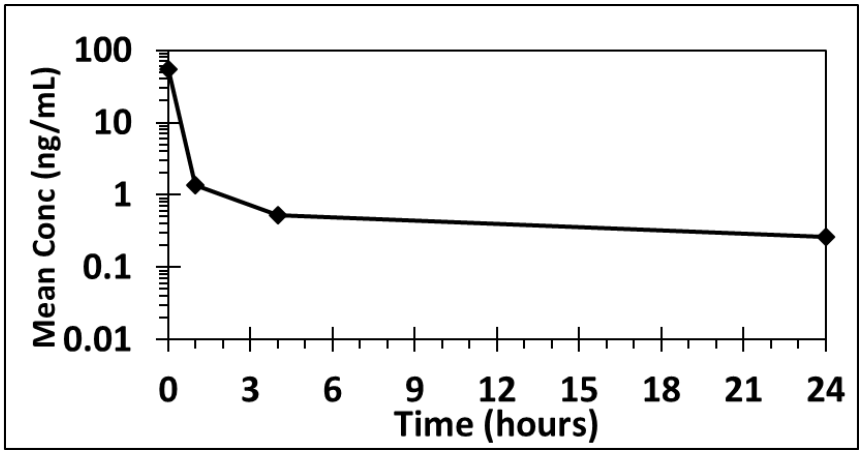
Stellarex coating designed for optimal tissue residency with rapid systemic clearance

Following use in humans, paclitaxel is not detectable in plasma after 24 hours

Porcine Iliofemoral Arterial Tissue



Human Blood (ILLUMENATE-PK)



Semi-log scale

Data on file

Stellarex clinical data

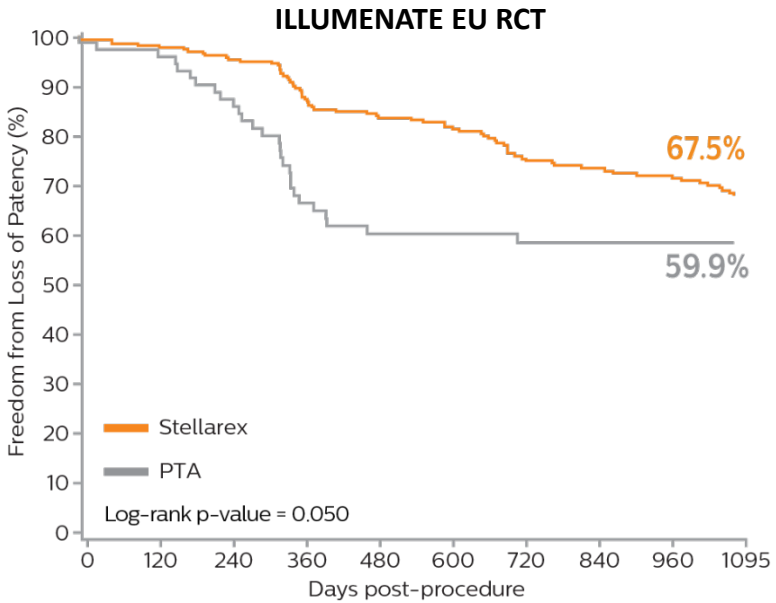
William A. Gray, MD FACC FSCAI

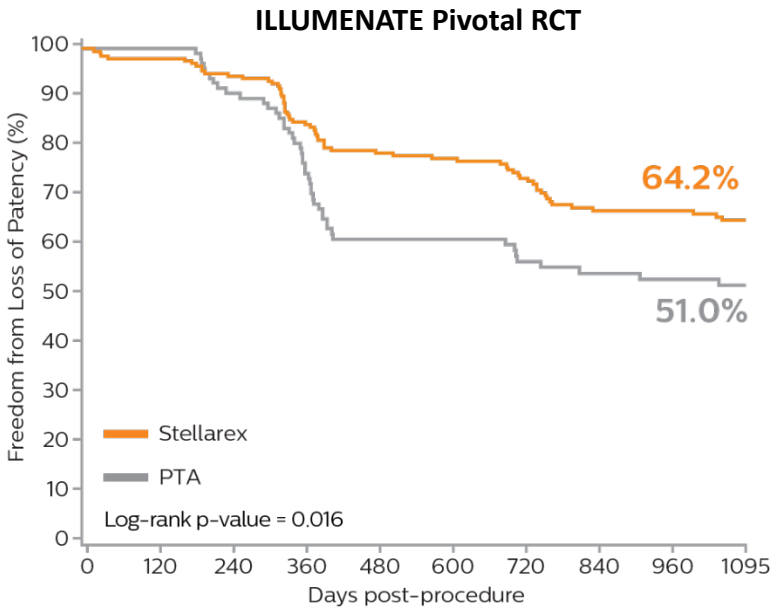
Large Stellarex clinical program designed to evaluate effectiveness and safety

Trial Name	Type	N (# patients)	# Sites	Region
ILLUMENATE FIH	First-in-Human	80	3	Europe
ILLUMENATE EU RCT	RCT	328	18	Europe
ILLUMENATE Pivotal	Pivotal RCT	300	43	US/Europe
ILLUMENATE Global	Single arm	371	37	Europe/Australia/New Zealand
ILLUMENATE Global-ISR	Single arm, Label expansion	130	26	Europe/Australia/New Zealand
ILLUMENATE PK	Single arm, pharmacokinetic	25	2	Australia/New Zealand
SAVER E-Registry	Registry, real-world evidence	2000+	70	Europe
Total Patients		**3234+**		

Durable patency through 3-years demonstrates effectiveness of Stellarex DCB

Improved quality of life with fewer re-interventions than uncoated balloon (PTA) means less patient procedural risk





Rigorous methodology utilized to conduct mortality analysis

This meta-analysis includes pre-specified, *patient-specific* pooled data of patients treated with Stellarex with a test for homogeneity (I^2 = 0%)

- The analysis was independently-performed
- Adjudicated by a blinded, 3rd party, independent CEC

- **Primary analysis**: The two randomized controlled trials (RCT) were pooled with a total N=589 patients (419 in the DCB arms and 170 in the PTA arms) to compare mortality through 3 years between Stellarex DCB and the PTA (control) cohorts

- **Supplementary analysis**: An additional integrated analysis was then performed including all patients treated with Stellarex DCBs of ATK lesions from all seven studies with a total N=2351

Excellent follow-up compliance rates strengthen conclusions

> 95% compliance with minimal lost to follow-up

Follow-up Compliance	ILLUMENATE Pivotal N=300		ILLUMENATE EU RCT N=294	
	DCB N=200	**PTA N=100**	**DCB N=222**	**PTA N=72**
12 Month (±30-45 days)				
Lost-to-follow-up	3 (1.6%)	0 (0.0%)	6 (3.6%)	1 (1.9%)
24 Month (±45-60 days)				
Lost-to-follow-up	0 (0.0%)	3 (3.4%)	4 (2.2%)	0 (0.0%)
36 Month (±60 days)				
Lost-to-follow-up	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative	4 (2.0%)	3 (3.0%)	10 (4.5%)	1 (1.4%)

Follow-up compliance numerators and denominators do not include those patients who are dead or withdrawn thru 36 months +/- 60 days
ILLUMENATE Pivotal withdrawn at 36 months +/- 60 days: DCB=16 (8.0%), PTA = 5 (5.0%)
ILLUMENATE EU RCT withdrawn at 36 months +/- 60 days : DCB=23 (10.4%), PTA = 13 (18.1%)

Stellarex: primary analysis shows no mortality signal

Supplementary analysis confirmed mortality rates comparable to the primary analysis

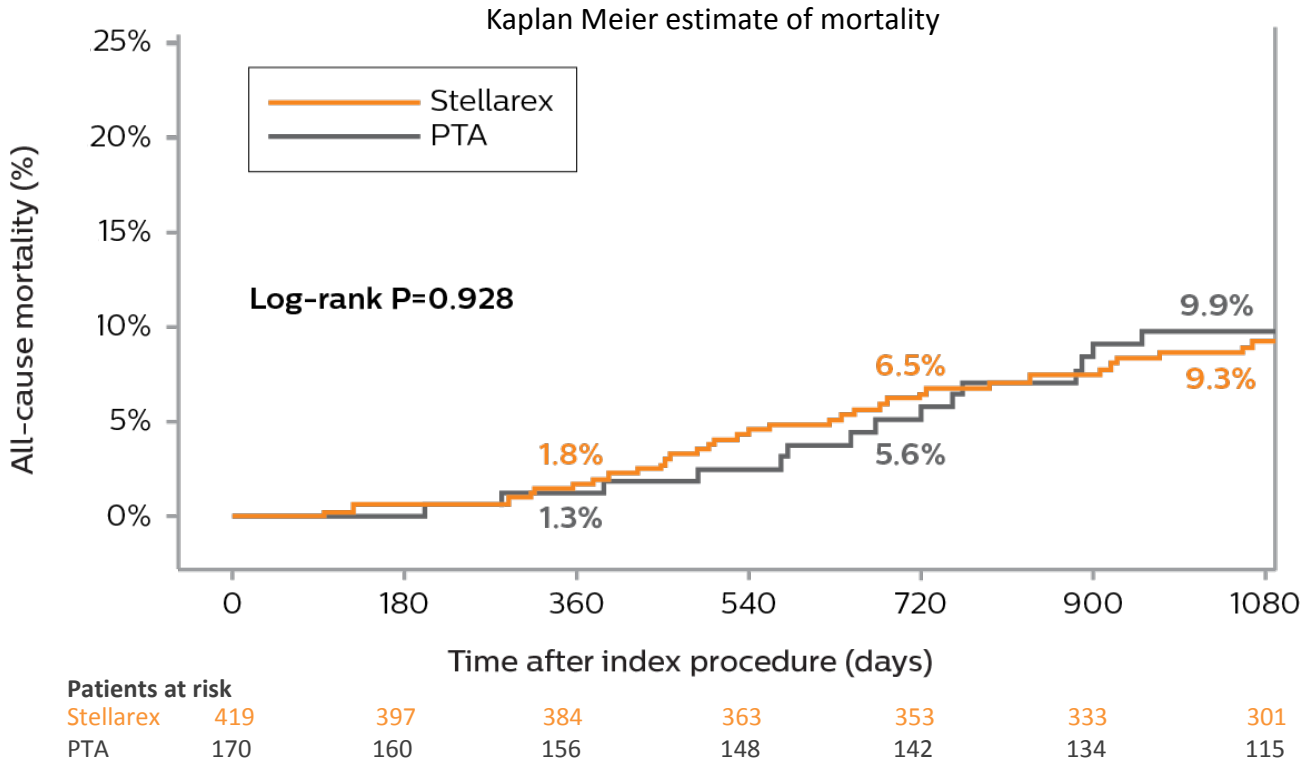
Endpoint	Primary (Pooled RCTs)		Supplementary (Pooled RCTs and non-RCTs)
	DCB KM Estimate N=419	PTA KM Estimate N=170	DCB KM Estimate N=2351
All-Cause Death			
1-year	1.8% (0.7%)	1.3% (0.9%)	2.0% (0.4%)
2-year	6.5% (1.3%)	5.9% (1.9%)	5.5% (0.7%)
3-year	**9.3% (1.5%)**	**9.9% (2.4%)**	**7.9% (0.9%)**
Log-rank p-value	P=0.928		NA

ITT hazard ratio of 1.06

PTA mortality rates are as expected in PAD population and as published in literature

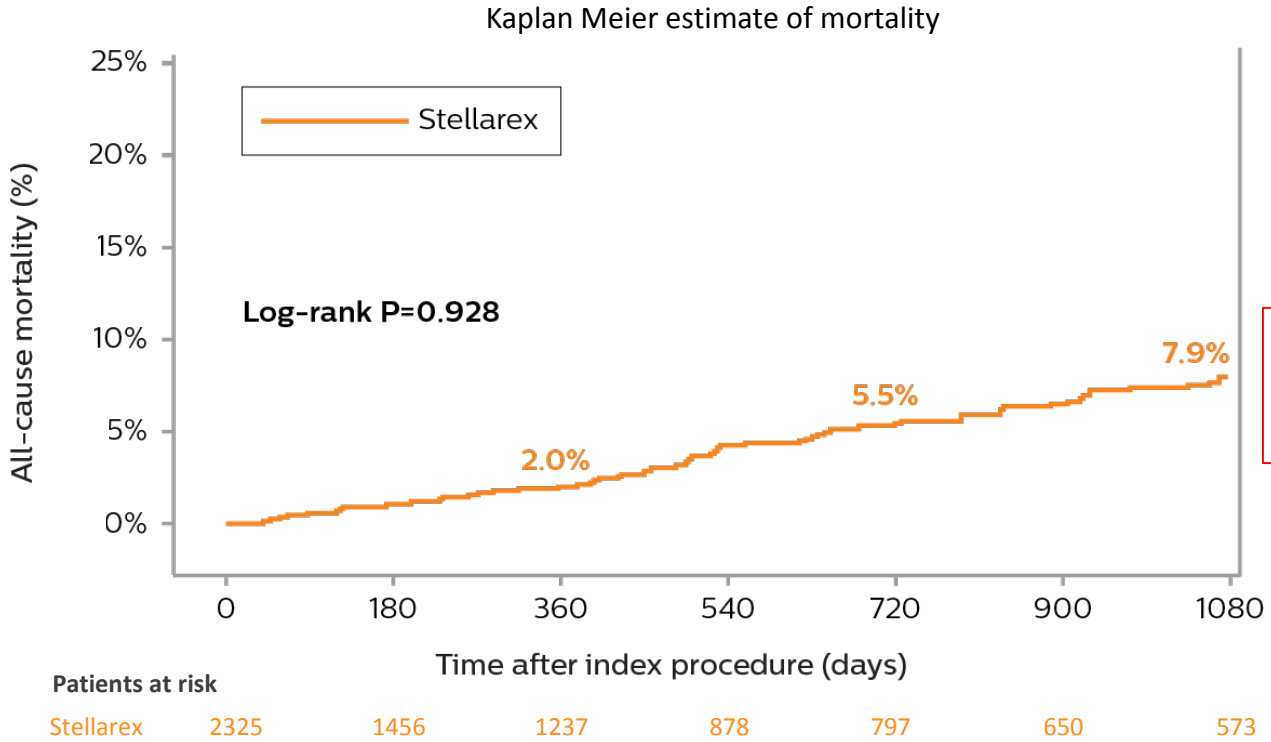
KM: Kaplan-Meier; Presented at LINC 2019

Pooled RCT mortality shows no difference between Stellarex and PTA through 3-year follow-up



 Lyden, LINC 2019

Integrated analysis of 7 Stellarex studies continues to support low all-cause mortality through 3-year



Compared to 9.3% pooled RCT Stellarex mortality rate

Lyden, LINC 2019

Neither paclitaxel, nor paclitaxel dose, is a predictor of death in Stellarex analysis

Top predictors of death: age, renal insufficiency and congestive heart failure

Multivariate Cox Proportional Hazards Model for Mortality

Covariate	Hazard Ratio (95% CI)	P-value
With paclitaxel exposure forced into the model		
Age (per year)	1.06 (1.04, 1.08)	<0.01
Congestive heart failure	1.86 (1.11, 3.12)	0.02
Diabetes	1.43 (1.01, 2.01)	0.04
Renal insufficiency	2.0 (1.33, 3.01)	<0.01
Paclitaxel	**1.02 (0.96, 1.08)**	**0.53**
With paclitaxel dose forced into the model		
Age (per year)	1.06 (1.04, 1.08)	<0.01
Congestive heart failure	1.89 (1.12, 3.19)	0.02
Diabetes	1.45 (1.03, 2.04)	0.04
Renal insufficiency	2.03 (1.35, 3.06)	<0.01
Paclitaxel dose (mg)	**1.04 (0.98, 1.10)**	**0.23**

Gray et al. *Circulation 2019* (in press)

Additional patient-level cross-over data with modified as-treated analysis

In Stellarex pooled RCTs, ~1 in 4 patients in PTA arm were not paclitaxel naïve due to retreatment

PTA patients exposed to paclitaxel maintain low mortality rates in pooled Stellarex RCTs

Post index procedure with a Paclitaxel device in the PTA group	
	PTA % (n/N)
Any post-index lower limb intervention including PTX	
Yes	**22.9% (39/170)**
No	71.7% (122/170)
Unknown	6.4% (11/170)
All-cause mortality among subjects with post-index PTX use	10.3% (4/39)
Median time from treatment assignment to cross-over	404 days

mAT – **Safety Set** of patients treated with paclitaxel coated balloon after index procedure for any reason (e.g., revascularization, add'l lesions etc.)

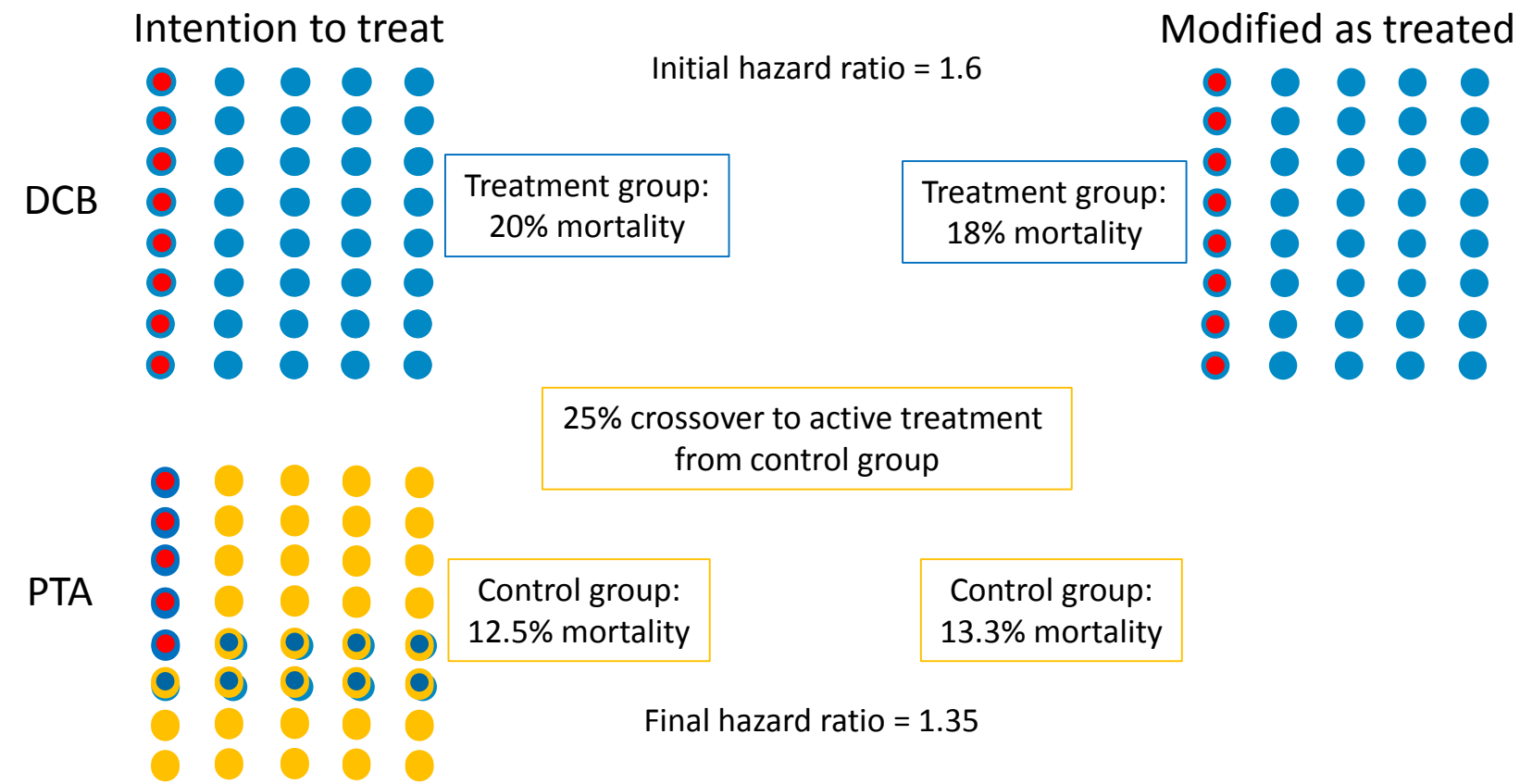
Analysis of all-paclitaxel exposure does not change mortality rates

Classifying patients with any paclitaxel exposure versus paclitaxel naïve has no impact on mortality rates

ILLUMENATE Pivotal and EU RCT Combined Summary of Deaths through 36 Months with Modified As Treated (mAT or Safety Set) Population				
Time Point	**PTX exposed (at any time)**	**Original DCB**	**PTX Naïve**	**Original PTA**
N	458	419	131	170
Overall mortality	8.7%	8.6%	8.3%	8.8%

ITT hazard ratio of 1.06

Cross-over simulation: potential impact to meta-analysis



Conclusions

- No mortality signal with Stellarex
  - Reliably shown by sizable meta-analysis purely of RCTs from a single DCB
  - Observation consistently confirmed across all subsequent third-party pooled analyses
- Lack of mortality signal further reinforced through PTX cross-over accounting
  - Comparing paclitaxel-exposure vs no-exposure further supports paclitaxel is not a contributing factor to mortality
  - Absent complete accounting of paclitaxel exposure, and its potential impact on mAT outcomes, any large scale analysis will be incomplete
- Benefits outweigh risk
  - Stellarex has proven both effectiveness and safety for improved benefit/risk for claudicants and high risk patients
  - Stellarex DCB should be used as first-line therapy in PAD patients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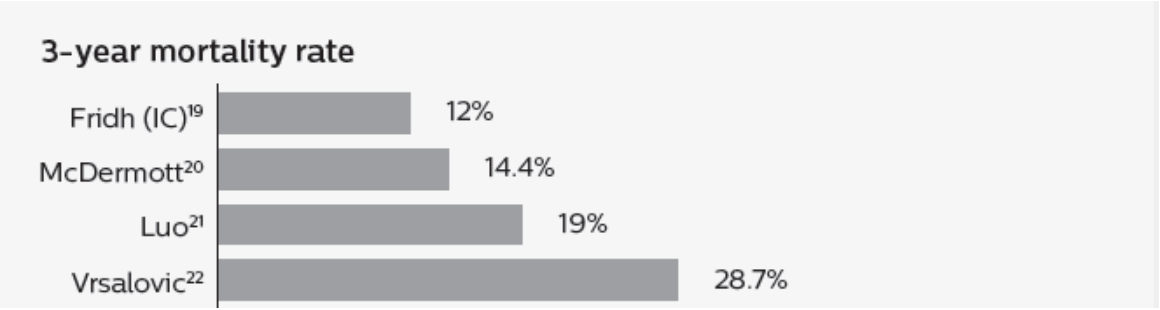
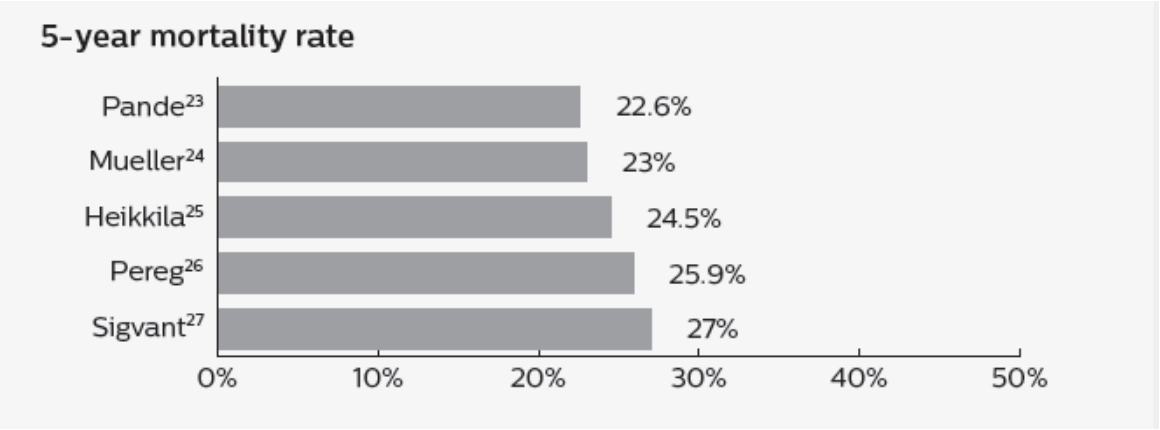
PAD mortality in general claudicant population

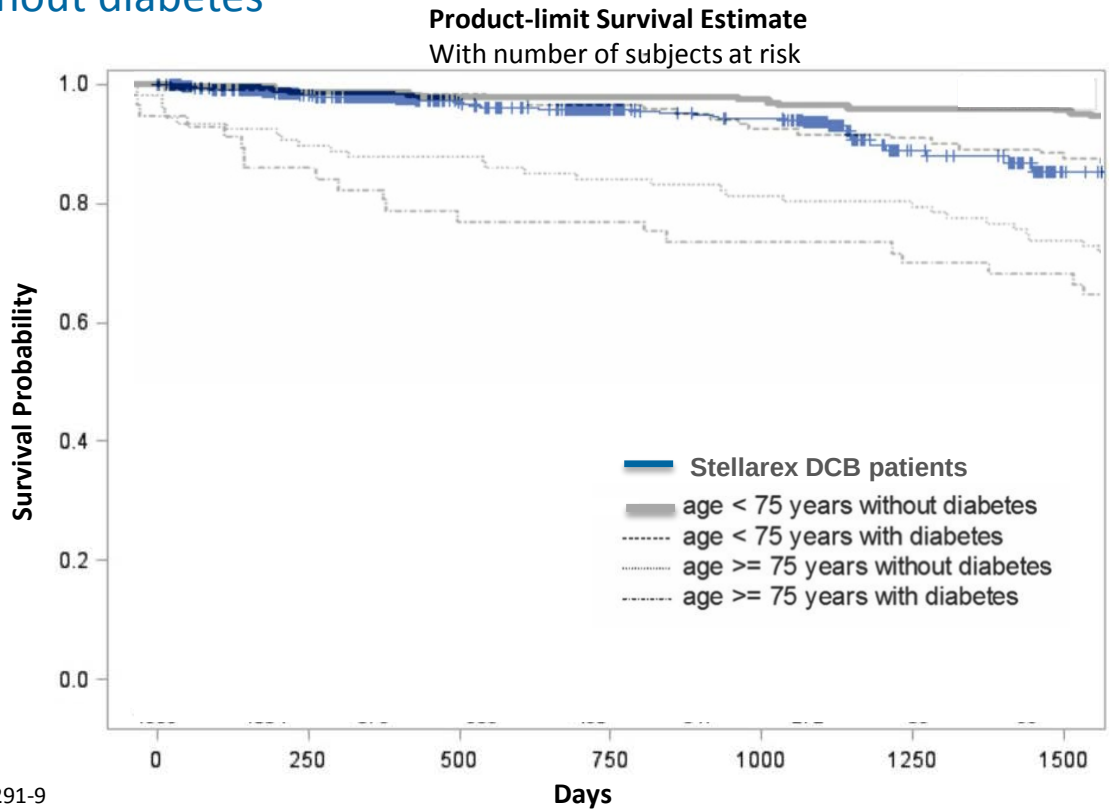
Stellarex PTA mortality in-line with general population mortality rates





Stellarex pooled RCT mortality in-line with PAD population

Stellarex all-cause mortality through 3 years compared to PAD patients with and without diabetes



Mueller et al. J Vasc Surg 2014;59:1291-9

Crude All -Cause Mortality Rates: Pooled RCT studies

ILLUMENATE Pivotal and EU RCT Combined Summary of Deaths by Year through 36 Months ITT Population		
Time Point (Windows)	**DCB % (n/N)**	**PTA % (n/N)**
Overall[1]	8.5% (36/422)	8.7% (15/172)
Month 12	2.2% (9/404)	1.9% (3/162)
Month 24	6.7% (26/389)	7.0% (11/158)
Month 36	9.7% (36/370)	10.0% (15/150)

[1]Overall rate of death through Month 36 follow-up window among all randomized subjects.
For yearly estimates the numerators are number of deaths through close of the window and denominators are number of subjects with either death or follow-up at or after window open.

Stellarex patient withdrawal and lost-to-follow-up cumulative through 3 years

Table 3: Overview of RCT Patient Disposition - Patient Withdrawal and Lost-to-Follow-up

ILLUMENATE EU RCT	**Randomized Cohort**		
36 Month (1095 Days ± 60 Days)	**DCB (N=222)**	**PTA (N=72)**	**Total[1] (N=294)**
Withdrawn	23 (10.4%)	13 (18.1%)	36 (12.2%)
Lost-to-follow-up	10 (4.5%)	1 (1.4%)	11 (3.7%)
ILLUMENATE Pivotal	**ITT Cohort**		
36 Month (1095 Days ± 60 Days)	**DCB (N=200)**	**PTA (N=100)**	**Total (N=300)**
Withdrawn	16 (8.0%)	5 (5.0%)	21 (7.0%)
Lost-to-follow-up	4 (2.0%)	3 (3.0%)	7 (2.3%)

[1]7 subjects were randomized to receive study treatment but were exited from the study due to not receiving a study device (DCB or PTA).

ILLUMENATE European (EU) Randomized Clinical Trial (RCT) Study Clinical Study Report: Tables, Listings, and Figures for PAS CSR and Month 36 Analyses. July 6, 2018

ILLUMENATE Pivotal Study Clinical Study Report: Tables, Listings, and Figures for PAS CSR and Month 36 Analyses. November 30, 2018