Sirolimus DCBs for Femoral-Popliteal Disease: Emerging Role and Future Directions

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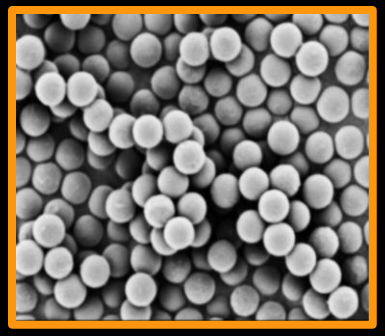


Endovascular Drug Coated Balloons

Company	Device	Drug	Coating / Excipient	Drug Dose µg/mm²	CE
Aachen Resonance	Elutax SV	PTX	None	2	Yes
Balton	mcPCB	PTX		3	No
Bard	Lutonix	PTX	Polysorbate / Sorbitol	2	Yes
Bayer-Medrad	Cotavance	PTX	Iopromide	3	Yes
Biotronik	Passeo-18 Lux	PTX	Butyryl-tri-hexyl Citrate	3	Yes
Boston Scientific	Ranger	PTX	Citrate Ester	2	Yes
Cardionovum	Legflow	PTX	Shellac	3	Yes
Cook	Advance 18 PTX	PTX	None	3	Yes
Covidien	Stellarex	PTX	Amphiphilic Polymer	2	Yes
Eurocor / Biosensors	Freeway / BioPath	PTX	Shellac	3	Yes
iVascular	Luminor	PTX	Water Reducer Ester	3	Yes
Medtronic	IN.PACT	PTX	Urea	3.5	Yes
Meril	Mozec	PTX	Nano-particles	3	No
Nano Therapeutics	Curex PTA	PTX		2.3	No
Vascular Nanotransfer Technologies		PTX	Nano-encapsulation		No
Surmodics		PTX	Microcrystalline	3	No
AngioScore	AngioSculpt*	PTX		3	No
TriReme Medical	Chocolate Touch*	PTX			No

Advantages and Disadvantages of Paclitaxel Drug Coated Balloons

Advantages

- Highly lipophilic compound with good tissue absorption
- Easily transferrable on a number of excipients
- Excellent tissue retention

Disadvantages

- Reduced effectiveness in calcified lesions
- Flaking of coatings with particulate embolization
- Safety profile-paclitaxel is cytotoxic with a relatively narrow therapeutic window

Paclitaxel Tissue Toxicity

- Tissue effects of paclitaxel and sirolimus in a vessel cuff animal model
  - Paclitaxel results in loss of smooth muscle cells and reduces collagen content as compared to sirolimus
  - Explains lack of safety of paclitaxel DCBs in sub-intimal PTA and DAART?

Table 2 Comparison of histological findings of cuffed femoral artery segments from 14-day control DEC, SEC and PEC (14 days normal cuff plus 14 days DEC)

	TUNEL+ cells (%)		SMC content (%)		Collagen content (%)			
	Media	Intima	Media	Intima	Media	Intima	IEL disruption¶	Medial macrophage¶
Control DEC	0.27 (0.24)	0.39 (0.24)	25.2 (2.3)	30.8 (2.7)	28.3 (4.9)	40.7 (2.4)	2.2 (0.6)	1.08 (0.08)
1% SEC	1.99 (0.68)	0.58 (0.24)	27.5 (2.7)	28.0 (1.1)	24.0 (3.4)	28.0 (5.8)	2.0 (0.5)	1.39 (0.15)
2.5% SEC	1.78 (0.77)	0.42 (0.21)	16.9 (2.9)*†	21.8 (2.8)	24.0 (3.1)	32.9 (4.9)	2.2 (0.5)	1.49 (0.16)*
1% PEC	0.84 (0.79)	0.95 (0.56)	2.6 (0.9)*†‡	10.3 (1.7)*†	18.6 (1.4)	19.0 (2.1)*‡	3.4 (0.4)	2.20 (0.39)*
2.5% PEC	19.2 (5.7)*†‡§	3.1 (3.08)	3.8 (0.9)*†‡	9.4 (3.1)*†	12.7 (2.0)*†‡	12.4 (6.4)*‡	5.2 (0.6)*†‡§	2.26 (0.33)*

Pires NM et al *Heart* 2007; 93(8): 922-927

Safety Concerns with the Coronary Application of Paclitaxel are well known…

JACC Cardiovasc Interv. 2011 May;4(5):530-42. doi: 10.1016/j.jcin.2011.03.005.

Long-term safety and efficacy of paclitaxel-eluting stents final 5-year analysis from the TAXUS Clinical Trial Program.

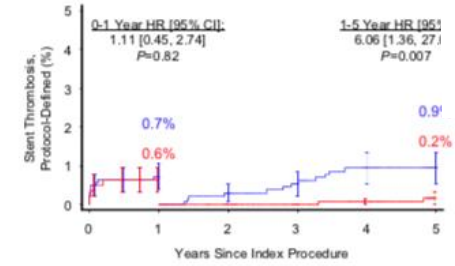
Stone GW[1], Ellis SG, Colombo A, Grube E, Popma JJ, Uchida T, Bleuit JS, Dawkins KD, Russell ME.

Author information

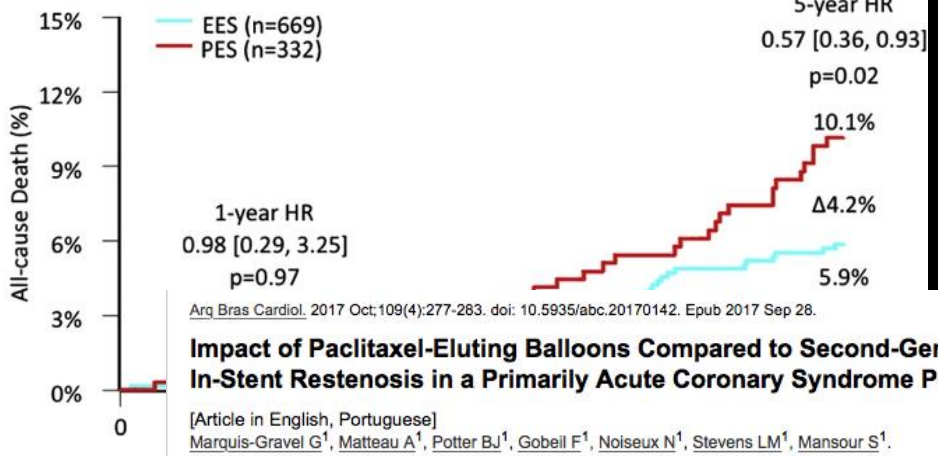
Abstract

OBJECTIVES: These studies sought to evalua
otherwise identical bare-metal stent (BMS).

CONCLUSIONS: In this pooled patient-level a
BMS resulted in a durable 47% reduction in t
lesions, with nonsignificant differences in the
cardiac death or MI and protocol-defined ste



SPIRIT III 5-Year All-Cause Mortality



Arq Bras Cardiol. 2017 Oct;109(4):277-283. doi: 10.5935/abc.20170142. Epub 2017 Sep 28.

Impact of Paclitaxel-Eluting Balloons Compared to Second-Generation Drug-Eluting Stents for of In-Stent Restenosis in a Primarily Acute Coronary Syndrome Population.

[Article in English, Portuguese]
Marquis-Gravel G[1], Matteau A[1], Potter BJ[1], Gobeil F[1], Noiseux N[1], Stevens LM[1], Mansour S[1].

Author information

Abstract

BACKGROUND: The place of drug-eluting balloons (DEB) in the treatment of in-stent restenosis (ISR) is not well-defined, particularly in a population of all-comers with acute coronary syndromes (ACS).

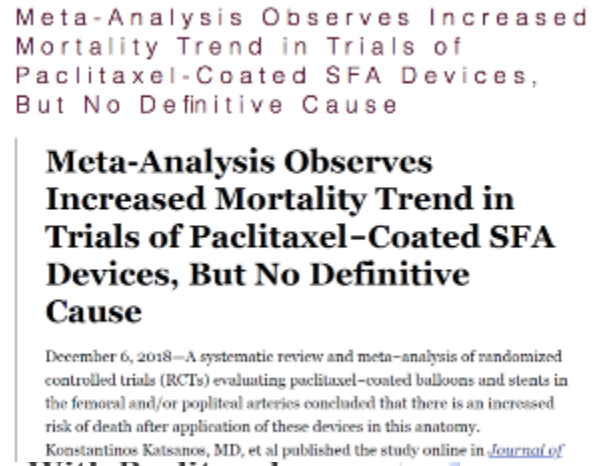
OBJECTIVE: Compare the clinical outcomes of DEB with second-generation drug-eluting stents (DES) for the treatment of ISR in a real-world population with a high proportion of ACS.

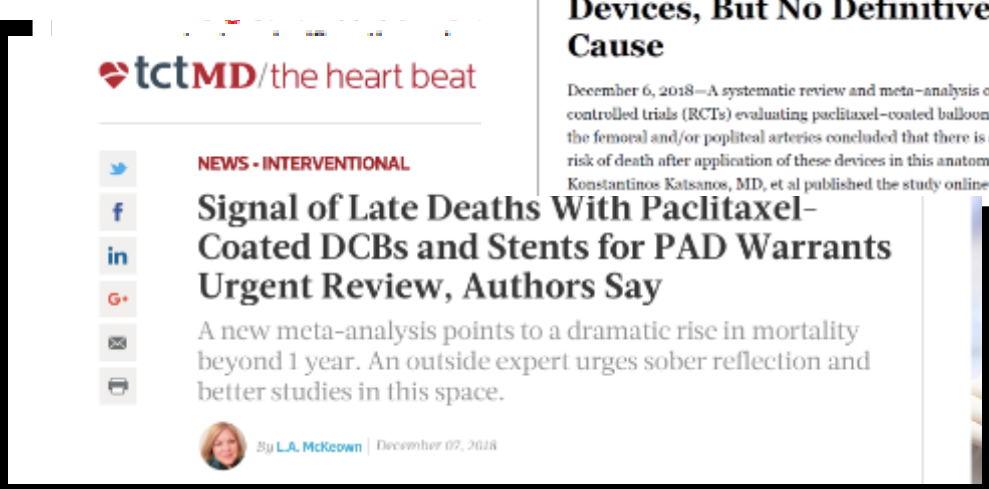
RESULTS: The cohort included 91 patients treated with a DEB and 89 patients treated with a DES (74% ACS). Median follow-up was 26 months. MACE occurred in 33 patients (36%) in the DEB group, compared to 17 patients (19%) in the DES group (p log-rank = 0.02). After multivariate adjustment, there was no significant difference between the groups (HR for DEB = 1.45 [95%CI: 0.75-2.83]; p = 0.27). Mortality rates at 1 year were 11% with DEB, and 3% with DES (p = 0.04; adjusted HR = 2.85 [95%CI: 0.98-8.32]; p = 0.06).

CONCLUSION: In a population with a high proportion of ACS, a non-significant numerical signal towards increased rates of MACE with DEB compared to second-generation DES for the treatment of ISR was observed, mainly driven by a higher mortality rate. An adequately-powered randomized controlled trial is necessary to confirm these findings.

Meta-Analysis of Paclitaxel Coated Balloons

Published December 6, 2018





Katsanos K et al *J Am Heart Assoc* 2018; 7:e011245

Sirolimus Drug Coated Balloons

- **Sirolimus offers potential benefits over Paclitaxel:**

Attribute	Sirolimus (or Analogs)	Paclitaxel
Mode of action	**Cytostatic**	**Cytotoxic**
Margin of safety	**10’000 fold**	**100 fold**
Therapeutic range	**Wide**	**Narrow**
Anti-restenotic	**Yes – lower late lumen loss**	**Yes**
Anti-inflammatory	**Yes**	**No**
Tissue absorption	***Slow***	***Fast***
Tissue retention	***Short***	***Long***

- **Sirolimus is the *drug of choice* for coronary DES supported by solid clinical evidence**

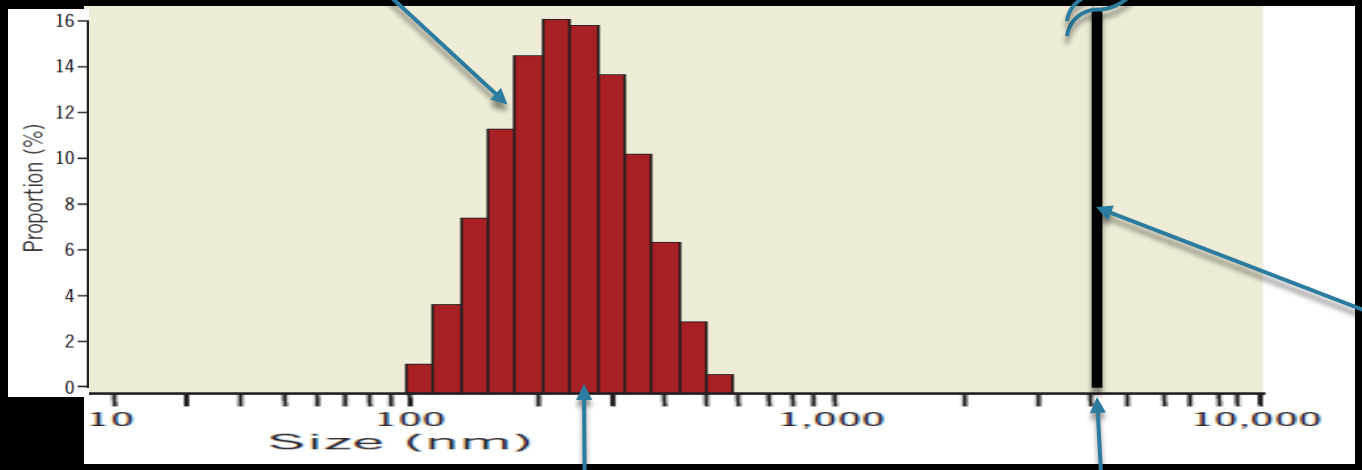
Sirolimus Coated Balloons - Landscape

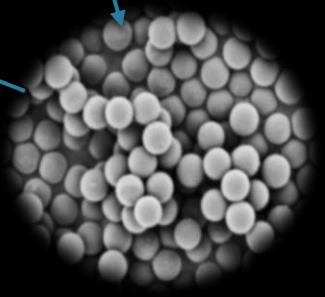
Company	Product	Drug	Concentration	Excipient
B. Braun	SeQuent SCB	crystalline sirolimus	4 µg/mm^2	Butylated hydroxy toluene
Concept Medical	Magic Touch DCB Xtreme Touch DCB	crystalline sirolimus 100-500 nm nanospheres	1.3 µg/mm^2 3.0 µg/mm^2	Phospholipid excipient
Med Alliance SA	Selution DCB	sirolimus 4 micron microspheres	1.0 µg/mm^2	PDLA with CAT-cell adherence technology
Minvasys Stentys	Devoir	crystalline sirolimus 100-500 nm nanospheres	1.3 µg/mm^2	Phospholipid excipient
Orchestra BioMed	Virtue DCB	sirolimus 40-250 nm nanospheres	3 mg	Weeping balloon with PLGA-PEG-PLGA triblock polymer coating

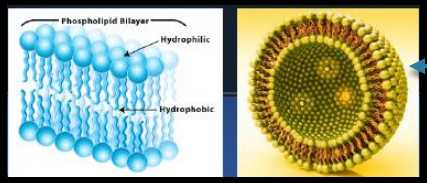
Elution time is programmable….

Magic Touch[1]
Variable Particle Size
High Total Surface Area
14-day elution time

Selution™[2]
Uniform Particle Size
Moderate Total Surface Area
90-day elution time





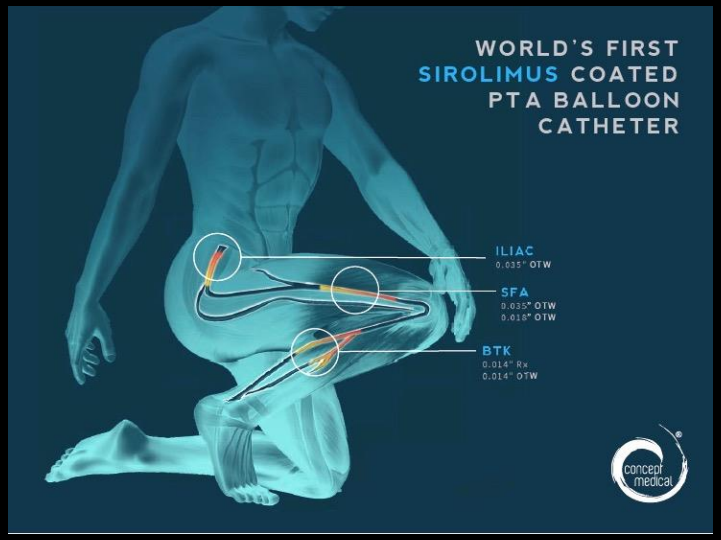


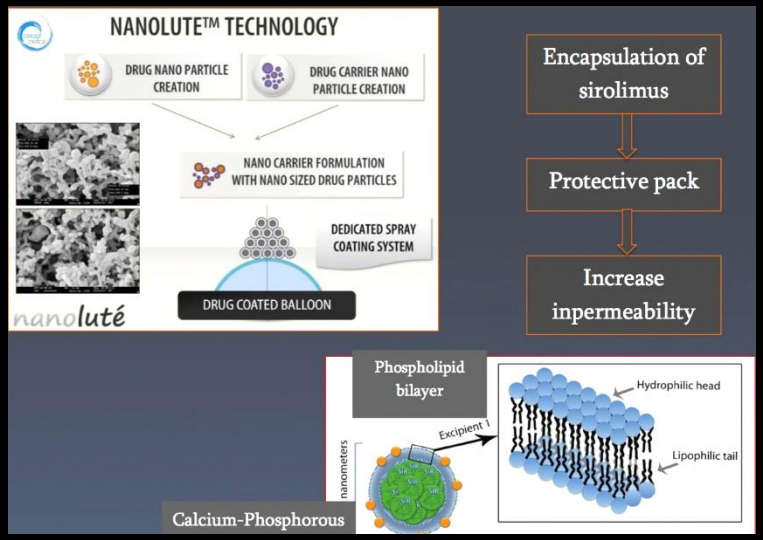
0.1µm-0.5µm

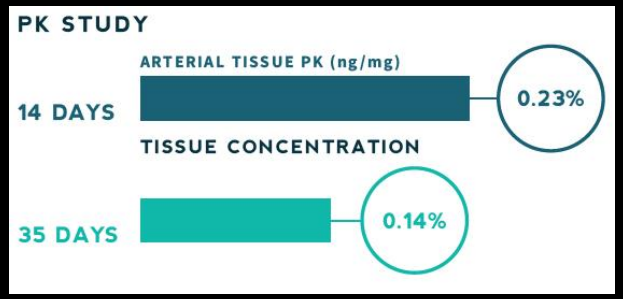
4µm

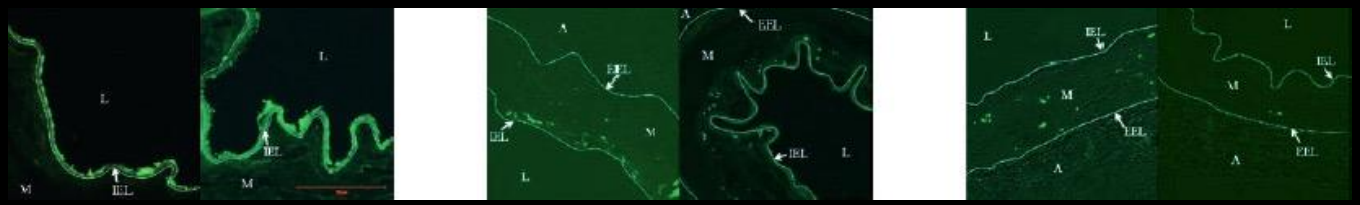
[1]Lemos P et al *Eurointervention* 2013; 9: 148-156
[2]Data on file MA-Medalliance SA

Xtreme Touch Neo



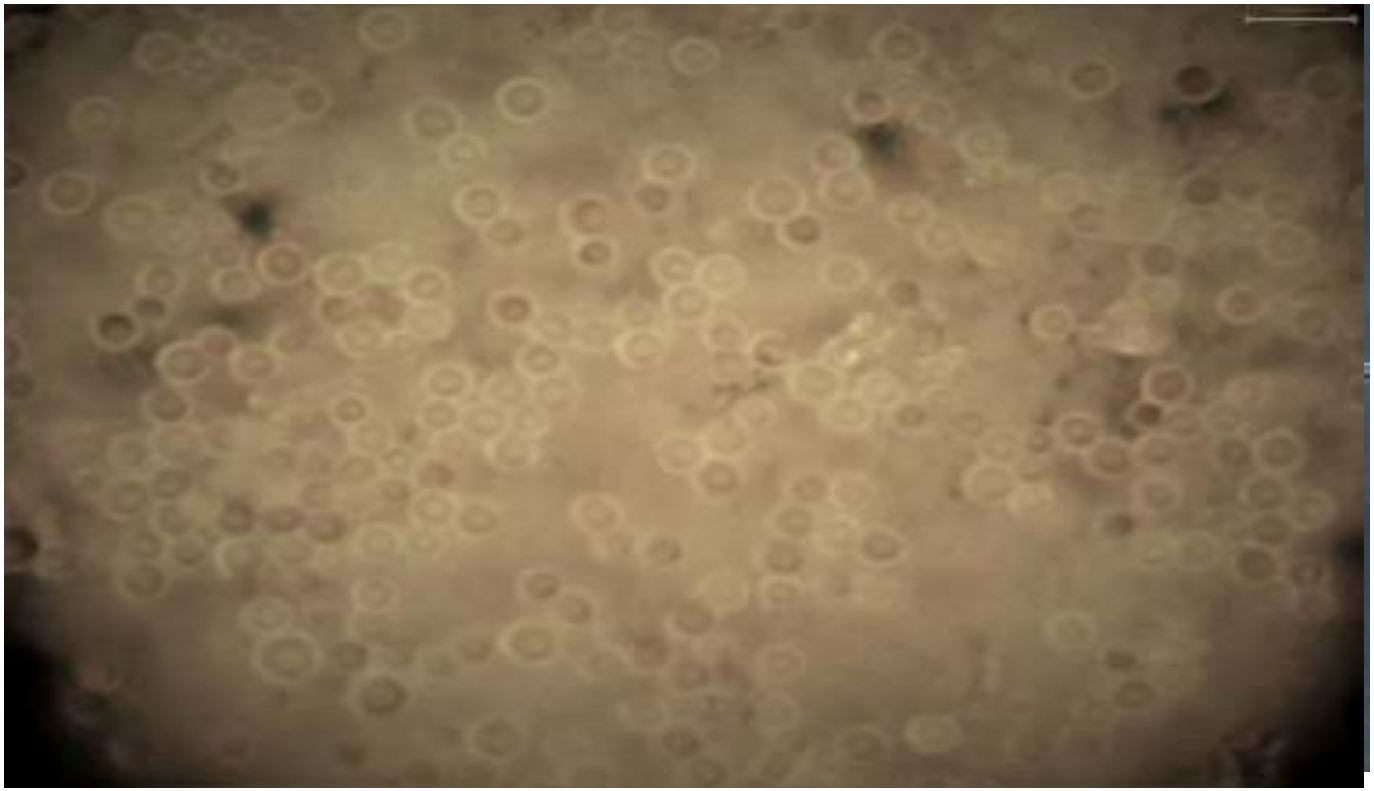


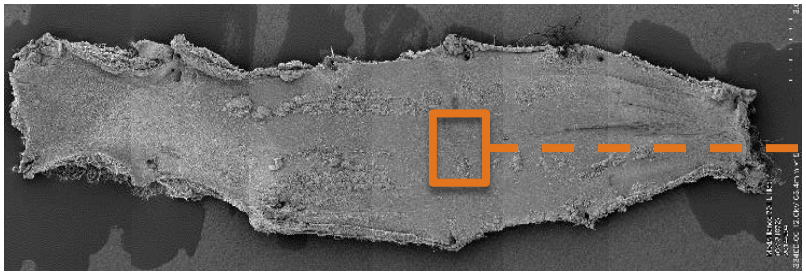




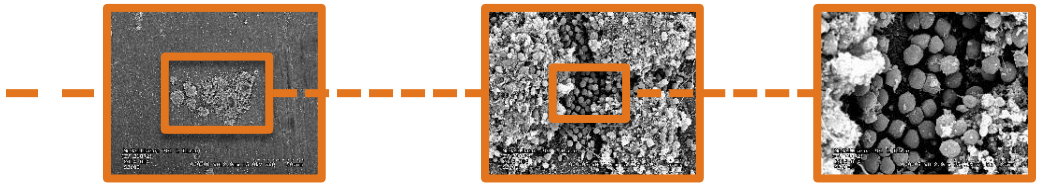
Xtreme Touch Neo Product Brochure

SELUTION™ CAT Technology



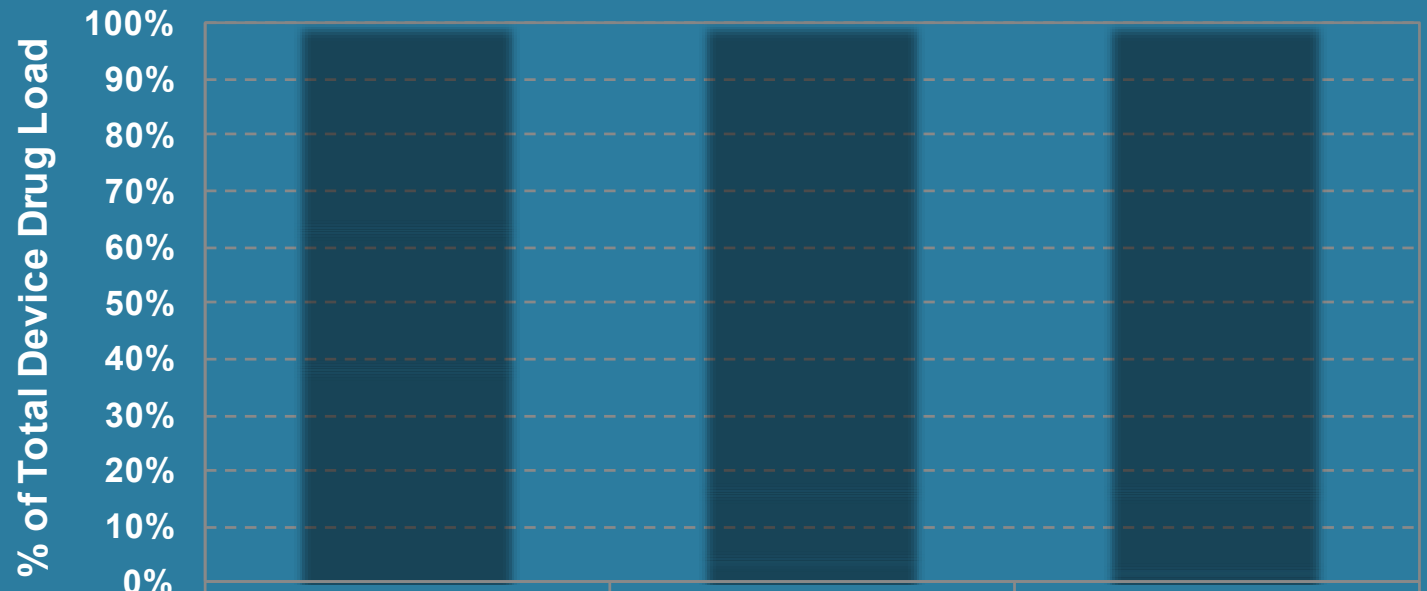


Scanning Electron Microscopy at 24 hr



SELUTION™ Sirolimus DCB

Drug Delivery and Dispersion

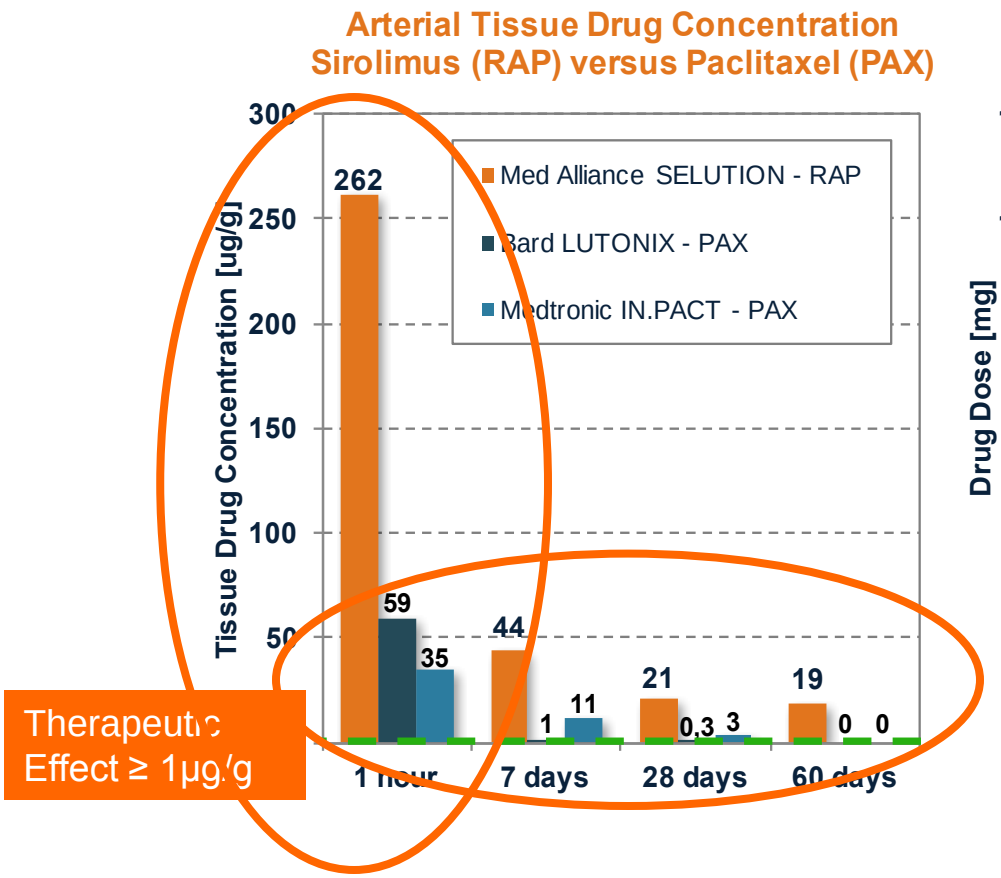


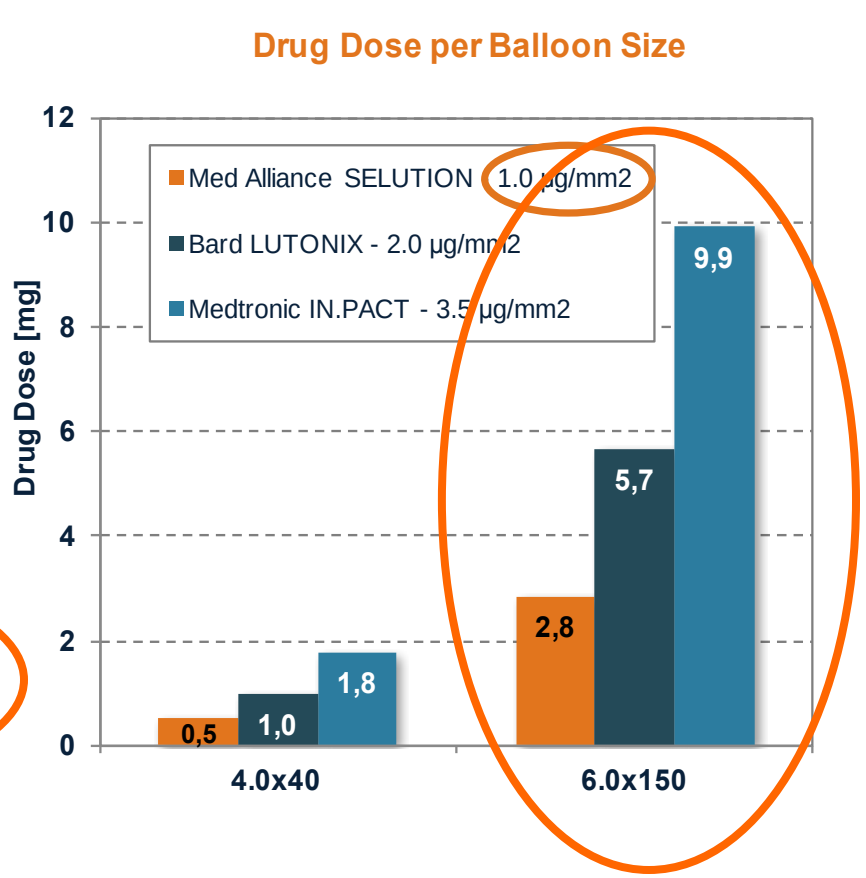
	Med Alliance SELUTION	Bard LUTONIX	Medtronic IN.PACT
Lost during procedure	36%	83%	83%
Retained on balloon	25%	12%	14%
Transferred to vessel (1 hr)	39%	5%	3%

Med Alliance – Bench Test Data on File
Bard-LUTONIX & Medtronic-IN.PACT – Granada J CRT 2014

SELUTION™ Sirolimus DCB

Drug Dosing and Tissue Drug Levels





Med Alliance – PK Study (2014-004)
Medtronic –Melder RJ LINC 2012
Bard – *Catheter Cardiovasc Interv* 2014; 83:132–140

SELUTION™ FIH Trial

ClinicalTrials.gov ID: NCT02941224

Objective	To assess clinical safety and inhibition of restenosis of SELUTION™ DCB in treatment of Superficial Femoral (SFA) or Popliteal (PA) Artery lesions
Design	▫ Prospective, Controlled, Multi-Center, Open, Single Arm ▫ N=60
Primary Endpoint	▫ **Angiographic Late Lumen Loss (LLL) by QVA** ▪ **6 months**
Secondary Endpoints	▫ Major Adverse Events (Death, TLR, Amputation) ▪ 6 months ▫ Primary Patency – Freedom from CD-TLR and Restenosis by DUS ▪ 6, 12 and 24 months ▫ Angiographic Binary Restenosis (ABR) by QVA ▪ 6 months ▫ Composite of Freedom from Amputation and Freedom from CD-TVR ▪ 12 and 24 months ▫ Change of ABI, WIQ and QoL ▪ 6, 12 and 24 months

SELUTION™ FIH Trial Management

Trial Centers:

Herzzentrum Bad Krozingen T. Zeller (PI)
Franziskus Krankenhaus, Berlin K. Brechtel
Vivantes Klinikum Neukoelln, Berlin T. Albrecht
Hubertus Krankenhaus, Berlin D. Meyer

Independent CEC committee:

P. Gaines, M. Lichtenberg, G. Tepe

CRO MD-CLINICALS

Core lab coreLab BLACK FOREST

Sponsor Med Alliance Swiss. Medical. Technology.

SELUTION™ FIH Trial

Baseline Clinical Characteristics

Clinical Characteristics	N=50
Age, Y ± SD	69.6 ± 10.4
Male, % (n)	58 % (29)
Previous Intervention, % (n)	30 % (13)
Myocardial Infarction, % (n)	6 % (3)
Renal Insufficiency, % (n)	22 % (11)
Hypertension, % (n)	80 % (40)
Hyperlipidemia, % (n)	90 % (45)
Diabetes (Type 2), % (n)	28 % (14)
Smoking History, % (n)	58 % (29)
Anticoagulation Therapy	22 % (11)
Angina Pectoris	14 % (7)

Lesion Characteristics	N=50
De Novo	96 % (48)
Lesion Length, mm ± SD	64.30 ± 42.8
RVD, mm ± SD	5.1 ± 0.8
% Diameter Stenosis, % ± SD	90 ± 8.0
Occlusion	30% (15)
Calcification	
None	12 % (6)
Mild	44 % (22)
Moderate	10 % (5)
Moderately severe	26 % (13)
Severe	8 % (4)
Target Lesion Location, % (n)	
SFA prox	12 % (6)
SFA mid	34 % (17)
SFA dist	54 % (27)
POP 1	24 % (12)
POP 2/ POP 3/ TPT	16 % (8)

SELUTION™ FIH Trial

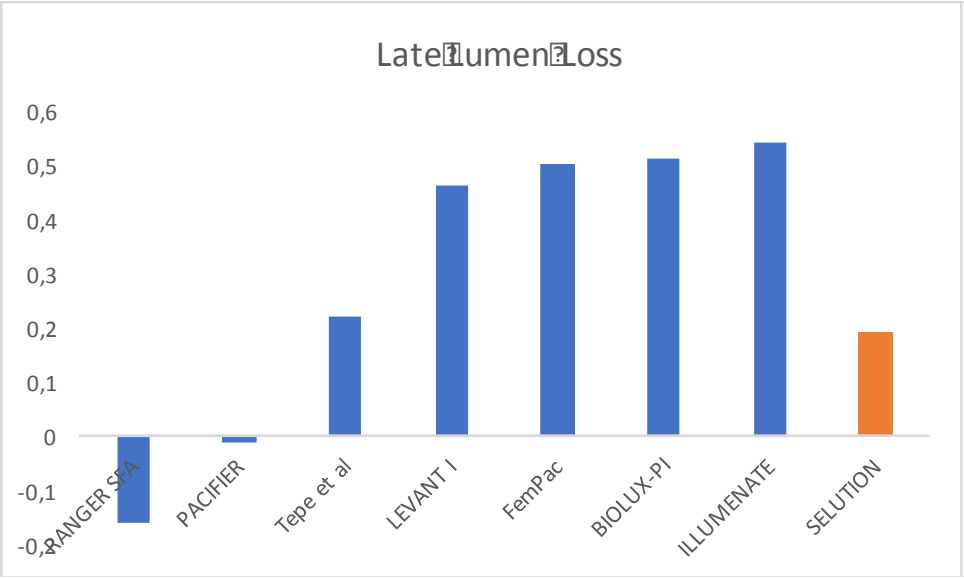
Late Lumen Loss at 6 Months

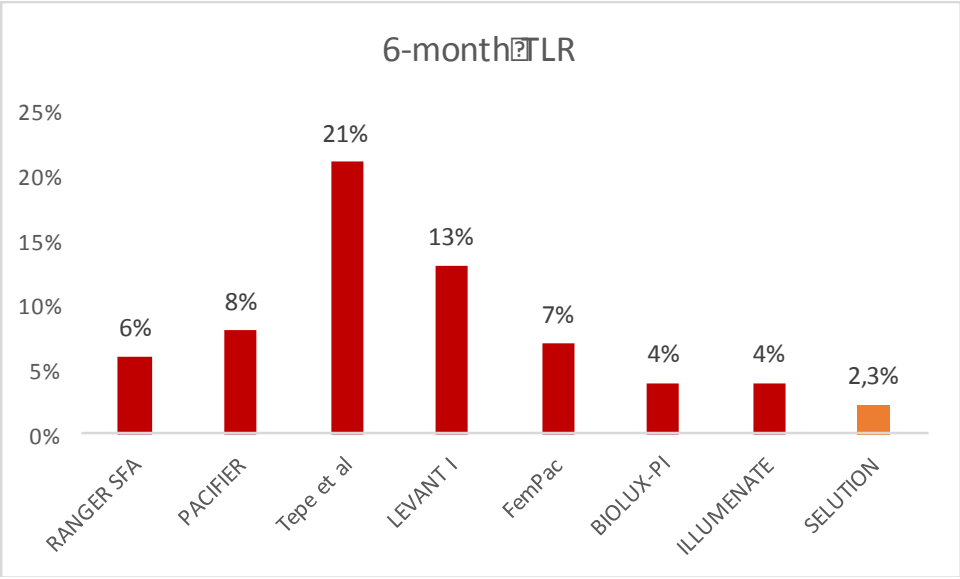
Primary Endpoint

ITT	SELUTION
Underwent 6M Clinical FU - N (%)	43 (86%)
Underwent 6M QVA – N (%)	34 (68%)
LLL (mm)	**0.19 (-1.16;3.07)**
cd TLR - % (N)	2.3 % (1)
Cumulative Clinical Events	
Death	0%
Major or Minor Amputation	0%
Change in Rutherford Class	
Improvement	73%
None	27%
Worsening	0%

SELUTION™ FIH Trial

Clinical Results in Context





Trial	RANGER SFA	PACIFIER	Tepe et al	LEVANT I	FemPac	BIOLUX-PI	ILLUMENATE	SELUTION
Therapy	Ranger	IN.PACT Pacific	DCB not specified	Lutonix	Ptx coated	Passeo-18 Lux	Stellarex	SELUTION
Mean Lesion Length (mm)	6.8	7.0	5.7	8.1	5.7	6.1	7.2	6.4
Bailout Stenting (%)	21%	21%	11%	3%	9%	N/A	5%	8%

Ranger SFA – Scheinert, D. CIRSE 2016.
PACIFIER – Werk, M. et al. Circ Cardiovasc Interv. 2012; 5(6):831-840.
Tepe, G. et al. J Endovasc Ther. 2015:727-33.
LEVANT I – Scheinert, D. et al. JACC Cardiovasc Interv. 2014;7(1):10-9.
FemPac – Werk, M. et al. Circulation. 2008;118(13):1358-65
BIOLUX PI – Scheinert, D. et al. J Endovasc Ther. 2015;22(1):14-21
ILLUMENATE - Schroeder, H. et al Catheter Cardiovasc Intervent. 2015;86(2):278-86
SELUTION – Zeller, T. LINC 2018

SELUTION™ FIH Trial

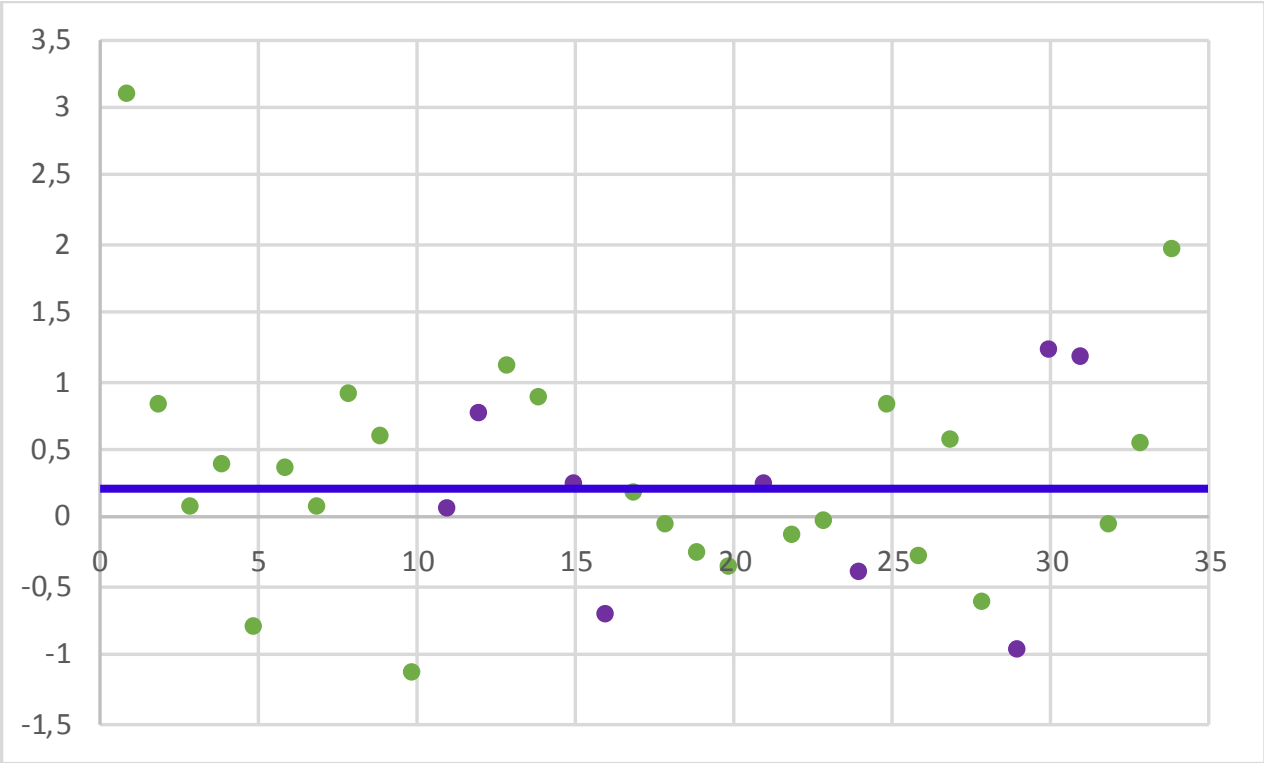
Baseline Characteristics Long Lesions

Lesion Characteristics	Overall Population (mean 6.4 cm) N=50	Long Lesion Subset (>8 cm) N = 12
Lesion Length, mm ± SD	51.30 ± 40.34	112.05 ± 25.31
RVD, mm ± SD	5.1 ± 0.8	4.62 ± 0.38
% Diameter Stenosis, % ± SD	90 ± 8.0	91.6 ± 14.13
Occlusion	30% (15)	58% (7)
Calcification		
None	12 % (6)	8 % (1)
Mild	44 % (22)	42 % (5)
Moderate	10 % (5)	0% (0)
Moderately severe	26 % (13)	33% (4)
Severe	8 % (4)	17% (2)
Target Lesion Location, % (n)		
SFA prox	12 % (6)	0 % (0)
SFA mid	34 % (17)	58 % (7)
SFA dist	54 % (27)	25 % (3)
POP 1	24 % (12)	8 % (1)
POP 2/ POP 3/ TPT	16 % (8)	8 % (1)

SELUTION™ FIH Trial

Long Lesion 6-mo Late Loss*

- Long lesions

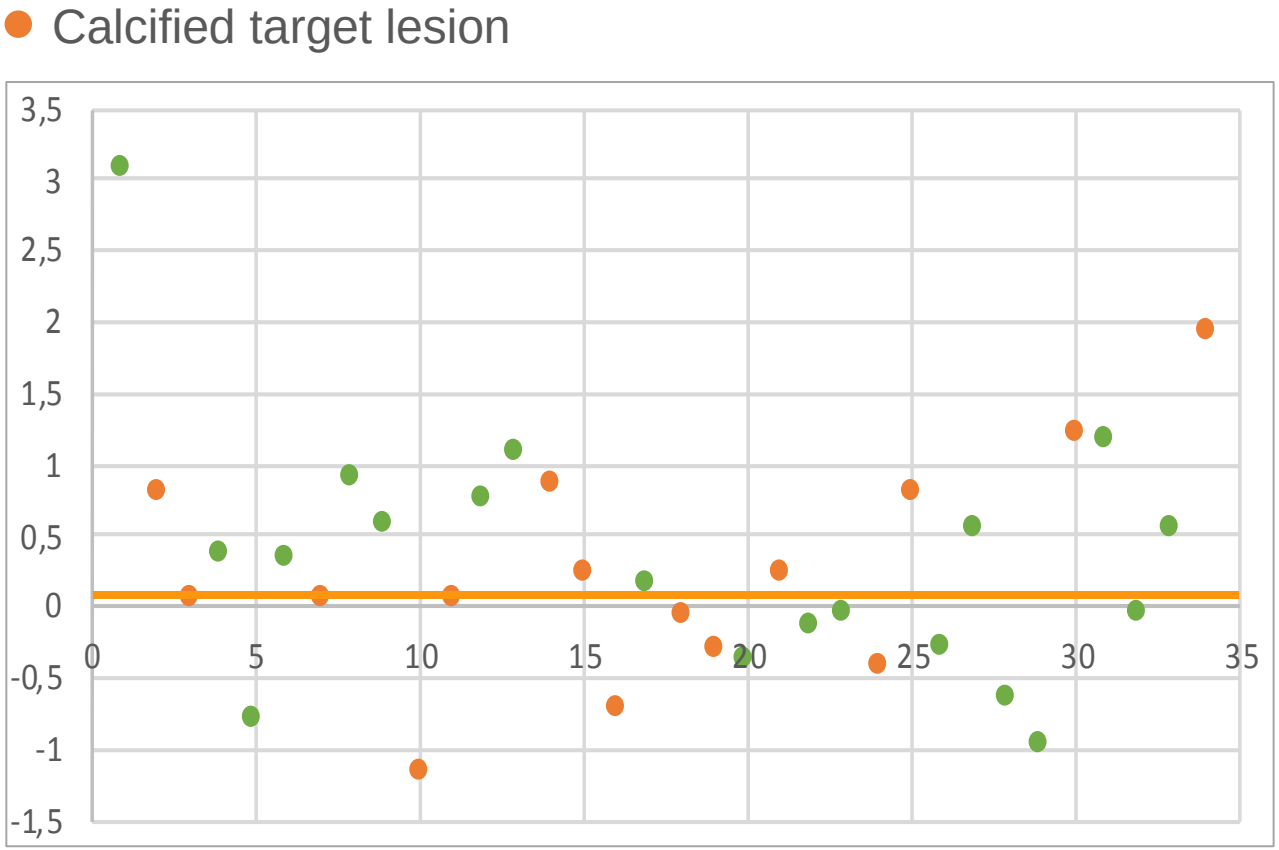


0.23 mm*
(-0.99; 1.25)

*Post-hoc analysis

SELUTION™ FIH Trial

Moderate or Severe Calcified Lesion 6-mo Late Loss*

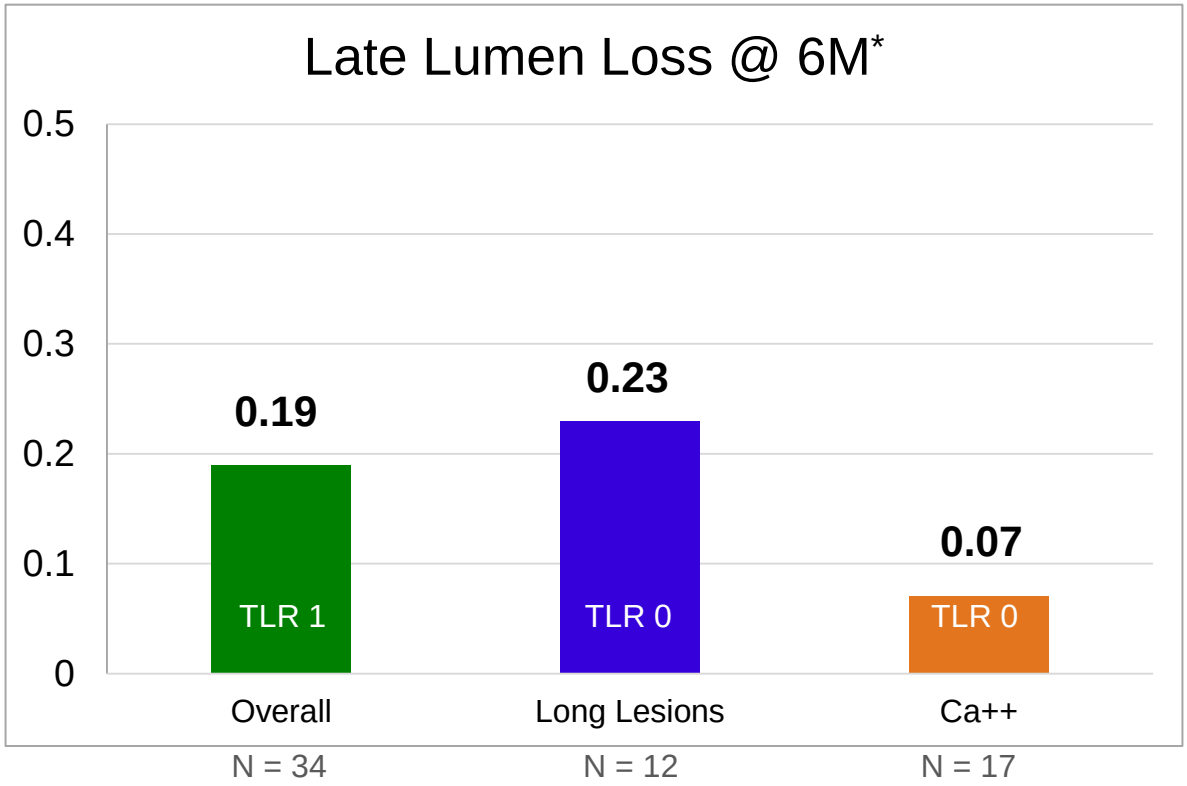


0.07 mm*
(-1.16; 1.98)

*Post-hoc analysis

SELUTION™ FIH Trial

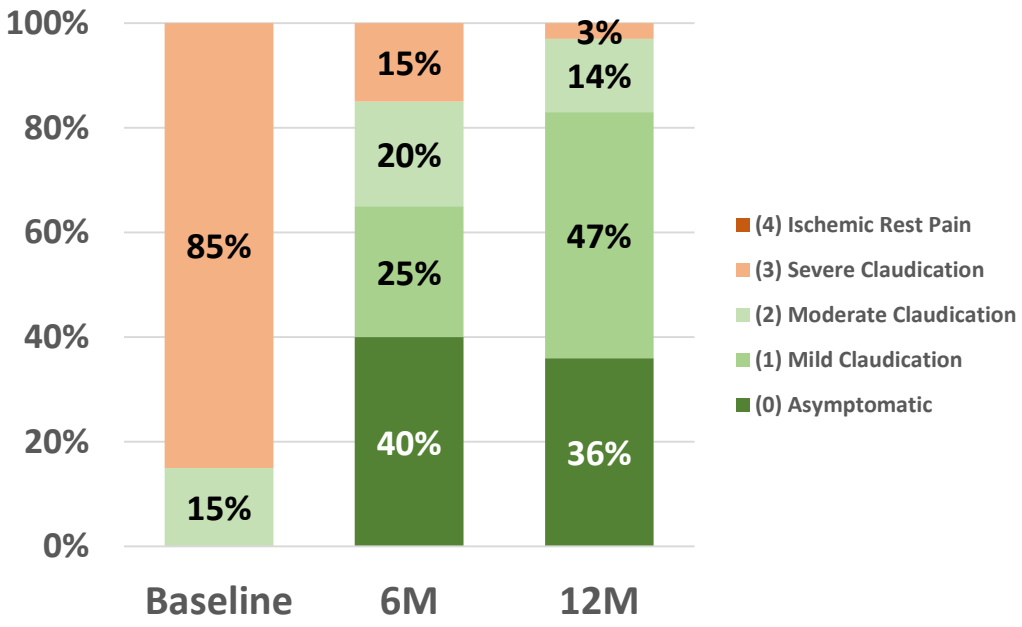
No Clinical Impact of Lesion Length or Calcification

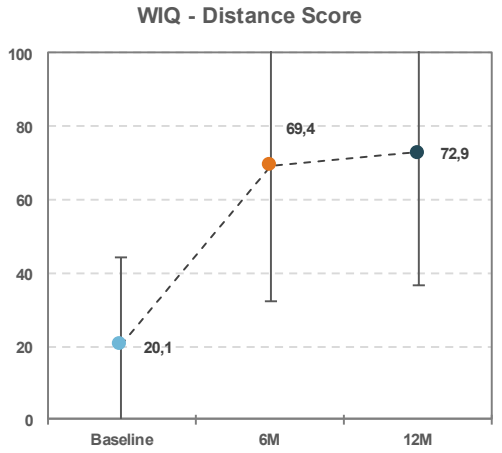


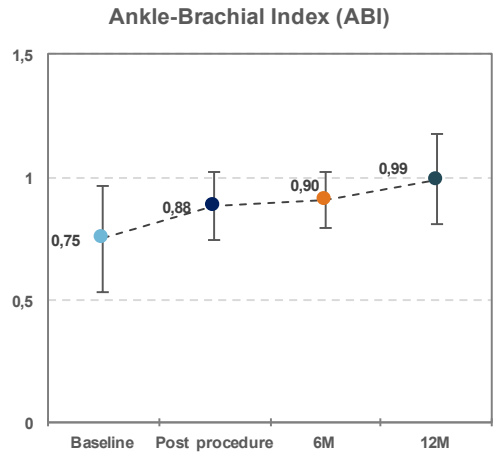
T Zeller T Long Lesion Subgroup –CRT 2018
T. Albrecht T Calcified Lesion Subgroup –CharingX 2018
* Primary Endpoint of Trial

SELUTION FIH Trial

Rutherford, WIQ & ABI







Change from Baseline to 12M: $p < 0.0001$
Change from 6M to 12M: $p = 0.0125$

SELUTION™ FIH Trial Conclusions

- First demonstration of sirolimus safety and efficacy in femoral-popliteal interventions
- Met the primary endpoint of LLL (0.19mm) at 6-months
- SELUTION 6-month clinical outcomes are non-inferior to other FIH studies using paclitaxel balloons
- Low 6-month CD TLR 2.2%
- Excellent outcomes despite 34% moderate or heavy Ca^{+2}
- Long lesion and calcified lesion subgroups demonstrated similar performance compared to the overall cohort
- Further studies are required to confirm these findings in larger patient populations