CACVS 2017

FMRP
Flanders Medical Research Program

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Drug Eluting Balloons: Are the results durable ?

Koen Keirse, MD
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Disclosure slide

Speaker name: **Koen Keirse, MD**

☐ I have the following potential conflicts of interest to report:

- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s)

☑ I do not have any potential conflict of interest

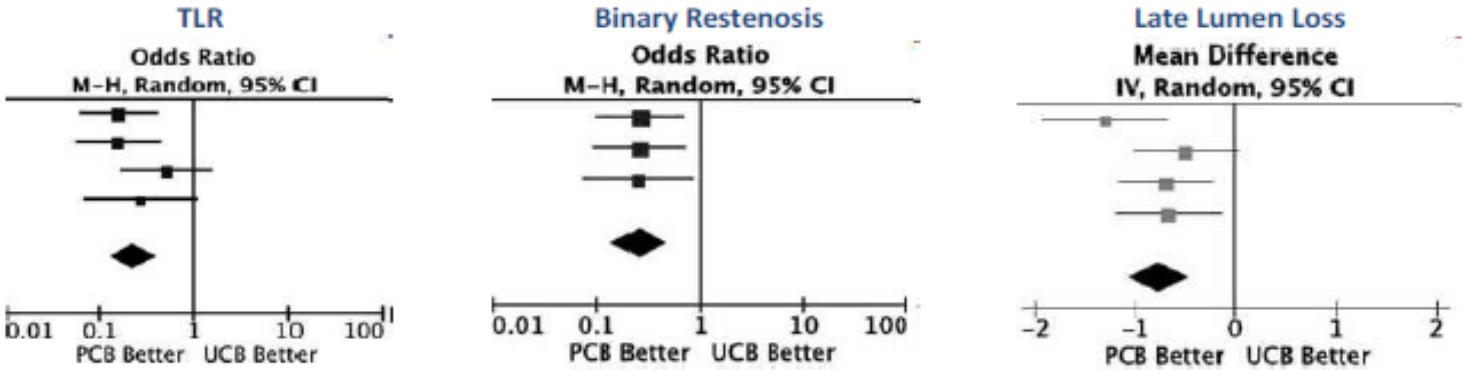
Will DEB be the future for the SFA? DURABLE ?

Need for … more studies … more time ?

The evidence behind the enthusiasm

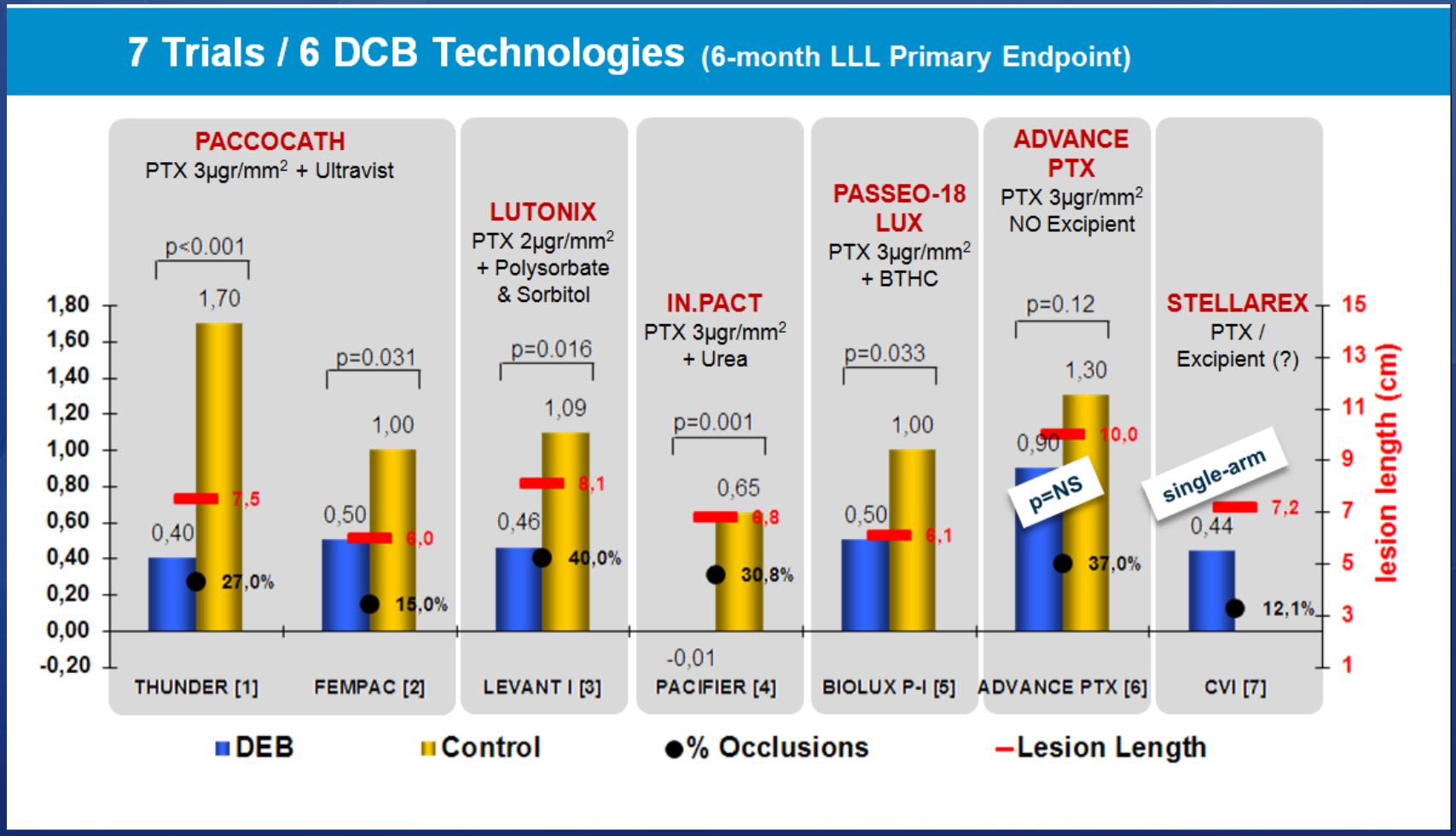
- 5 proof-of-concept Trials
- 6 Randomized
- 2-year Functional Outcomes
- 5-year Clinical Follow up (TLR)
- 2 meta-analyses
- All support DEB in TASC A+B lesions
- Promising initial evidence building on long, TASC C-D lesions and ISR

Meta Analysis of major endpoints: Drug Eluting Balloon (PCB) vs. Uncoated Balloon (UCB)



G.Tepe et al. THUNDER N Engl J Med 2008; M.Werk et al. FEMPAC Circulation. 2008; D.Scheinert LEVANT I TCT 2010 Oral Presentation; M.Werk et al. PACIFIER Circ Cardiovasc Interv. 2012; Cassese et al. Circulation CI 2012 / Cassese et al. TCT abstract #173

Proof of concept



[1] G.Tepe et al. - NEJM 2008; [2] M.Werk et al. - Circulation 2008; [3] D.Scheinert - TCT 2012 oral presentation; [4] M.Werk et al. - Circulation CI 2012; [5] D.Scheinert – EuroPCR 2012 oral presentation; [6] D.Scheinert – LINC 2013 oral presentation; [7] S.Duda – EuroPCR 2013 oral presentation

Remarks concerning DEB of SFA

- RCT data confirms First-in-Human study results (TASC A B)
- Global trials for real-world lesions show promising results also including longer and complexer lesions

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- Improved Clinical Outcome has been demonstrated (WQ, Rutherford and ABI)

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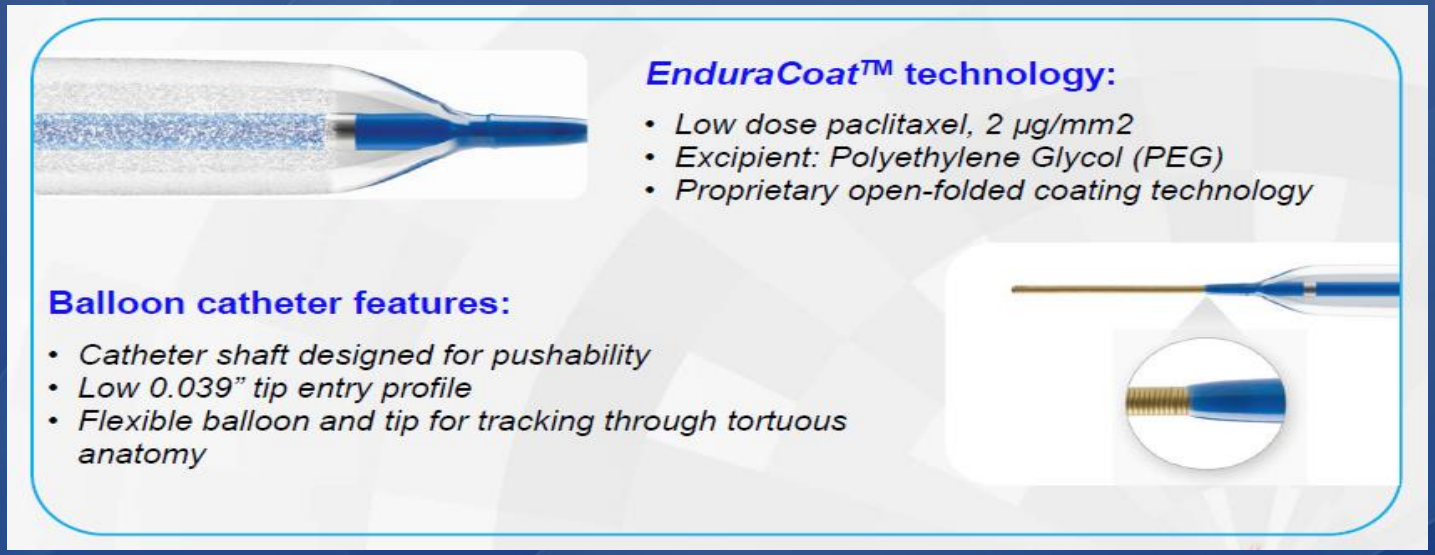
- Improved Clinical (en demonstrated (WQ, Rutherford a

DURABLE ?

- Effectiveness is judged by Primary Patency and TLR rates
- Most available results, however, are limited to 12-24 months …..

Stellarex™ Drug-Coated Angioplasty Balloon



Balloon Catheter

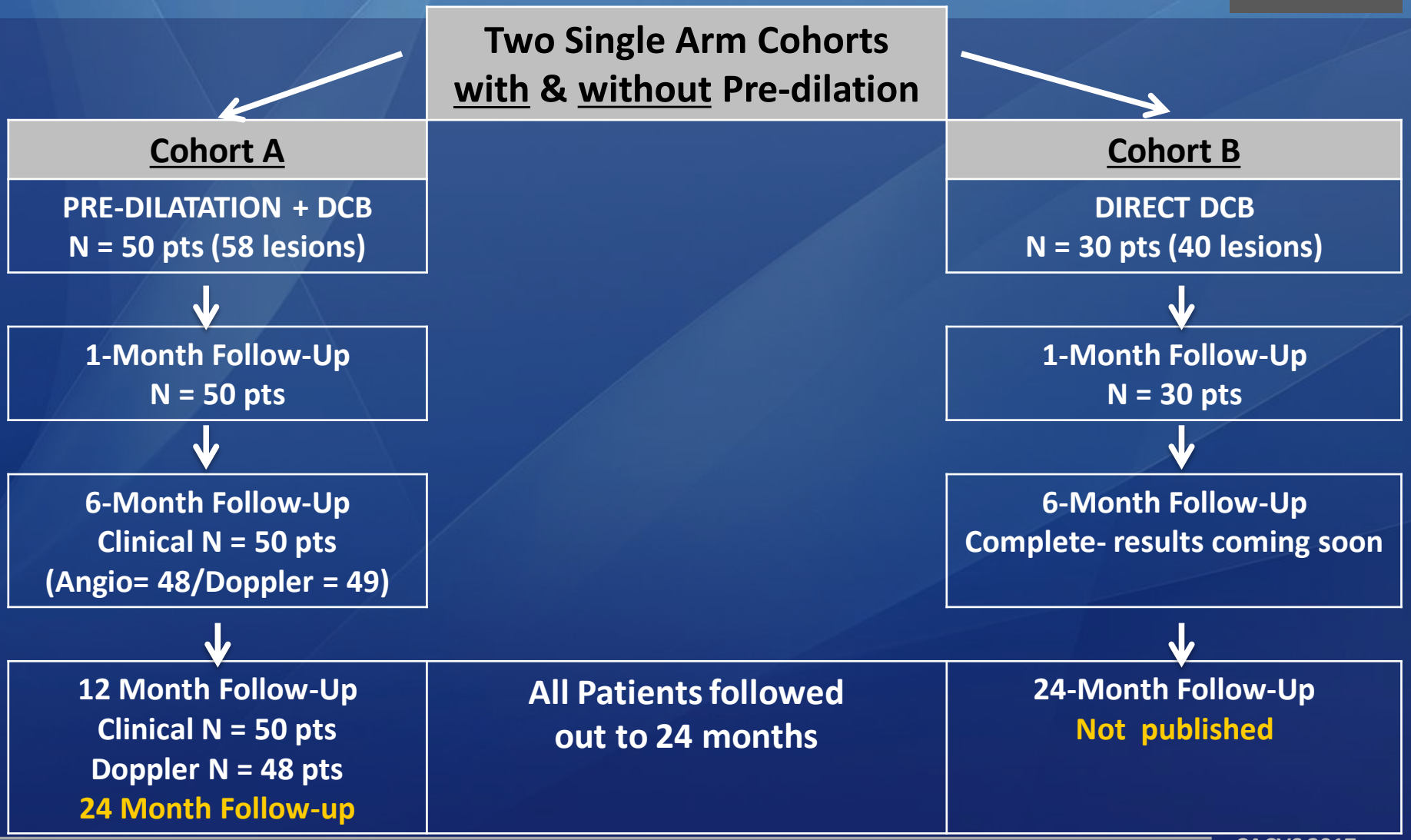
- Covidien EverCross™ 0.035 PTA Balloon Catheter
- Balloon sizes: 4-6 mm diameter, 40, 80 120 mm length

Proprietary Coating Process

- Demonstrated high patency rates in early outcomes
- Durable paclitaxel carrier (2.0µg/mm^2) for optimized drug delivery
- Uniform coating of balloon treatment area

ILLUMENATE FIH Study Flow Chart

2011-2012
n 78



Cohort 1 data published (Cath Cardiovasc Interv 86: 278-286; 2015)

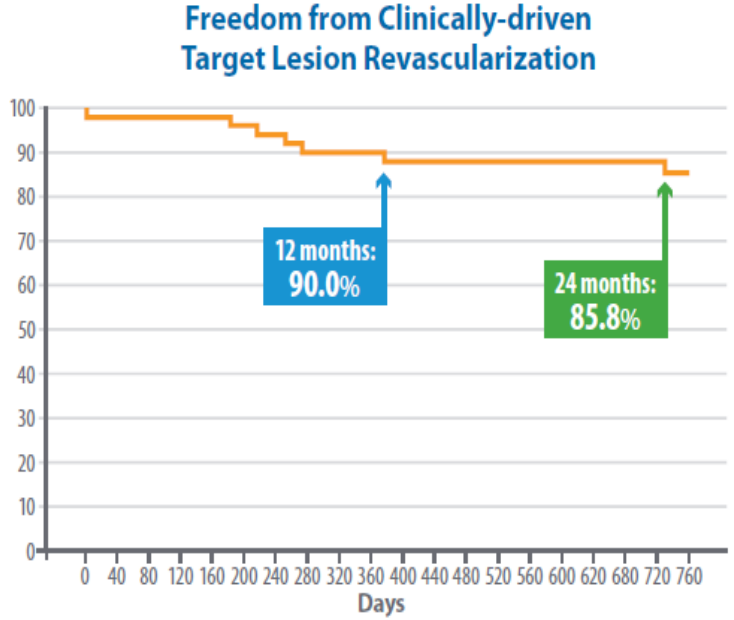
Durability ?

Primary Patency at 24 Months: 80.3 %

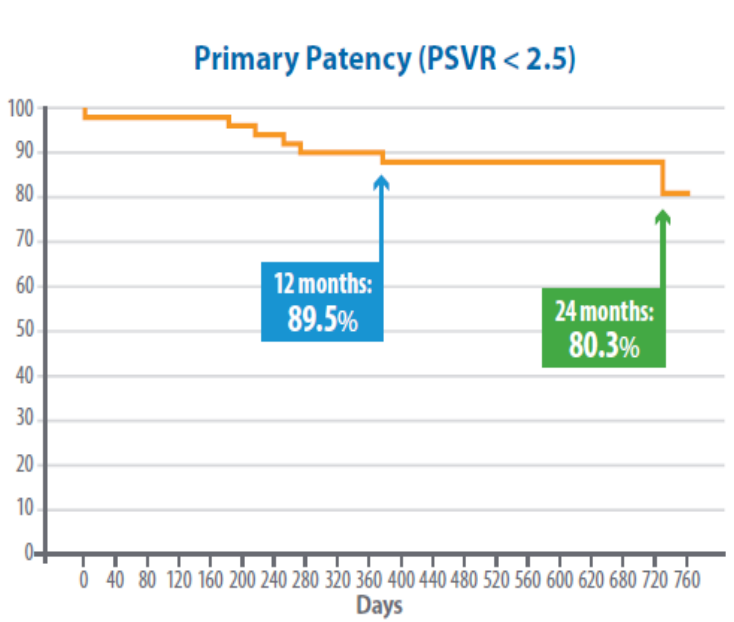
compares favorably to other FIH DEB 24-months patency rates

TLR at 24 Months: 14.2 %

minimal drop off from 12 months through 24 months

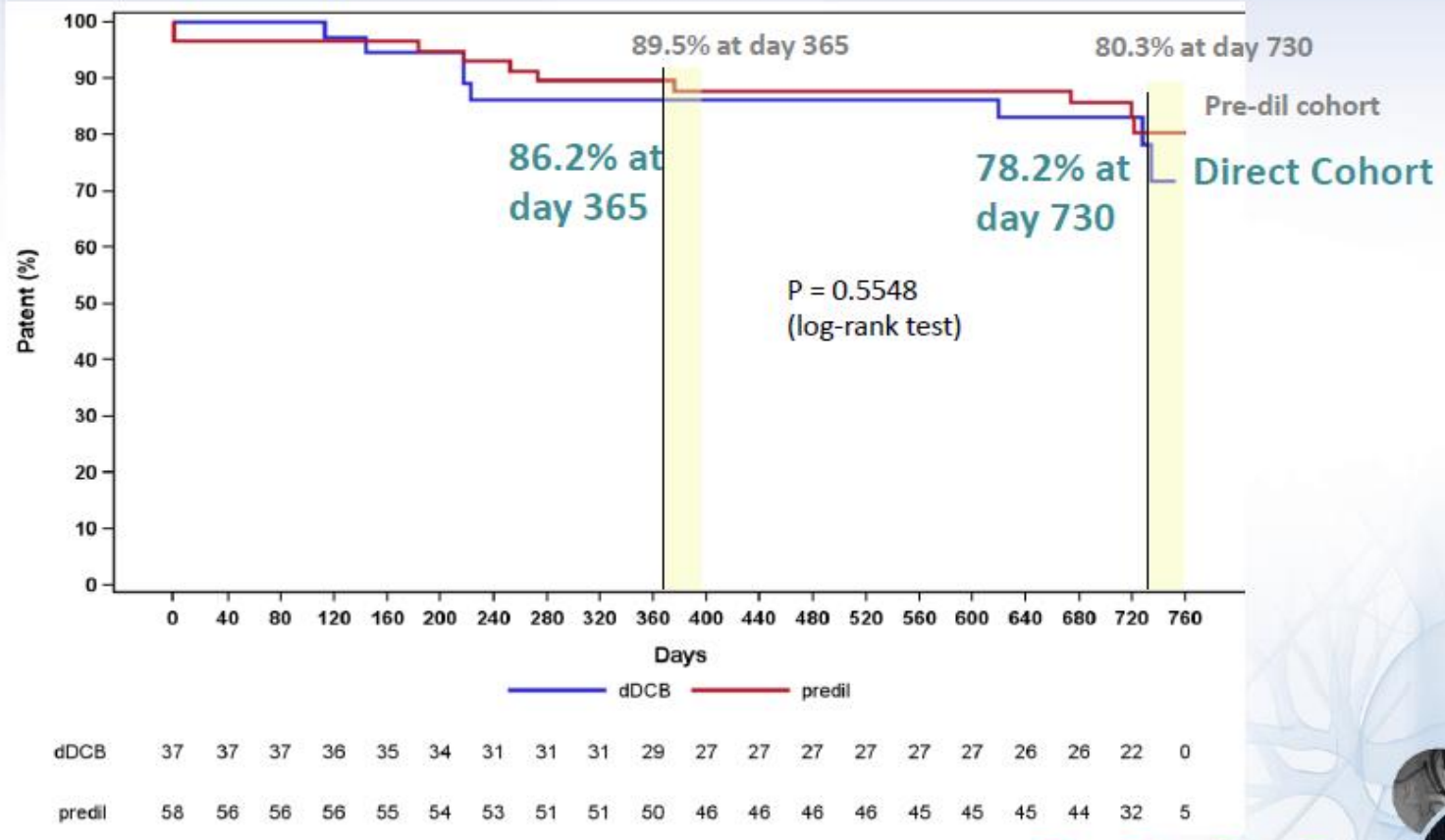


Clinically- driven TLR by KM estimation at upper level of FU intervals = 87.9% (390-day) and 85.8% (760-day)



Primary Patency rates by KM estimation at upper level of FU intervals = 87.7% (390-day) and 80.3% (760-day)

Primary Patency

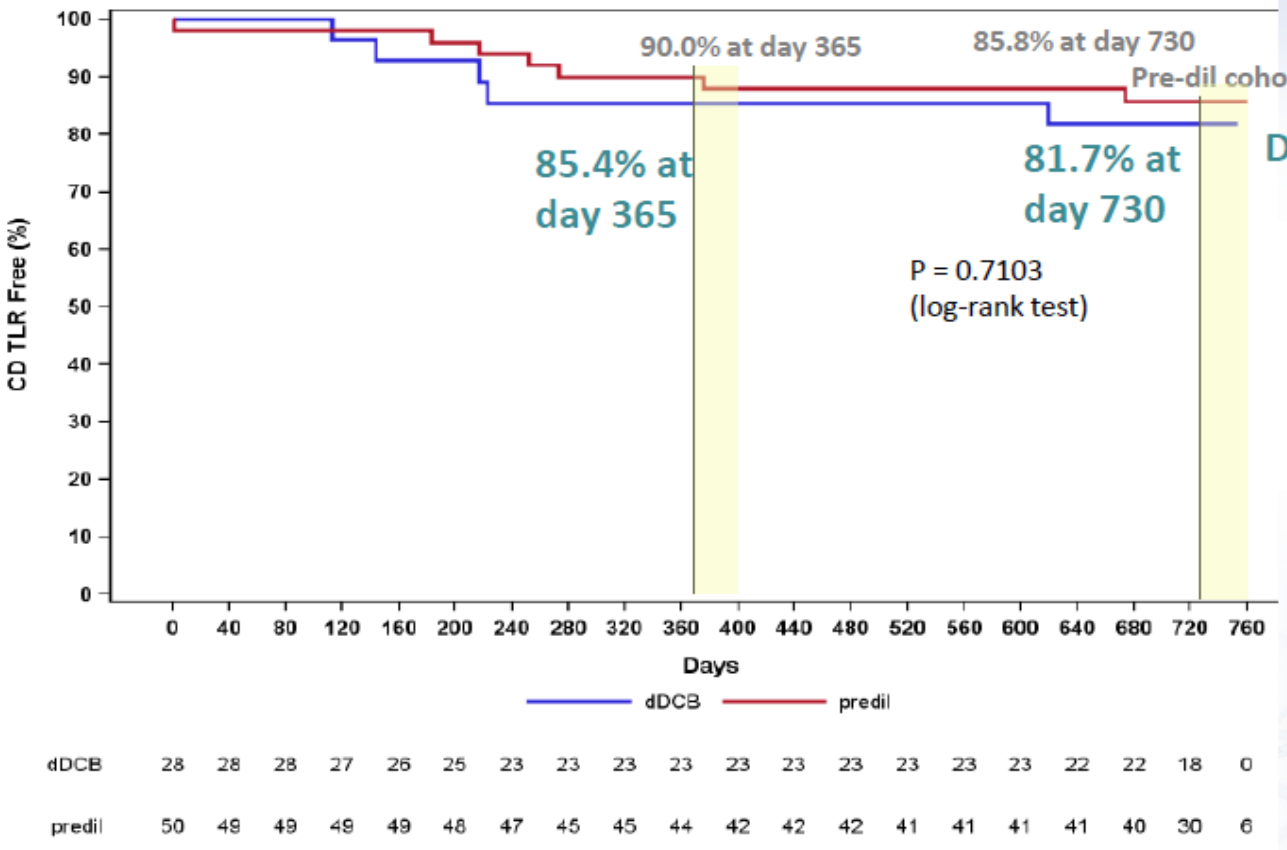


dDCB	37	37	37	36	35	34	31	31	31	29	27	27	27	27	27	27	26	26	22	0
predil	58	56	56	56	55	54	53	51	51	50	46	46	46	46	45	45	45	44	32	5

Primary Patency survival estimates at upper bound of follow up windows for 1 and 2 years:
pre-dil cohort: 87.9% at 395-day and 80.3% at 760-day
direct cohort: 86.2% at 395-day and 71.7% at 753-day (last observed follow up)

Two TLRs in direct cohort were due to thrombotic occlusions in patients that were not compliant with prescribed anti-platelet medications

Freedom from TLR



dDCB	28	28	28	27	26	25	23	23	23	23	23	23	23	23	23	23	22	22	18	0
predil	50	49	49	49	49	48	47	45	45	44	42	42	42	41	41	41	41	40	30	6

Freedom from TLR survival estimates at upper bound of follow up windows for 1 and 2 years:
pre-dil cohort: 87.9% at 395-day and 85.8% at 760-day
direct cohort: 85.4% at 395-day and 81.7% at 753-day (last observed follow up)

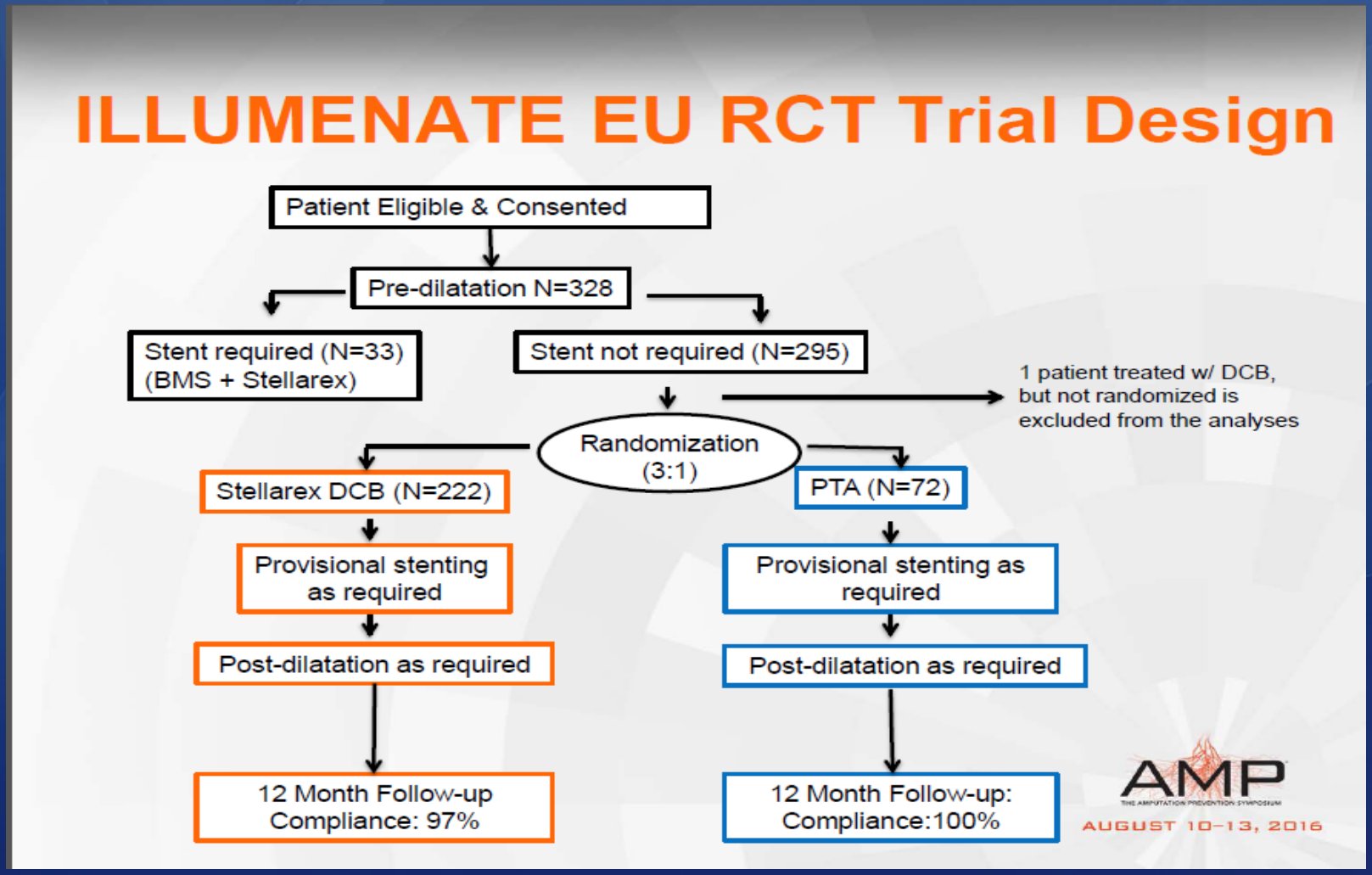
Two TLRs in direct cohort were due to thrombotic occlusions in patients that were not compliant with prescribed anti-platelet medications

VIVA 15

With courtesy to Prakash Krishnan

ILLUMENATE EU RCT

2011-2012
n 294

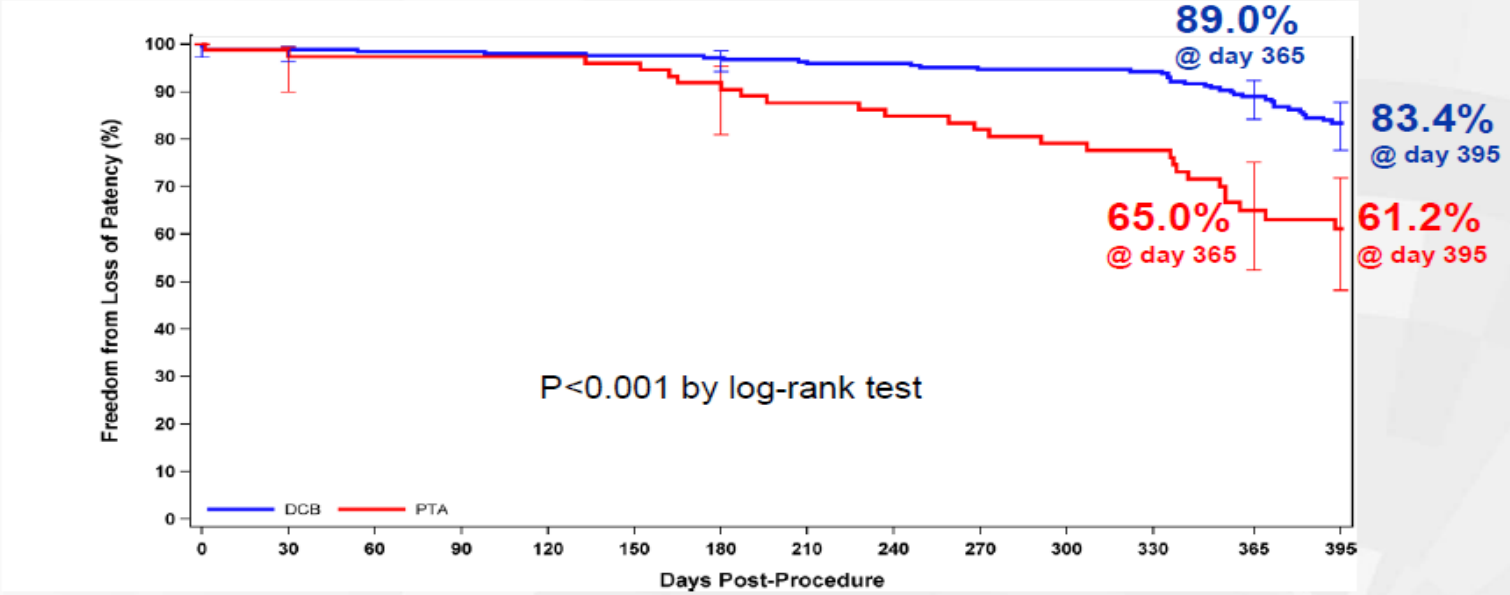


With courtesy to Marianne Brodmann

ILLUMENATE EU RCT

Primary Patency at 12 Months: 89.0%

ILLUMENATE EU RCT ITT Data Set



Primary patency is defined as freedom from restenosis (determined by duplex ultrasound PSVR threshold of 2.5) and freedom from clinically-driven TLR at 12 months. Assessed per lesion.
KM estimates reported at day 395 to capture all patients and events within the full (and legitimate) 335-395 follow-up window. Rates from the middle of the protocol visit window (365 days) reported for consistency and comparative purposes with other trials.

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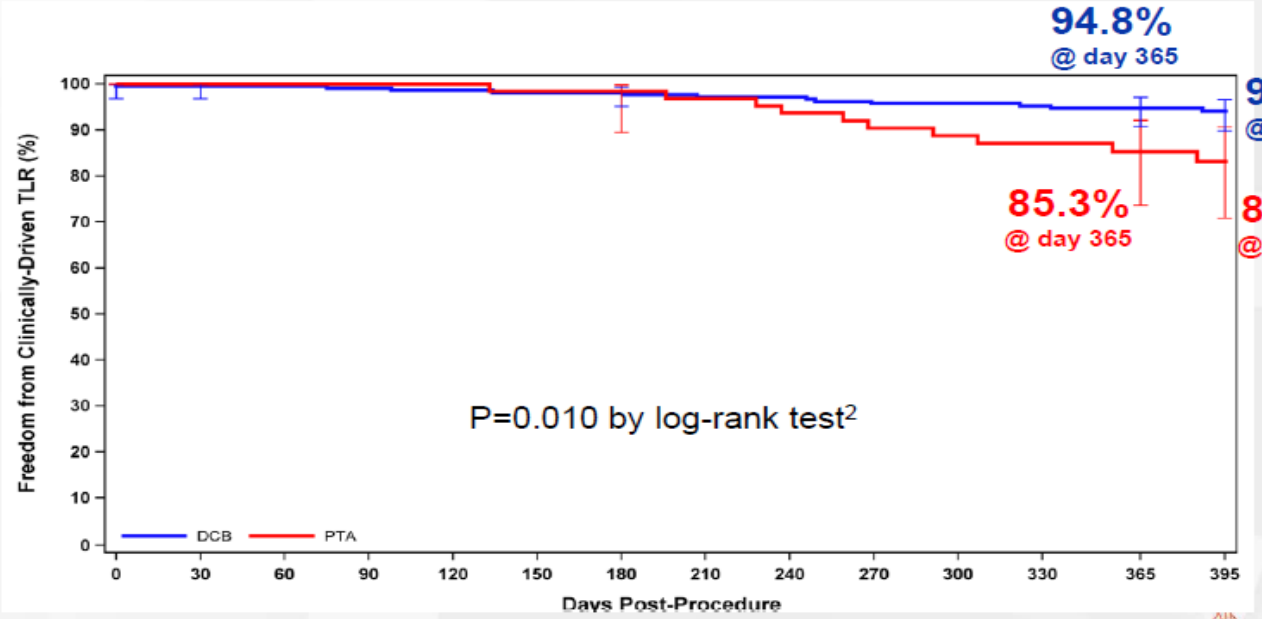
With courtesy to Marianne Brodmann

ILLUMENATE EU RCT

CD-TLR[1] Free at 12 Months: 94.8%

ILLUMENATE EU RCT ITT[3] Data Set



1. Clinically-driven TLR defined as reintervention due to PSVR≥2.5 (or >50% stenosis via angio) due to an increase in the RCC >1 category or deterioration in the ABI by >0.15 compared to maximum early post-procedural level. Per subject analysis.
2. Descriptive, post-hoc analyses; Hypothesis testing was not pre-specified. Log-rank p-value is post-hoc.
3. As-treated data set is considered the primary data set for the endpoint

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With courtesy to Marianne Brodmann

ILLUMINATE EU RCT

Endpoint	DEB	PTA	p-value
12 months			
Primary patency @ 12m	89.0 %	65.0 %	P < 0.001
Freedom CD – TLR	94.8 %	85.3 %	P = 0.010
24 months			
Primary patency @ 24m			
Freedom CD – TLR			

ILLUMINATE Pivotal Trial (RCT)

2012-2015
n 300

Endpoint	DEB	PTA	p-value
12 months			
Primary patency @ 12m	82.3 %	70.9 %	
Freedom CD – TLR @ 12m	93.6 %	87.3 %	
24 months			
Primary patency @ 24m			
Freedom CD – TLR			

POOLED DATA from 2 RCT

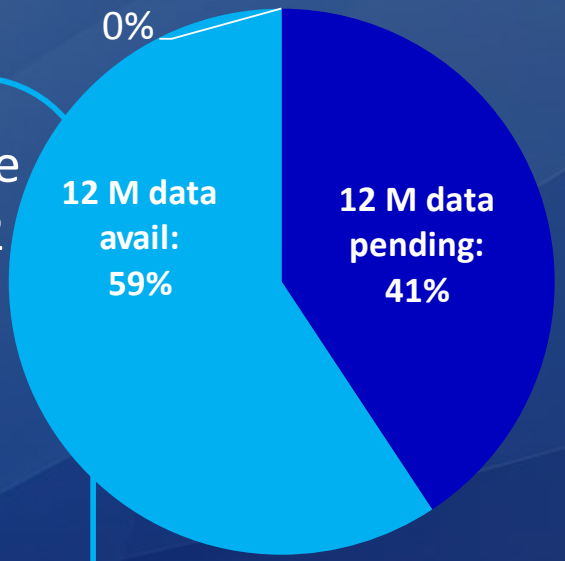
Endpoint	DEB
Primary patency @ 12m	86.0 %
Freedom CD – TLR @ 12m	94.2 %

ILLUMENATE Global Study

2013-2015
n 371

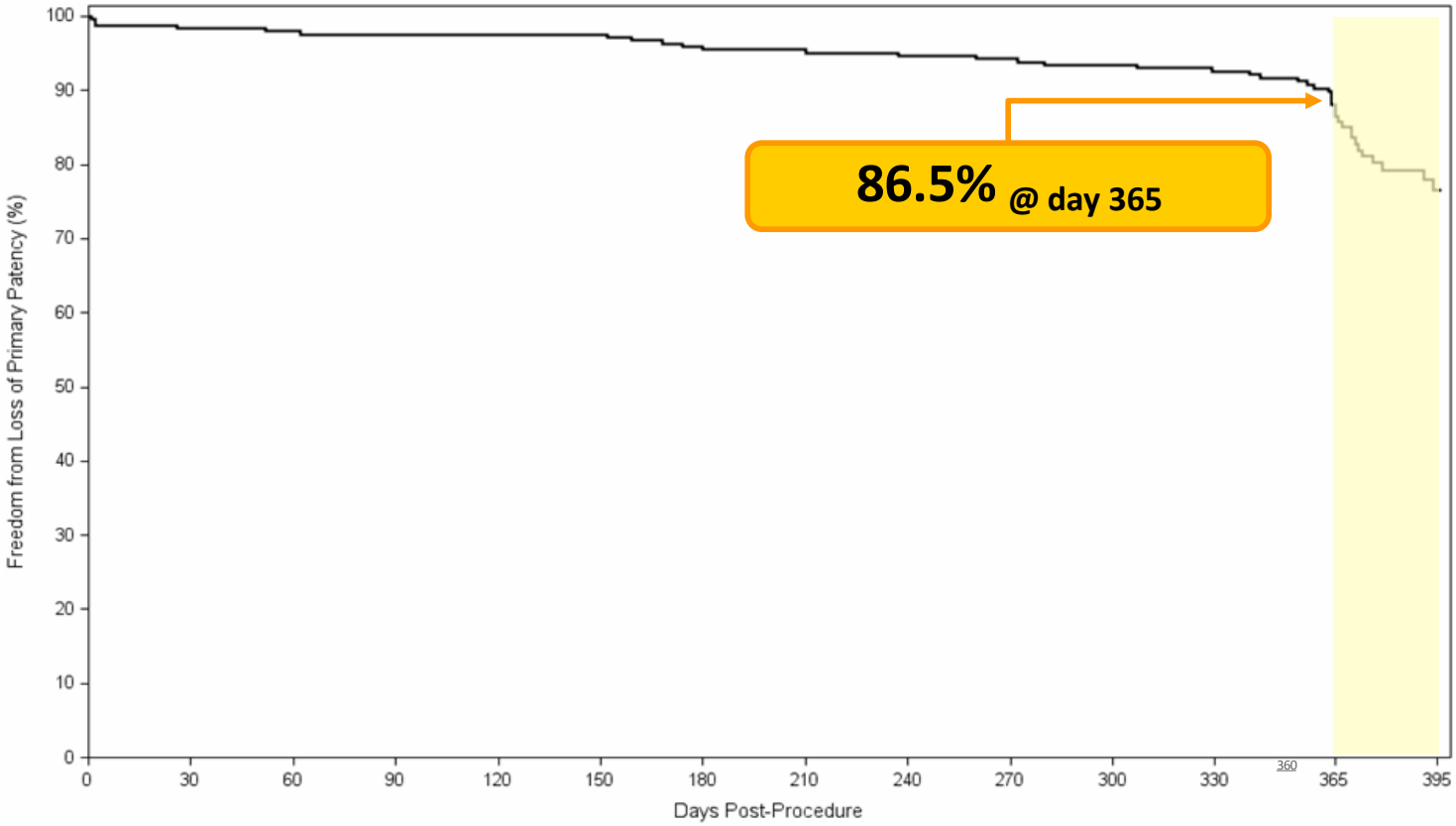
Second Interim Analysis

- The following Interim analysis includes data on the first 220 subjects who have been seen for their 12 month follow-up visit
- N=220 subjects (of the 371 enrolled)
- All presented data/images were monitored, adjudicated and assessed by the appropriate core lab as outlined in the protocol
- ITT analysis



Freedom From Loss of Primary Patency

by Duplex Core Lab Evaluation

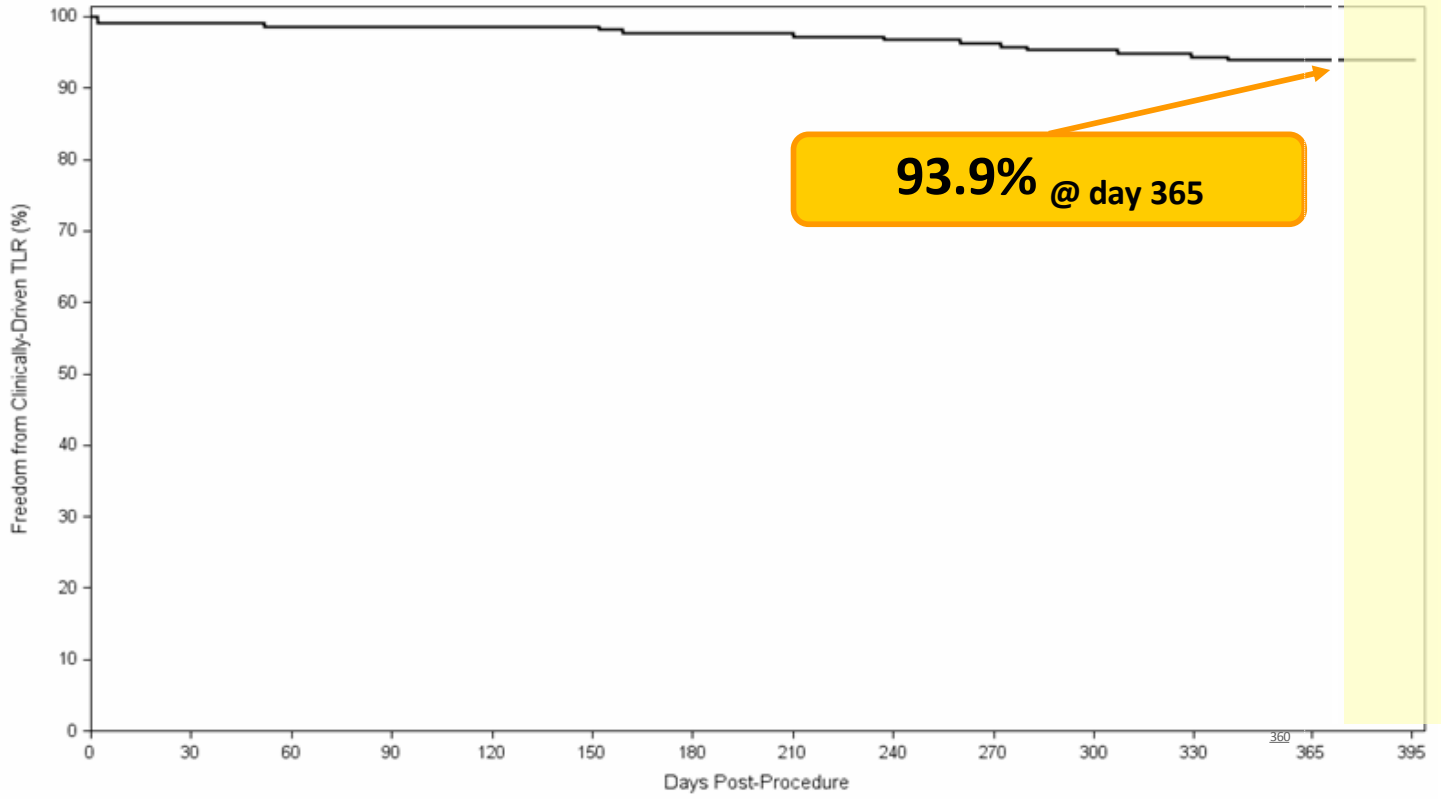


Day	0	30			360	365	395
At Risk	247	242		232	185	158	57
Event	0	4		11	23	30	41
Survival (%)	100	98.4		95.5	90.3	86.5	76.6

Primary Patency defined as freedom from Duplex derived restenosis (PSVR ≤ 2.5) and clinically-driven TLR
Number at risk at day 395 is 57 since follow-up is still in progress

Freedom From CD-TLR*

by Clinical Events Committee Adjudication



Day	0	30	180	360	365	395
At	220	217	208	168	143	54
Event	0	2	5	13	13	13
Survival (%)	100	99.1	97.7	93.9	93.9	93.9

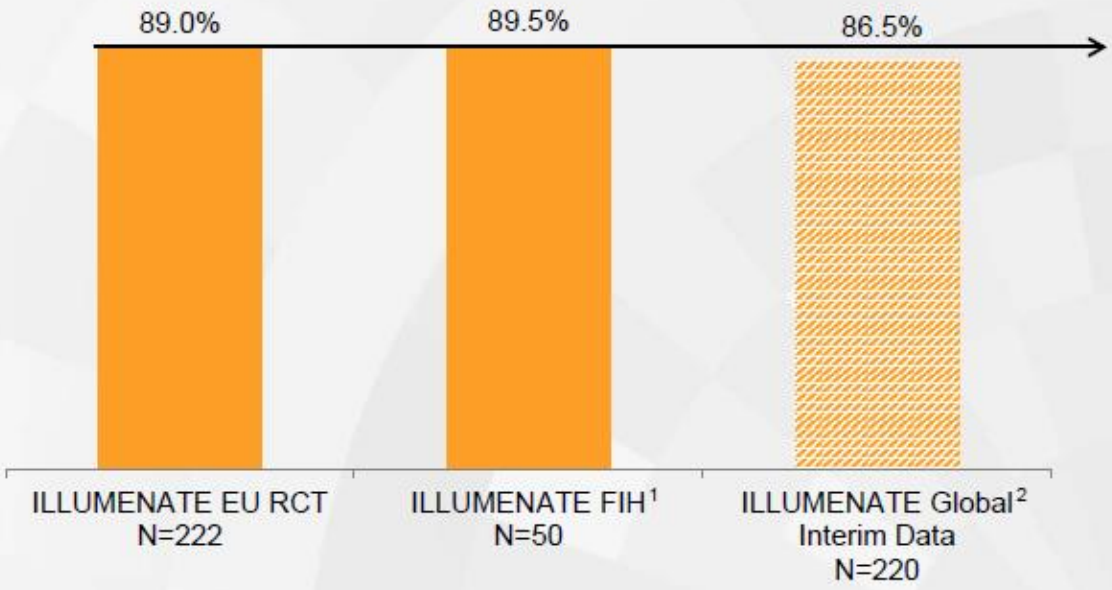
* Defined as revascularization associated with PSVR ≥ 2.5 or >50% stenosis via angiogram and worsening of RCC by more than 1 or ABI decrease of >0.15 from the maximum early post-procedure level, that is clearly referable to the target lesion

ILLUMINATE Conclusions

- RCT data (2) confirms First-in-Human study results
- The Stellarex is a low-dose DEB with consistently positive results (significant improved compared to PTA):
- RCT: - Primary Patency @ 12m: 86.0 %
  - Freedom from CD-TLR @ 12m: 94.2 %

- ILLUMINATE Global trial will provide more data and shows promising results concerning durability

Consistent Patency Rates Observed across 3 separate studies with Stellarex



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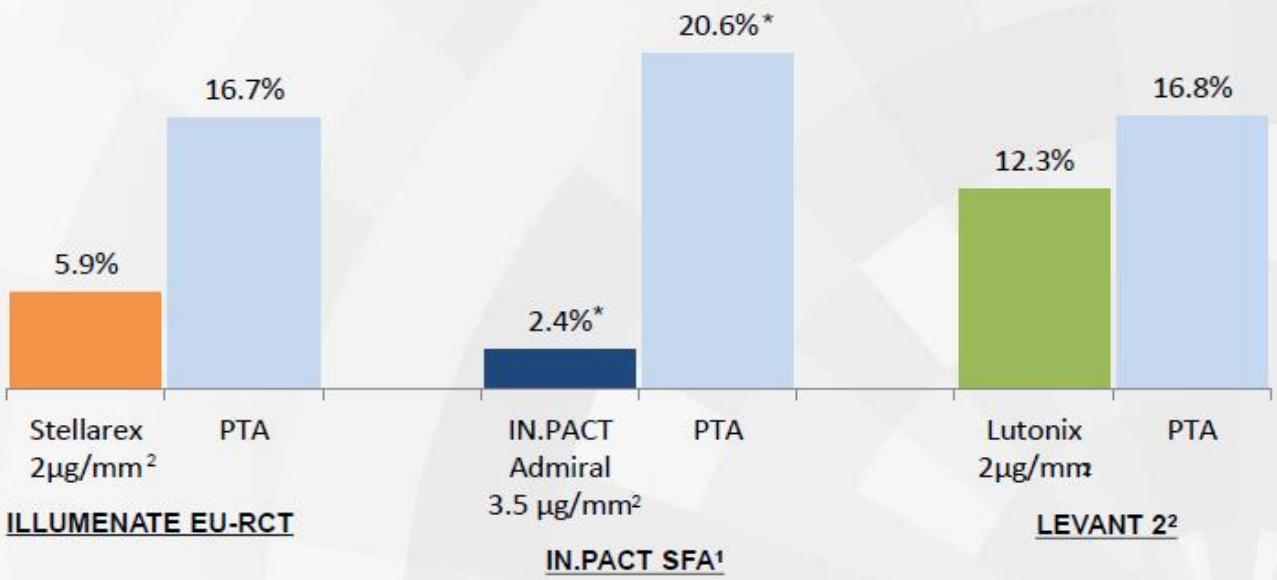
Kaplan-Meier estimates at day 365 shown

1. H. Schroeder et al. *Catheter Cardiovasc Interv. 86:278-286* (2015). 2. P. Krishnan oral presentation. NCVH, New Orleans, June 2016.

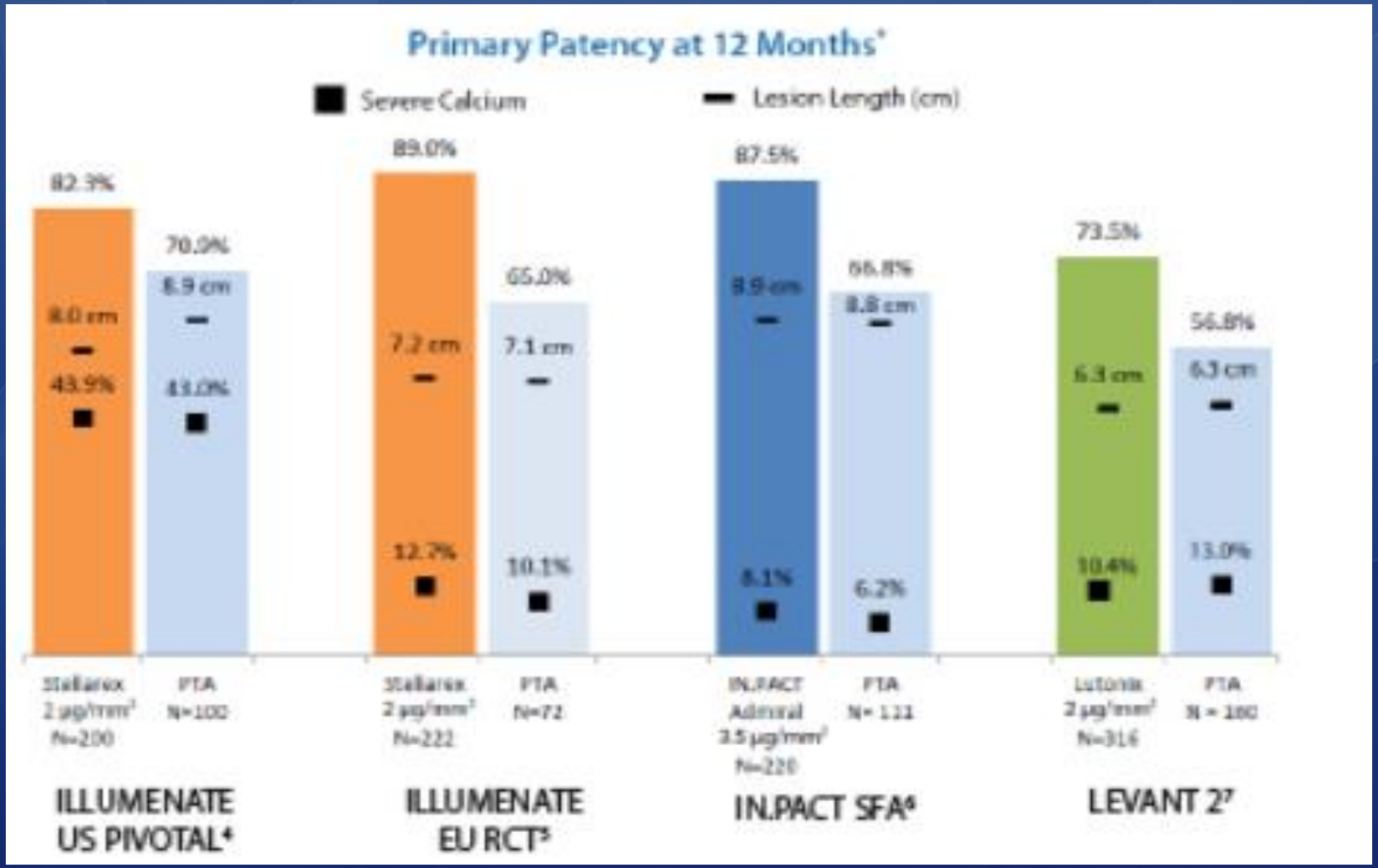
Data in Context: Clinically-Driven TLR at 12 Months



* Includes only data through day 360, other studies report data through full follow-up window (day 395)

1. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation*. 2015;131(5):495-502 2. Rosenfield K, Jaff MR, White CJ et al. NEJM 2015;373:145-53

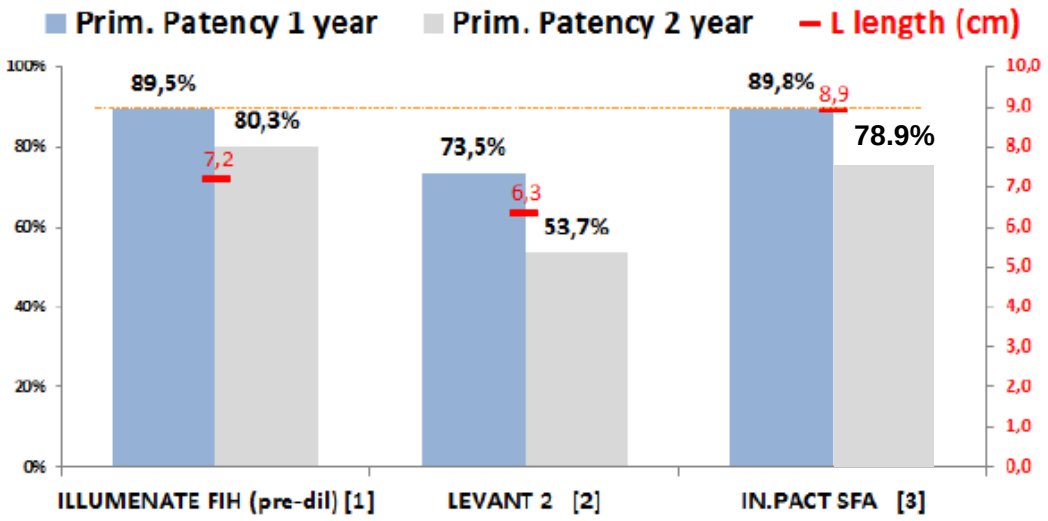
AMP THE AMPUTATION PREVENTION SYMPOSIUM AUGUST 10–13, 2016


Primary Patency at 12 Months*
Severe Calcium
Lesion Length (cm)
82.3%
8.0 cm
43.9%
70.0%
8.9 cm
43.0%
89.0%
7.2 cm
12.7%
65.0%
7.1 cm
10.1%
87.5%
8.9 cm
8.1%
66.8%
8.8 cm
6.2%
73.5%
6.3 cm
10.4%
56.8%
6.3 cm
13.0%
Stellarex 2 µg/mm² N=200
PTA N=100
Stellarex 2 µg/mm² N=222
PTA N=72
IN.PACT Admiral 3.5 µg/mm² N=220
PTA N= 111
Lutonix 2 µg/mm² N=316
PTA N = 160
ILLUMENATE US PIVOTAL⁴
ILLUMENATE EU RCT⁵
IN.PACT SFA⁶
LEVANT 2⁷

Durability ?

Stellarex DCB Evidence in Context

Primary Patency from multicenter, Duplex Corelab* adjudicated DCB Trials

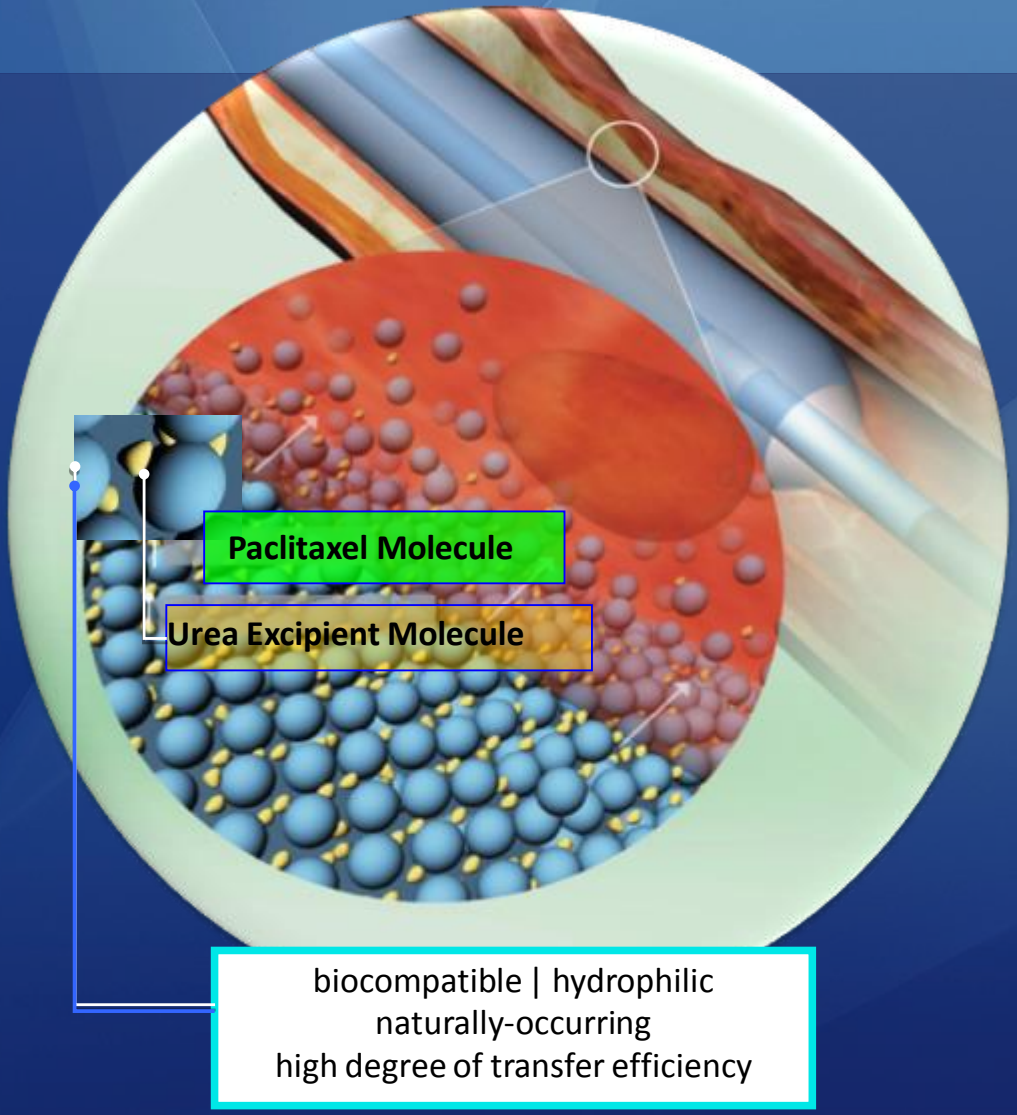


* VascCore DUS Core lab (Boston, MA, USA); PSVR threshold < or ≤ 2.5

[1] Schroeder H *Catheter Cardiovasc Interv*. Accepted manuscript online: 23FEB2015: DOI: 10.1002/ccd.25900 [2] United States, Department of Health and Human Services. FDA Executive Summary: Circulatory System Devices Advisory Panel June 12 ,2014: Bard Lutonix® 035 Drug Coated Balloon PTA Catheter [3] G.Tepe, Presentation; IN.PACT SFA 1-year Primary Outcomes; Charing Cross; London United Kingdom, April 5-8, 2014

Spectranetics
Always Reaching Farther

IN.PACT™ Admiral DEB with FreePac™ Coating Technology



IN.PACT™

- Medtronic-Invatec DEB balloon line

FreePac™

- Proprietary hydrophilic coating formulation
  - Urea separates Paclitaxel molecules
  - Increased drug solubility and optimal diffusion into vessel wall
  - Urea facilitates Paclitaxel absorption into the vessel wall

IN.PACT SFA 1:2 RCT DEB vs POBA

2010-2013
n 331

IN.PACT SFA: Investigators and Sites

IN.PACT SFA I

150 subjects enrolled at 13 EU sites Sep 2010-Apr 2011

M. Brodmann, Graz, Austria
G. Tepe, Rosenheim, Germany
T. Zeller, Bad Krozingen, Germany
D. Scheinert, Leipzig, Germany
A. Micari, Palermo, Italy
I. Baumgartner, Bern, Switzerland
S. Sixt, Hamburg, Germany
G. Sorropago, Mercogliano, Italy
P. Peeters, Bonheiden, Belgium
F. Vermassen, Gent, Belgium
C. Trani, Rome, Italy
M. Bosiers, Dendermonde, Belgium
J. Van den Berg, Lugano, Switzerland

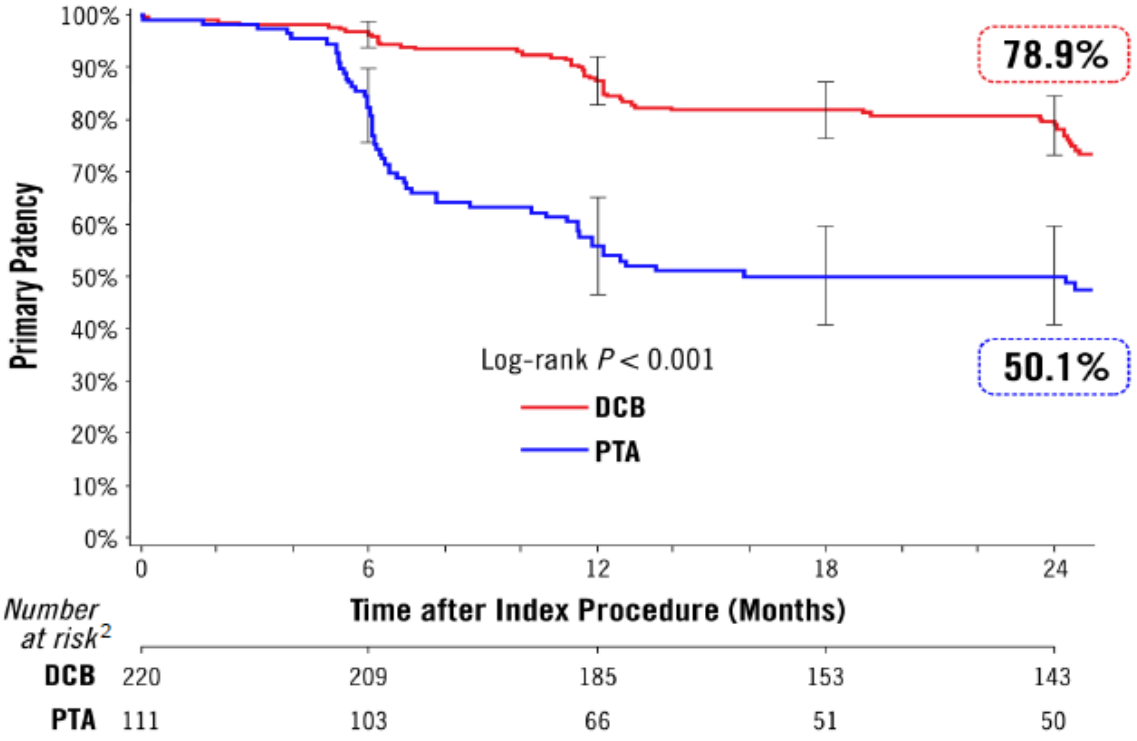
IN.PACT SFA II

181 subjects enrolled at 44 US sites Apr 2012-Jan 2013

P. Krishnan, New York, NY, USA
C. Metzger, Kingsport, TN, USA
A. Jain, Fremont, CA, USA
R. Sachar, Raleigh, NC, USA
N. Farhat, Elyria, OH, USA
L. Garcia, Boston, MA, USA
R. Malhotra, Glendale, AZ, USA
S. Germanwala, Longview, TX, USA
A. Pershad, Phoenix, AZ, USA
B. Bigelow, Indianapolis, IN, USA
J. Zidar, Raleigh, NC, USA
S. Ahanchi, Norfolk, VA, USA
R. Feldman, Ocala, FL, USA
R. Kovach, Brown Mills, NJ, USA
M. Goodwin, Naperville, IL, USA
L. Marone, Pittsburgh, PA, USA
M. Shishehbor, Cleveland, OH, USA
D. Chew, Des Moines, IA, USA
P. Soukas, Providence, RI, USA
M. Garcia, Newark, DE, USA
M. Mewissen, Milwaukee, WI, USA
R. Brown, Waco, TX, USA
C. Walker, Houma, LA, USA
N. Strickman, Houston, TX, USA
R. Fairman, Philadelphia, PA, USA
S. Laster, Kansas City, MO, USA
W. Gray, New York, NY, USA
V. Ramaiah, Phoenix, AZ, USA
P. Alden, Minneapolis, MN, USA
C. Stinis, La Jolla, CA, USA
R. Dave, Camp Hill, PA, USA
R. Gallino, Washington, DC, USA
G. Ansel, Columbus, OH, USA
M. Schermerhorn, Boston, MA, USA
M. Hunter, Cincinnati, OH, USA
M. Dake, Stanford, CA, USA
J. Benenati, Miami, FL, USA
P. Schneider, Honolulu, HI, USA
R. Serry, Poway, CA, USA
J. Angle, Charlottesville, VA, USA
K. Gupta, Kansas City, KS, USA
P. Jones, Chicago, IL, USA
G. Petrossian, Roslyn, NY, USA
A. Patel, Morristown, NJ, USA

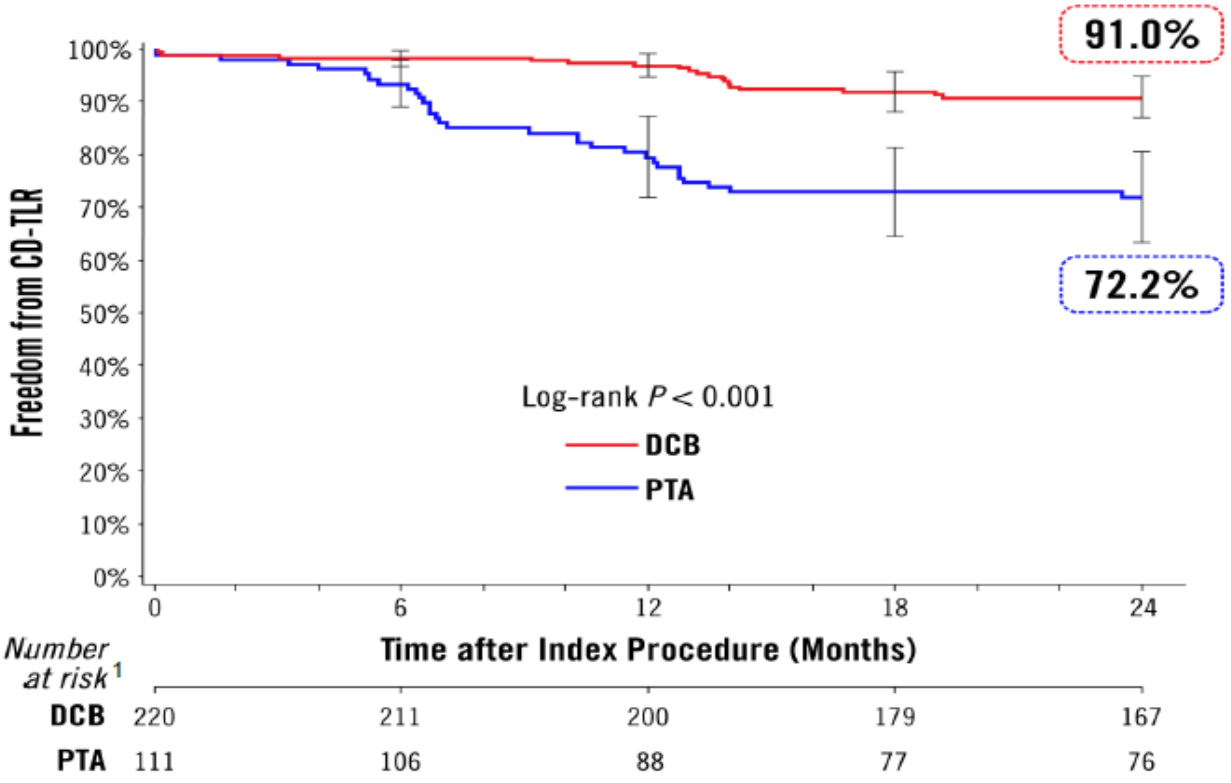
24-Month Results of IN.PACT SFA
Published by Laird et al (J Am College Cardiology 2015

Primary Patency[1] Results through 2 Years



1. *Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)*
2. *Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval*

Freedom from CD-TLR through 2 Years



1. *Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval*

IN.PACT SFA Trial (RCT):

Endpoint	DEB	PTA	p-value
Primary patency @ 12m	89.8 %	66.8 %	< 0.001
Primary patency @ 24m	78.9 %	50.1 %	< 0.001
@ 36m	69.5 %	45.1 %	
Freedom from CD-TLR @ 36m	84.8 %	69.9 %	0.002

IN.PACT Global Study

2012-2014
N 1535

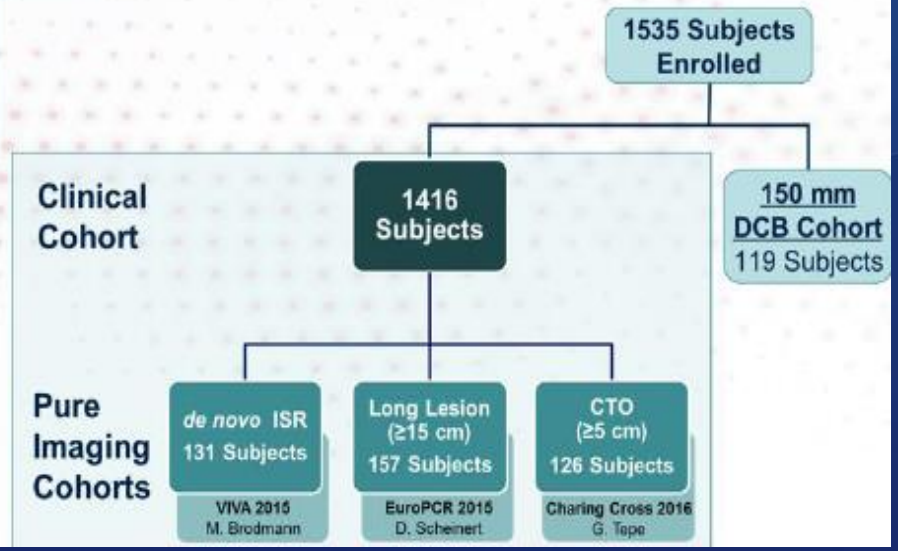
Real-world, prospective, multicenter, single arm independently-adjudicated femoropopliteal study

All-comers (RCC 2-4)

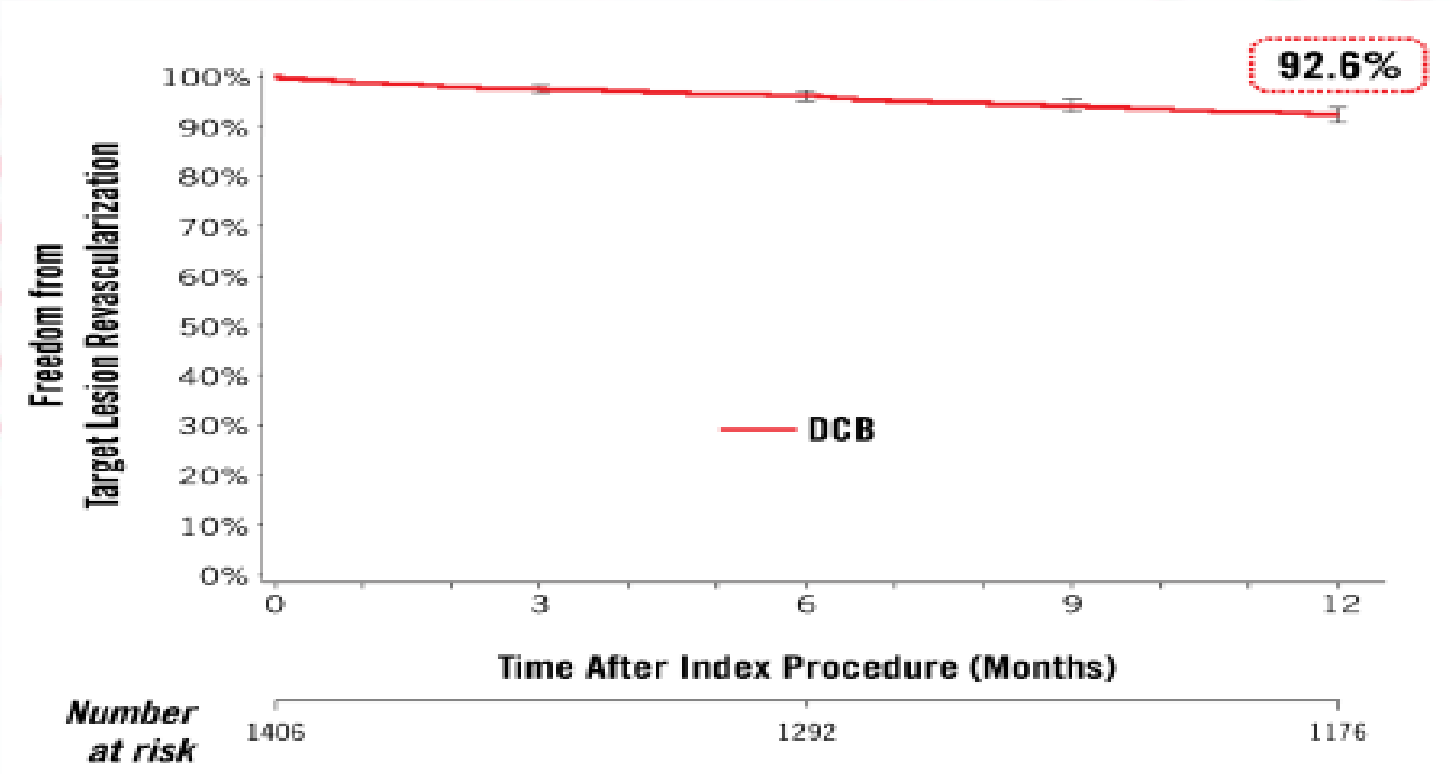
- ☑ Bilateral disease
- ☑ Multiple lesions
- ☑ SFA and Popliteal Artery
- ☑ TASC A, B, C, D
- ☑ de novo ISR
- ☑ Long Lesions
- ☑ CTOs

- 1535 patients 64 sites (EU, Mid-East, Latin America, Asia)
- Independent adjudication by Clinical Events Committee[1]
- Prospective subset analysis with core lab[2,3] reported results
  (de novo ISR, long lesions ≥15 cm, CTOs ≥5 cm)

1. Syntactx Clinical Events Committee, New York, NY, US
2. VasCore DUS Core Lab, Boston, MA, US
3. SynvaCor Angiographic Core Lab, Springfield, IL, US



Freedom from TLR



IN.PACT Global Trial: n 1535

Endpoint	DEB
Primary patency @ 12m	
CTO subcohort (n 126)	85.3 %
Long lesion subcohorts (n 157)	91.1 %
ISR subcohort (n 131)	88.7%
Freedom from CD-TLR Full cohort @ 12m	92.5 %

IN.PACT Conclusions

- RCT 24m data (2) demonstrate durability and continued superiority of IN.PACT DEB over PTA
  Consistent results in subgroups incl. females and diabetics

- RCT 36 Month Results available
  - Primary Patency @ 36m: 69.5 %
  - Freedom from CD-TLR @ 36m: 84.8 %

- IN.PACT Global trial shows promising results concerning durability and gives new data for ISR, CTO and LL

Passeo-18 Lux™ Drug-Coated Angioplasty Balloon

Drug

- Paclitaxel (3.0 µg/mm²)
- Anti-proliferative, lipophilic and allow fast absorption

Excipient

- BTHC (Butyryl-tri-hexyl Citrate)
- Keeps paclitaxel in micro-crystalline structure
- Degrades to citric acid and alcohol

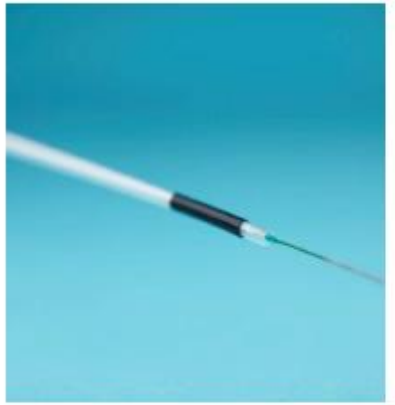
Matrix Coating

- Guarantees high bioavailability of paclitaxel at target lesion for rapid drug absorption by tissue

Balloon platform

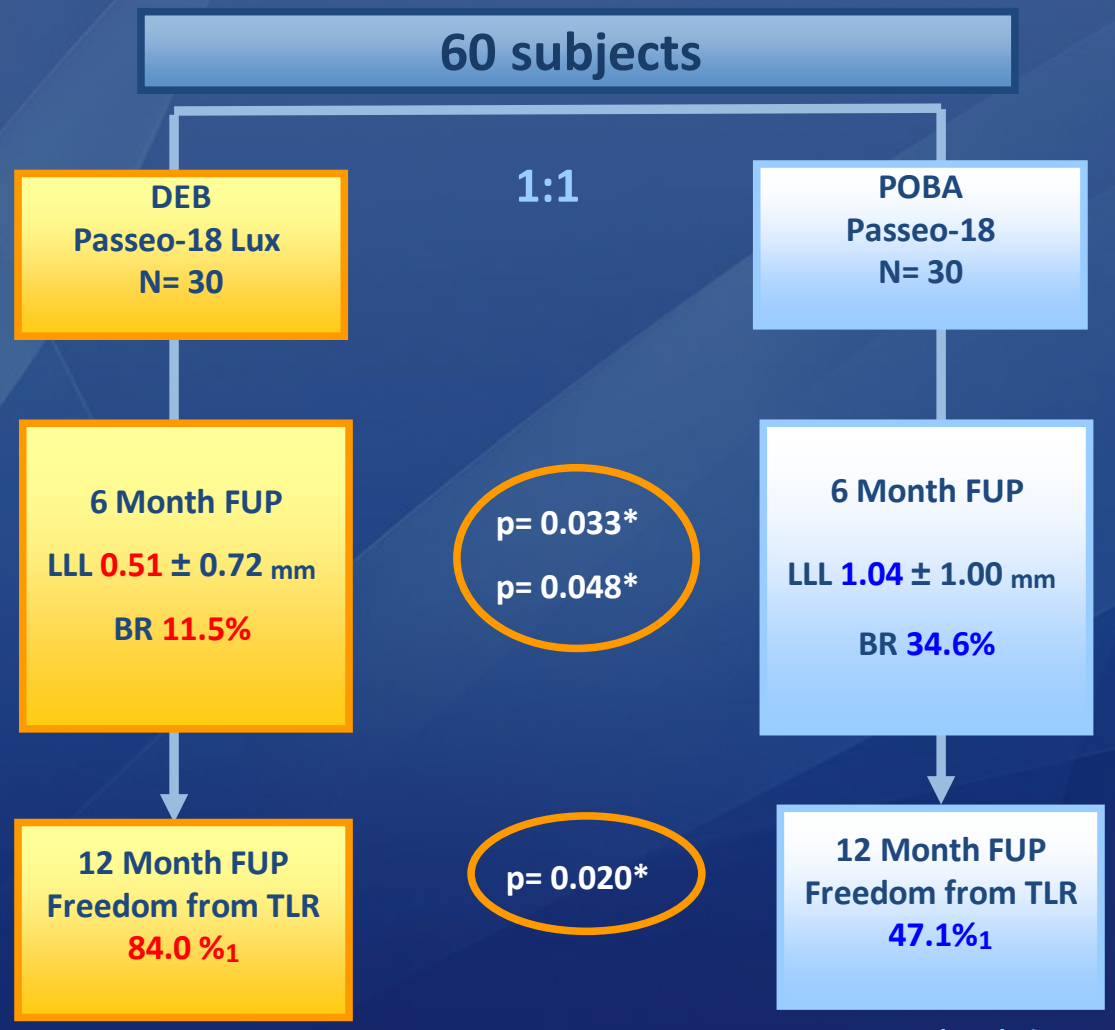
- Well established **Passeo-18 platform**
- Available in diameters 2.0 – 7.0 mm and lengths 40 – 120 mm
- Excellent deliverability and crossability
- **Innovative insertion aid** eases device handling and protects coating

Passeo-18 Lux



BIOLUX P-I Study: 1:1 RCT DEB vs PTA

2012-2013
N 60

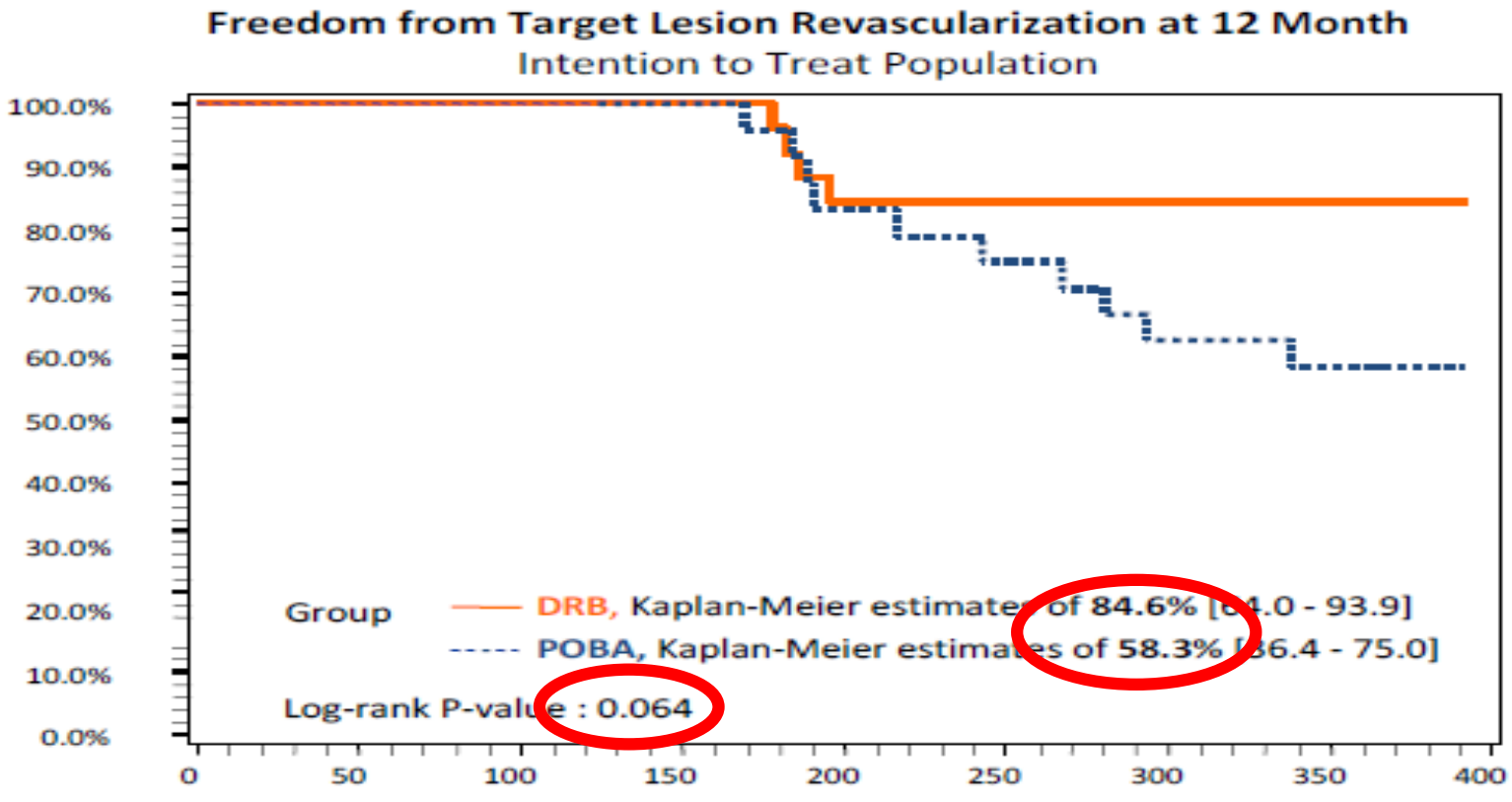


Primary
Late Lumen Loss at 6 months

Secondary
Binary restenosis at 6 months

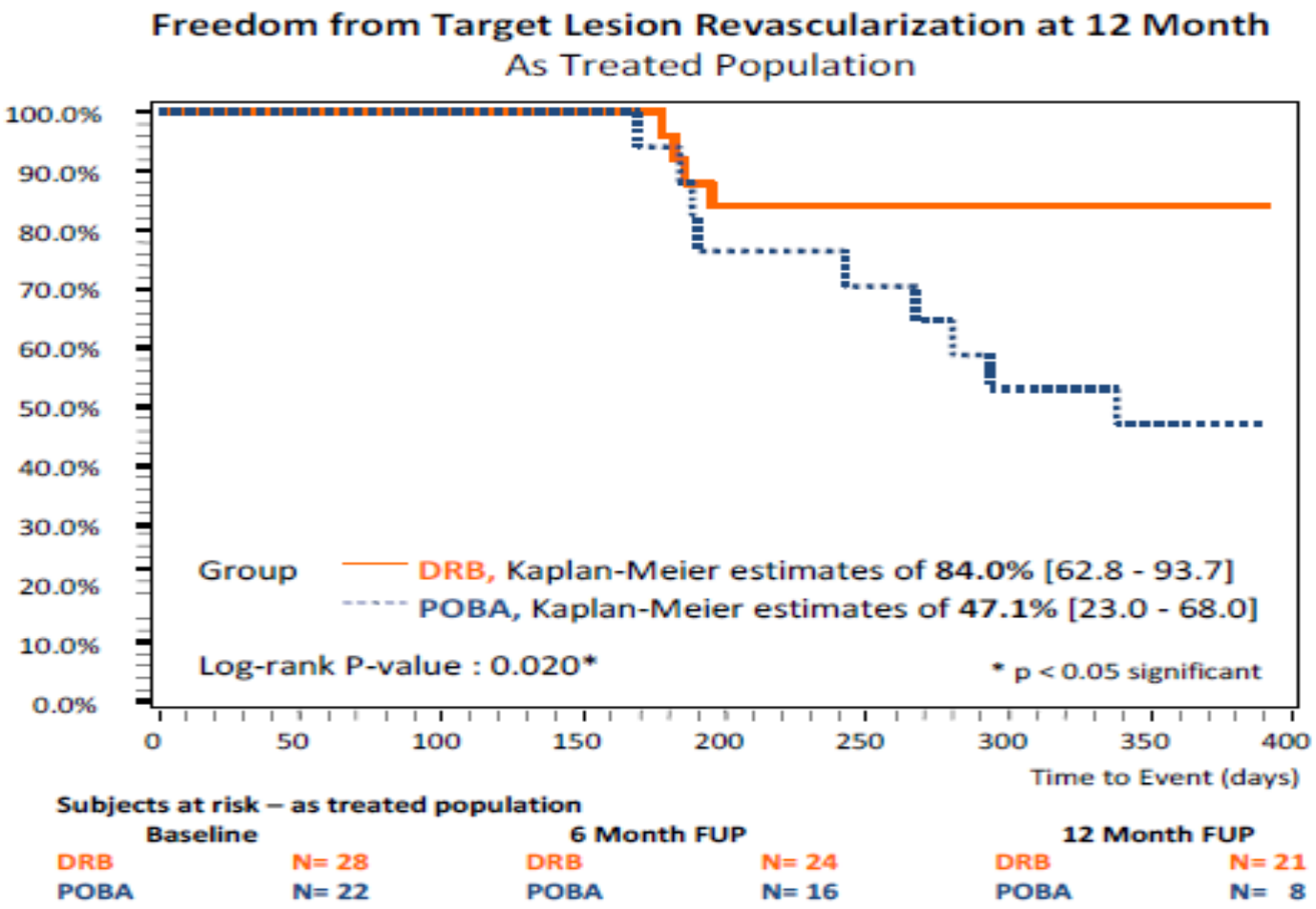
Secondary
Freedom from TLR at 12 months

12 Months Results: Freedom from TLR - ITT



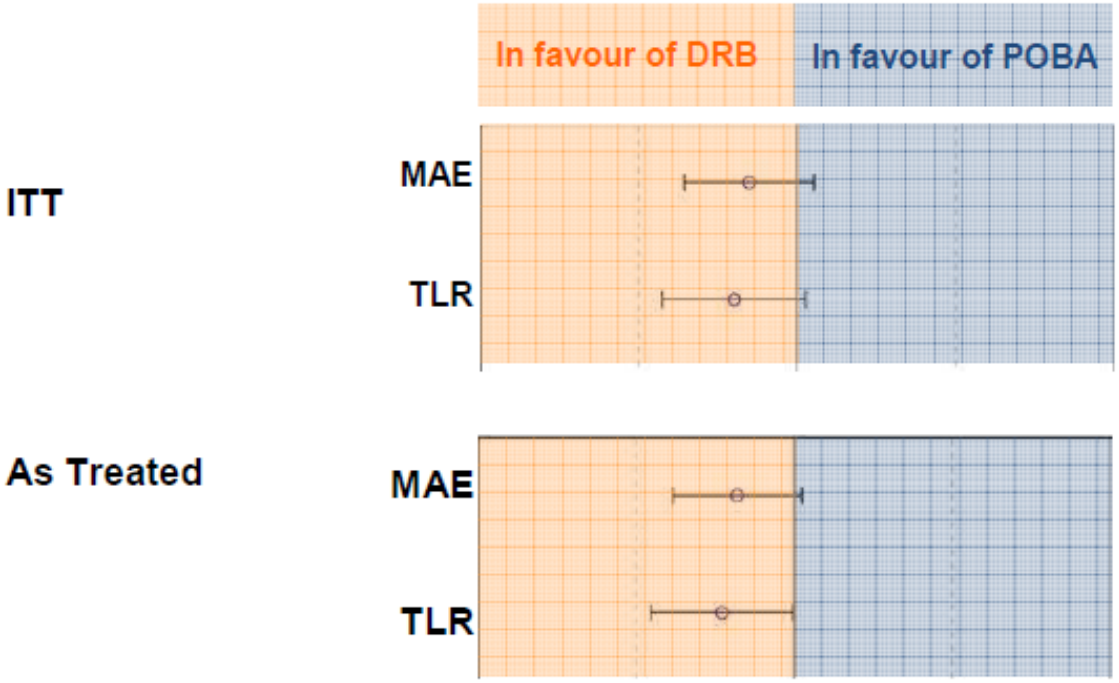
With courtesy to Dirk Scheinert – TCT 25

Freedom from TLR – As Treated



With courtesy to Dirk Scheinert – TCT 25

12 Months Results: Relative Risk Ratio



With courtesy to Dirk Scheinert – TCT 25

Global BIOLUX P-III All-Comers Registry using Passeo-18 Lux DEB (Infra-Inguinal)

2014-2016
N 790

All-Comers Current Status

Subgroups (No. of subjects) :

- ✓ Heavily calcified lesions (>110)
- ✓ TASC C lesions (>150)
- ✓ TASC D lesions (>110)
- ✓ Occlusions (> 200)
- ✓ Popliteal lesions (> 75)
- ✓ Rutherford >=3 (> 450)
- ✓ Renal Insufficiency (> 200)
- ✓ Diabetes (> 200)
- ✓ Age ≥ 65 (> 120)

All-Comers cohort ≥ 900

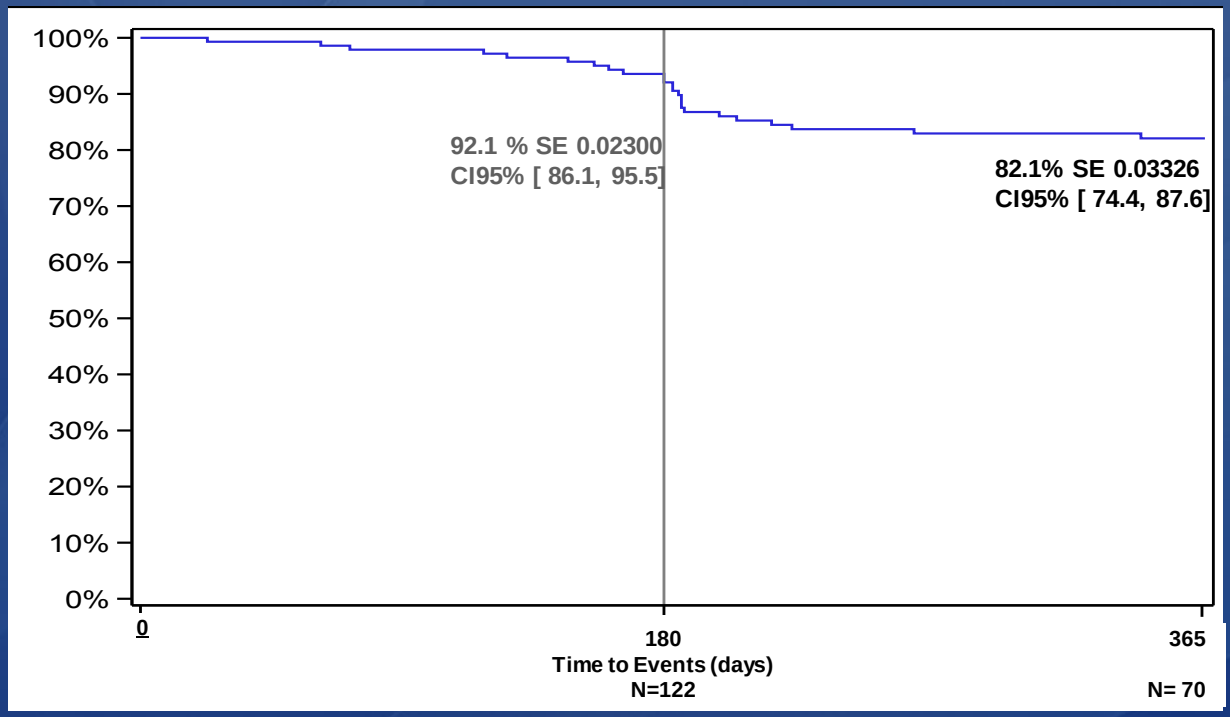
Infrapopliteal lesions (150)

Feb 2016
700 subjects
Minimum number enrolled

Sept 2016
860 subjects

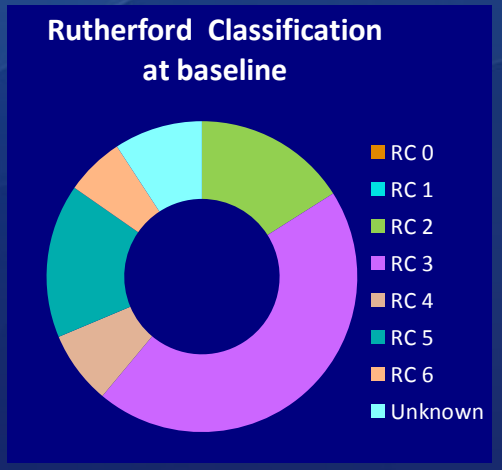
Dec 2016
End of subgroups enrolment

Primary Patency – SFA



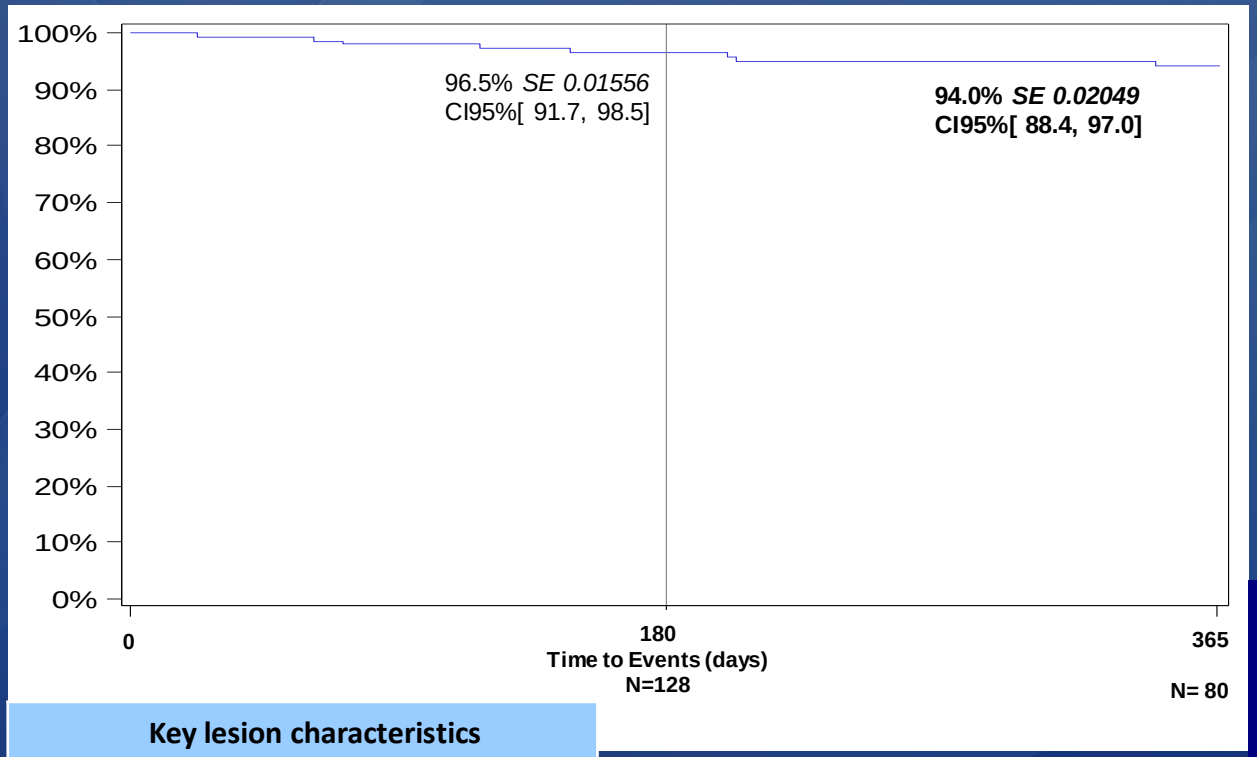
Key lesion characteristics	
TASC D/C	21.4%
CLI	29.7%
Calcification	80.7% (51.7% moderate/heavy)

30% subject with RC>3 at baseline



With courtesy to Prof. Dr. G. Tepe and the BIOLUX P-III Investigators

Freedom From Clinically Driven Target Lesion Revascularization[1] – SFA (adjudicated by an independent CEC)



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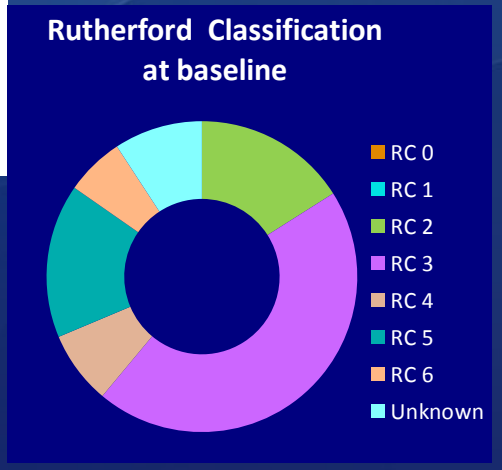


(1) Any re-intervention performed for ≥ 50% diameter stenosis (visual estimate) at the target lesion after documentation of recurrent clinical symptoms of the patient

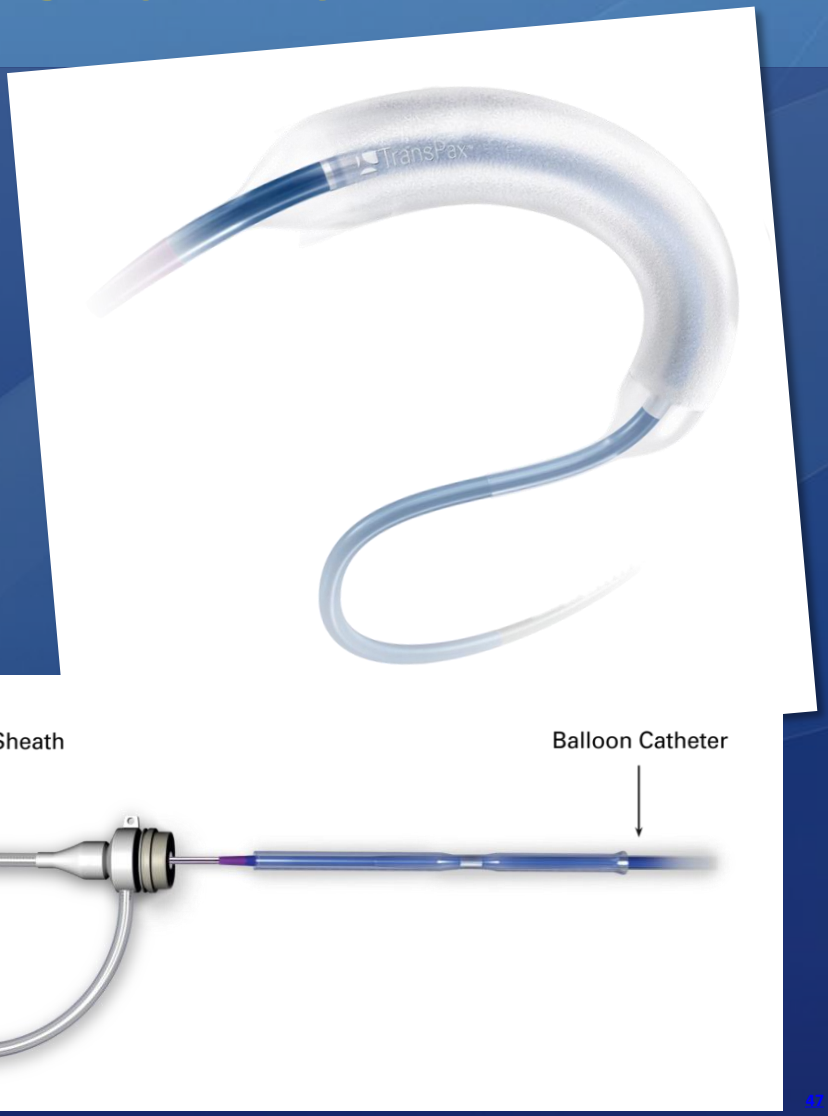
BIOLUX Conclusions

- RCT 12 month data show freedom from TLR of 84.6 %
- 12-month results of the first 200 subjects PIII tend to confirm efficacy of Paseo-18 LUX as a stand alone therapy of the SFA
  Freedom from CD-TLR: 94.0 %
- Analysis of subgroups will provide additional information

RANGER™ Drug-Coated Angioplasty Balloon

- Sterling 0.018” balloon platform
- TransPax™ coating technology
- Ranger™ DCB loading tool designed to protects the drug coating

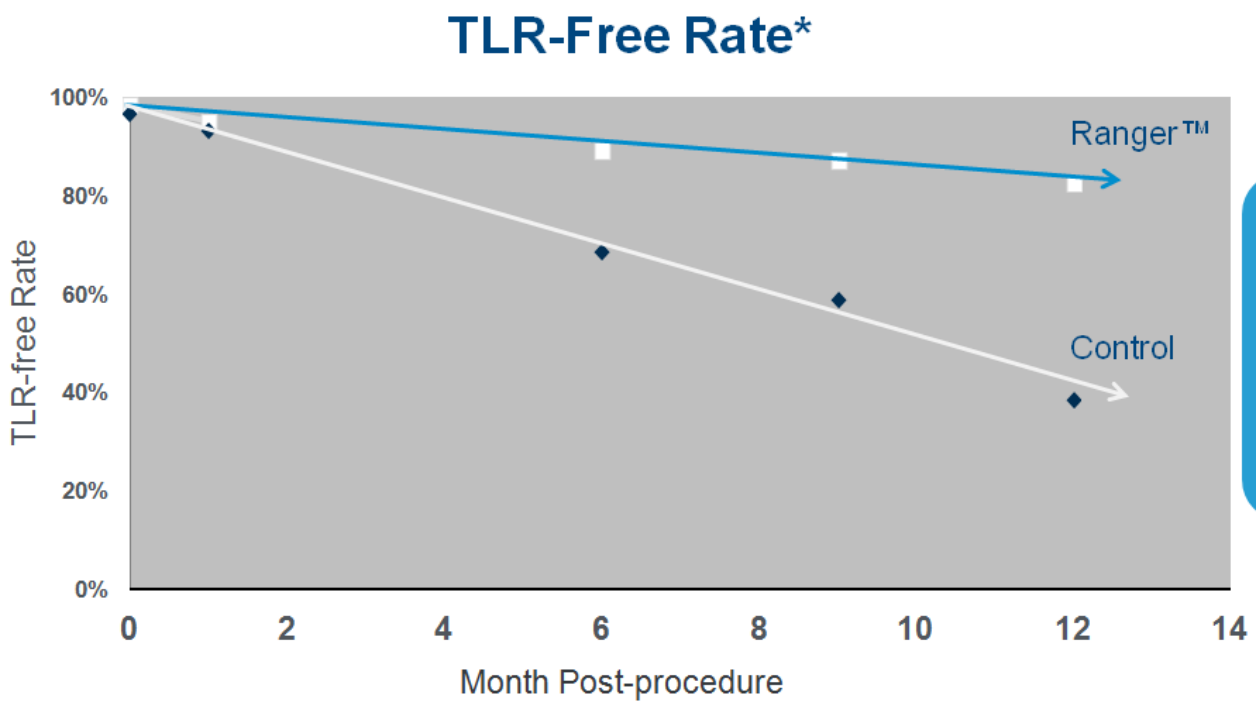
- Size matrix:
  - SFA: 4-8 mm; 30-100 mm



RangerTM DCB is manufactured by Hemoteq AG and distributed by Boston Scientific. Ranger is an investigational device not for sale in the U

RANGER™ SFA RCT (Interim Data)

2014-2015
N 105

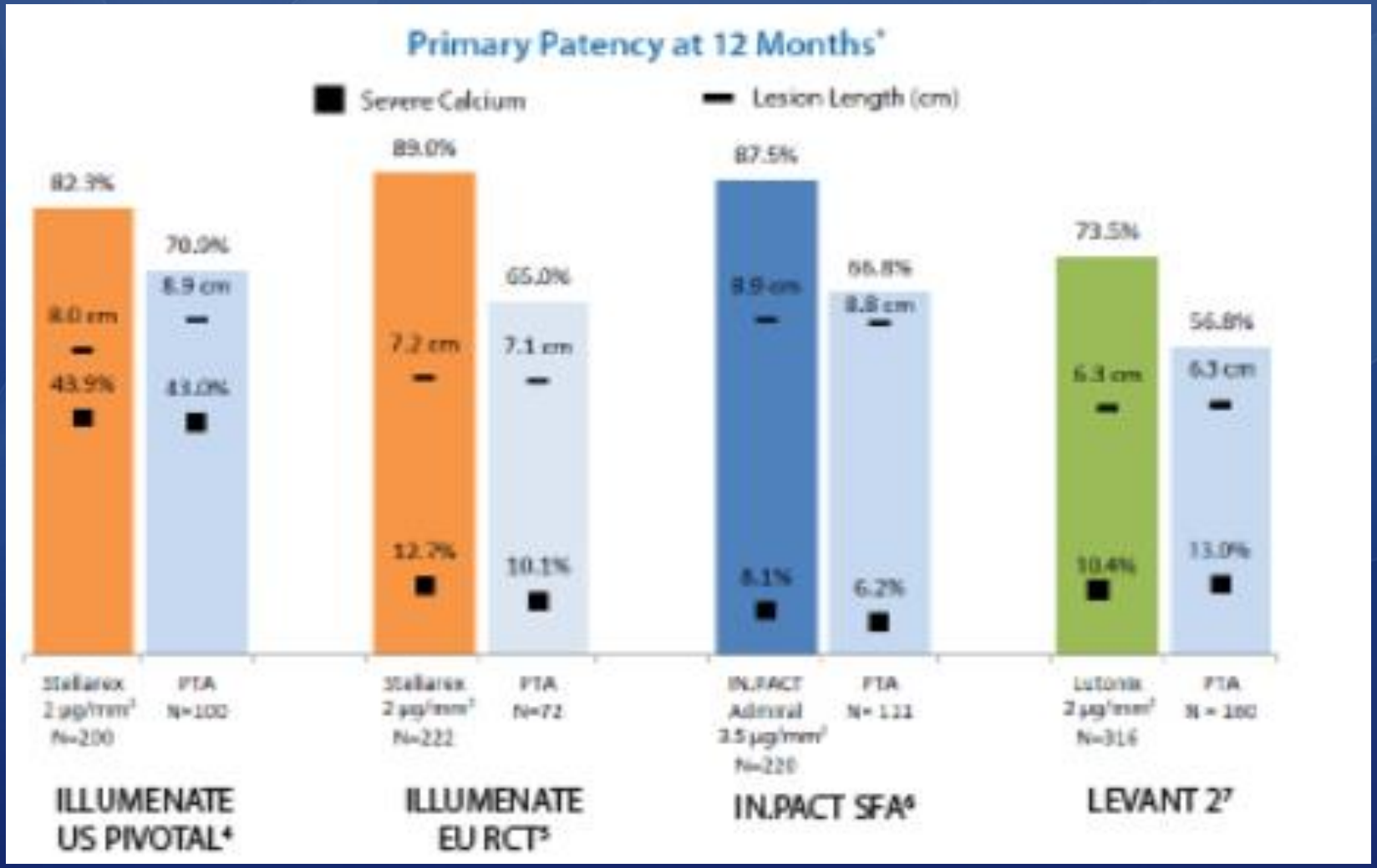


Δ between DCB and PTA continues to grow over time

*Sample size is the # of patients for whom the designated amount of time has elapsed since the index procedure

CONCLUSION I: RCT

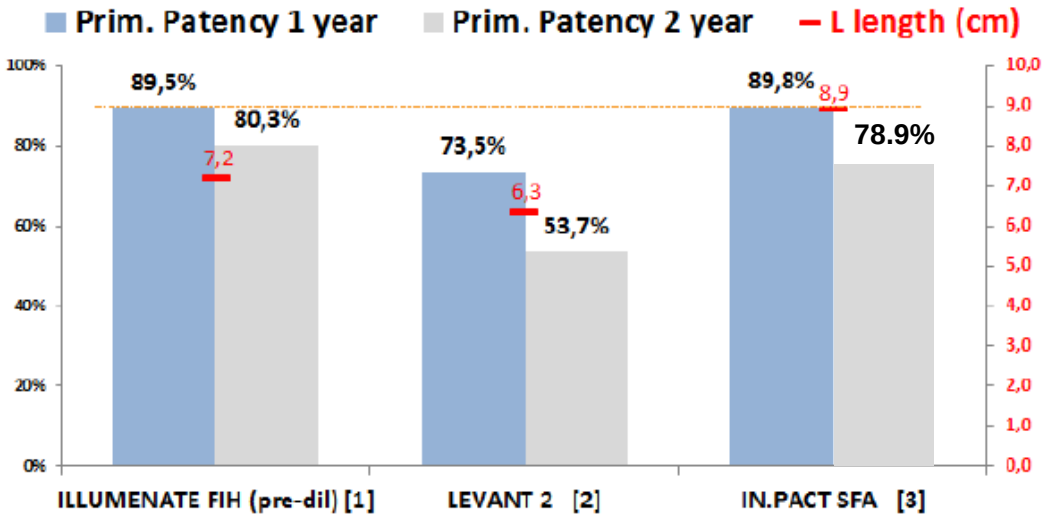
Confirmed improved results at 12m (vs PTA)



CONCLUSION II:
Durable results for at least two years

Stellarex DCB Evidence in Context

Primary Patency from multicenter, Duplex Corelab* adjudicated DCB Trials

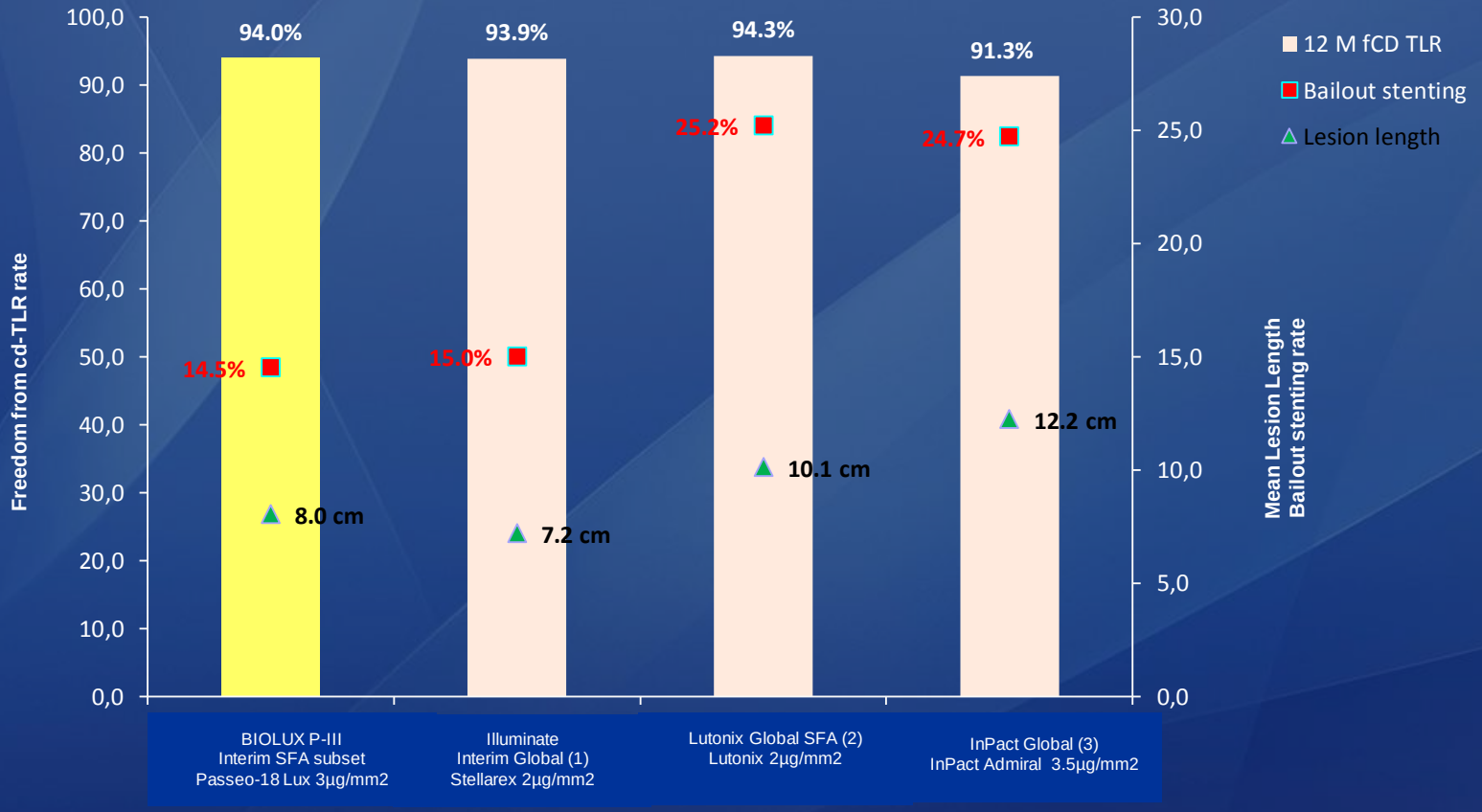


* VascCore DUS Core lab (Boston, MA, USA); PSVR threshold < or ≤ 2.5

[1] Schroeder H *Catheter Cardiovasc Interv*. Accepted manuscript online: 23FEB2015: DOI: 10.1002/ccd.25900 [2] United States, Department of Health and Human Services. FDA Executive Summary: Circulatory System Devices Advisory Panel June 12 ,2014: Bard Lutonix® 035 Drug Coated Balloon PTA Catheter [3] G.Tepe, Presentation; IN.PACT SFA 1-year Primary Outcomes; Charing Cross; London United Kingdom, April 5-8, 2014

Spectranetics
Always Reaching Farther

CONCLUSION III (Real world lesions):
Low TLR rates @ 12m in 4 global trials …



Data overview for informational purposes only and not for head-to head comparison

(1) Krishnan P. 12-Month Interim Results of ILLUMENATE Global Study with the Stellarex DCB. Oral presentation. NCHV, June 01-03 2016
(2) Thieme M. Lutonix Global SFA Real-World Registry: 12 Month Outcomes. Oral presentation. TCT, October 11-15, 2015
(3) Ansel G. The IN.PACT Global Registry: One-Year Outcomes Using the IN.PACT DCB in an Unrestricted, Real-World Environment. Oral presentation. TCT, October 11-15, 2015