New Drug Coated Balloon Technologies for Femoral-Popliteal Disease

Robert M. Bersin, MD, FACC, FSCAI

Medical Director, Endovascular Services

Swedish Medical Center

Seattle, Washington

Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Robert M. Bersin, MD

Abbott Vascular C, P, SB
Ablative Solutions EI
Boston Scientific AB, C, EI, P, SB
Cook Medical, Inc. C, P
Med Alliance SA, AB, EI
Medtronic, Inc. C, P
Omeros Corp, EI
QT Vascular, EI
Transverse Medical AB, EI, SO
Vatrix Medical EI
W.L. Gore C, P

AB: Advisory Board
C: Consulting Relationship
EI: Equity Interest
GS: Grant Support
P: Proctor or Training Course Sponsorships
SB: Speakers Bureau
SE: Spouse Employee
SO: Stock Options or Positions

DCB Technology Development

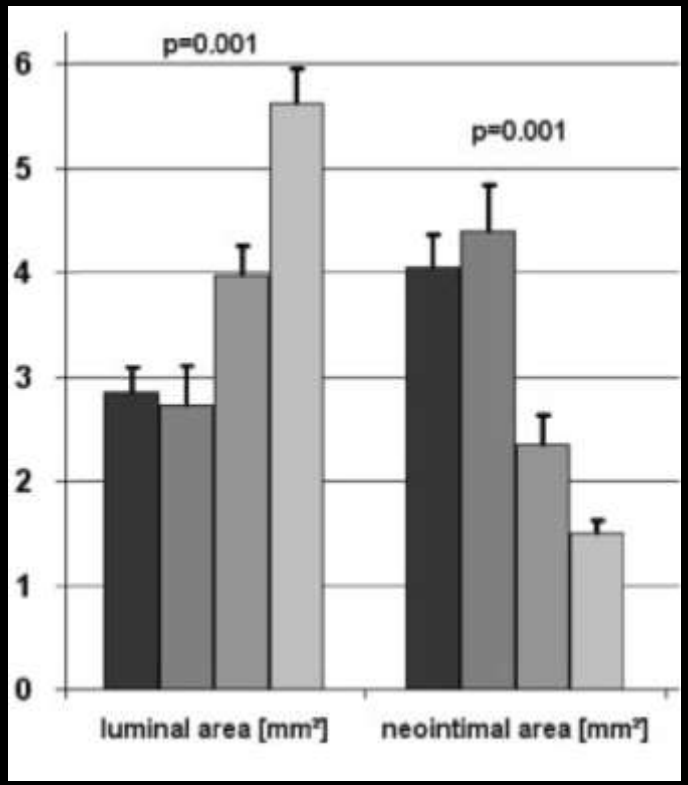
- Prof. Ulrich Speck invents contrast medium iopromide (Ultravist®) in 1979
- Supported by SCHERING, Prof Ulrich Speck combines contrast media Ultravist® with Paclitaxel to develop the DEB prototype PACCOCATH™
- Clinical results by Prof Bruno Scheller showed significant restenosis reduction vs. PTCA
- BAYER acquires Schering in 2006. One year later assigns PACCOCATH™ to one of its affiliates MEDRAD

Prof Ulich Speck and Prof med Bruno Scheller

DCB Technology Development

Additive Necessary for Drug Efficacy

- POBA control
- Paclitaxel 2.5 µg/mm² **WITHOUT additive**
- Paclitaxel 1.3 µg/mm² + **Ultravist additive**
- Paclitaxel 2.5 µg/mm² + **Ultravist additive**



Scheller B et al *Circulation* 2004; 110: 810-814

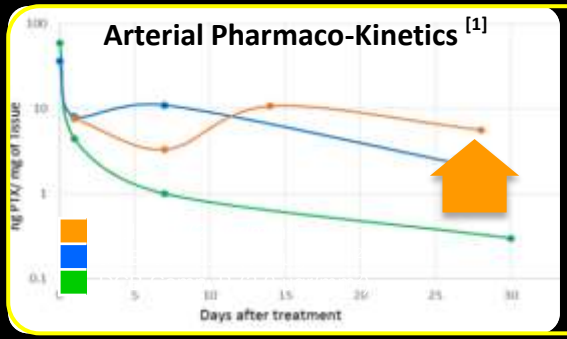
Drug Coated Balloon – Peripheral Devices

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

Stellarex DCB

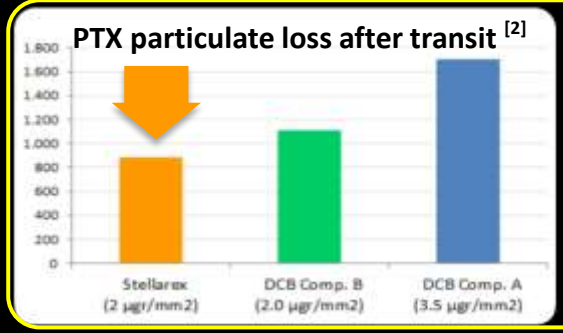
Spectranetics Proprietary open-folded coating technology

- **Low dose (2 µg/mm²) paclitaxel**
- **Hybrid-crystalline formulation**



- Effective drug tissue transfer and residency (≥ 28 days)

1. Superimposed PK curves from different datasets: R.Melder, EuroPCR 2012; Yazdani et.al. Catheterization and Cardivascular Interventions 83:132-140 (2014); data on file at Spectranetics

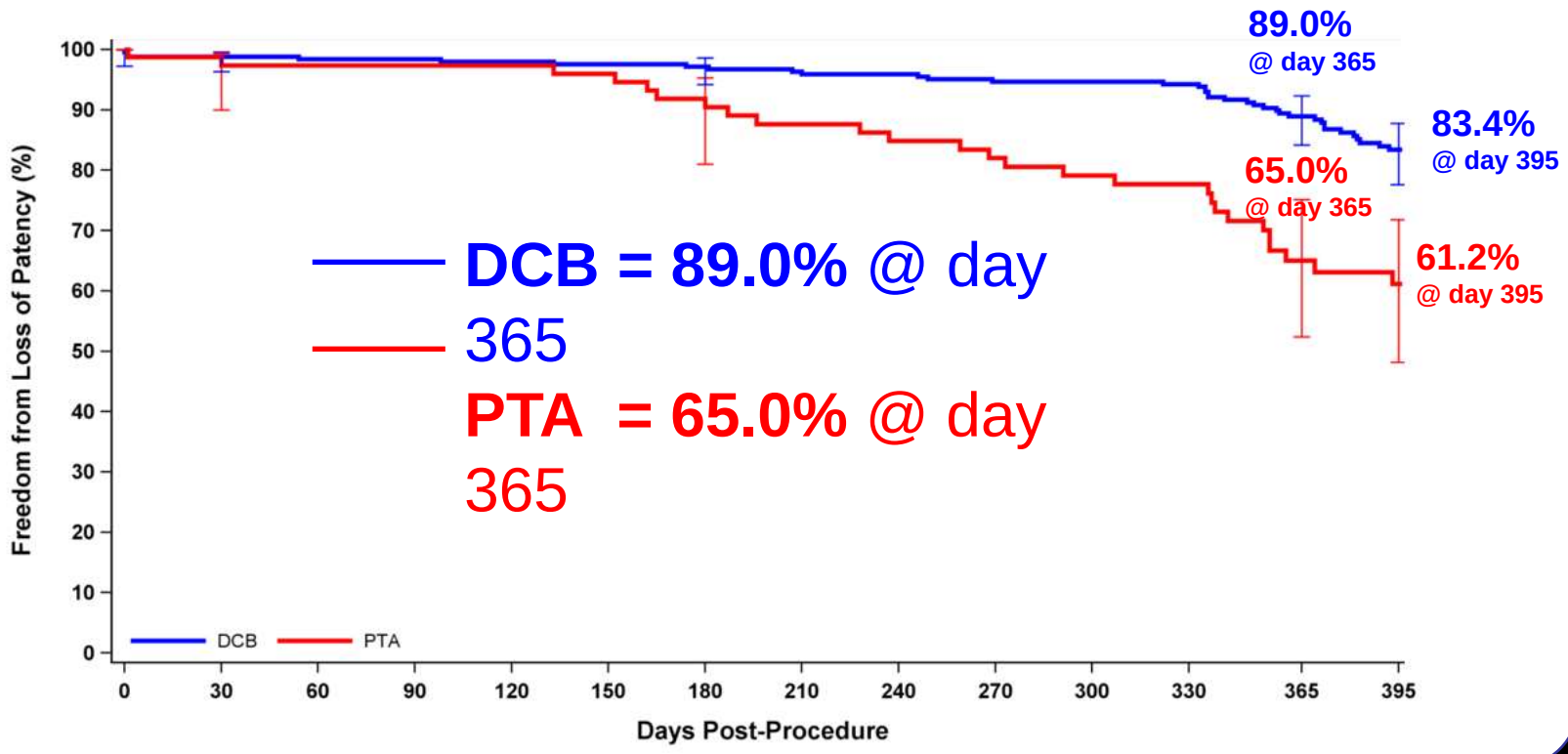


- Limited drug loss

2. Number of particulates ≥10µm/mm of DCB length lost during transit. Data on file at Spectranetics

ILLUMENATE EU RCT

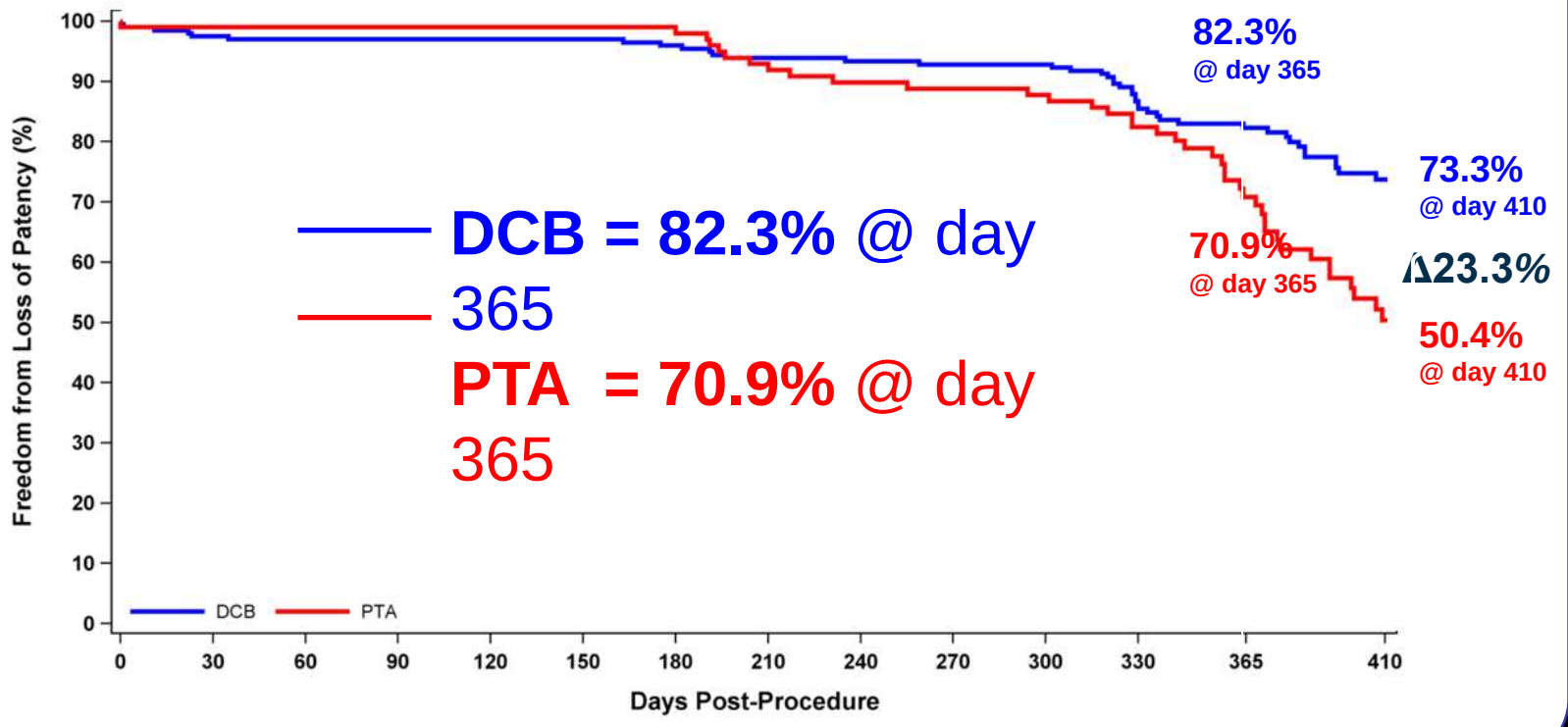
Primary patency 89% at 12 months



Primary patency defined as freedom from restenosis (determined by duplex ultrasound with PSVR ≤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.

ILLUMENATE US Pivotal

Primary patency 82.3% at 12 months

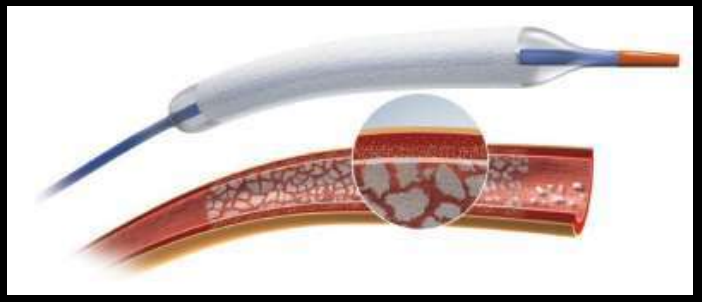


Primary patency defined as freedom from restenosis determined by duplex ultrasound PSVR ≤2.5 and freedom from clinically-driven TLR at 12 months. Assessed per lesion. KM estimates reported at day 410 to capture all patients and events within the full 320-410 follow-up window. Rates from the middle of the protocol visit window (365 days) reported for consistency and comparative purposes with other trials.

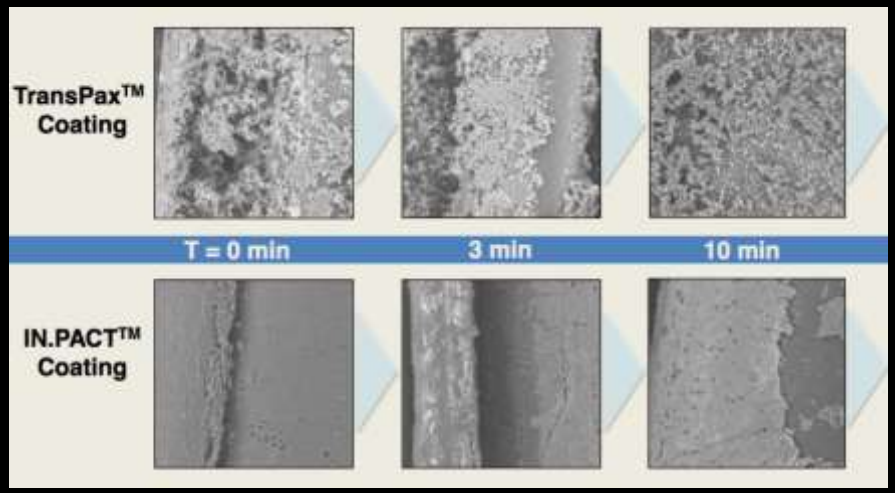
S.Lyden TCT 2016

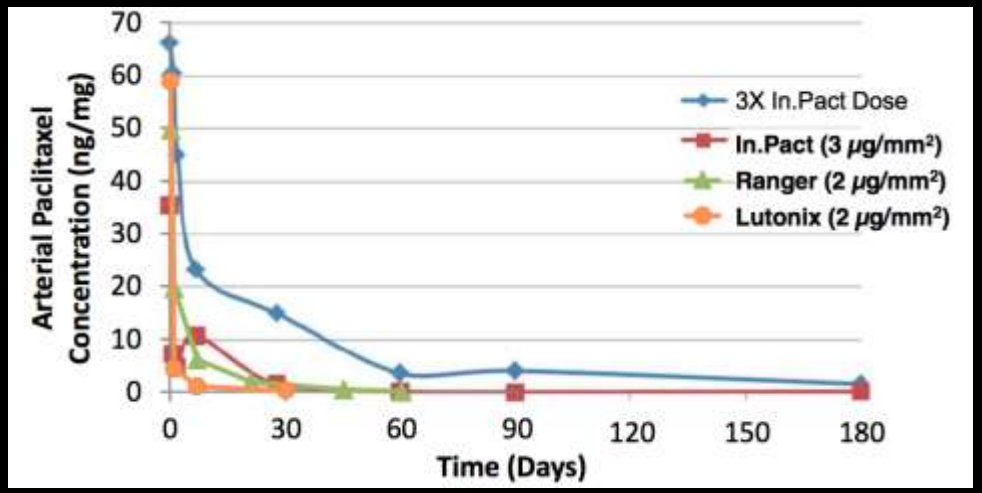
Ranger™ DCB

TransPaxTM Technology



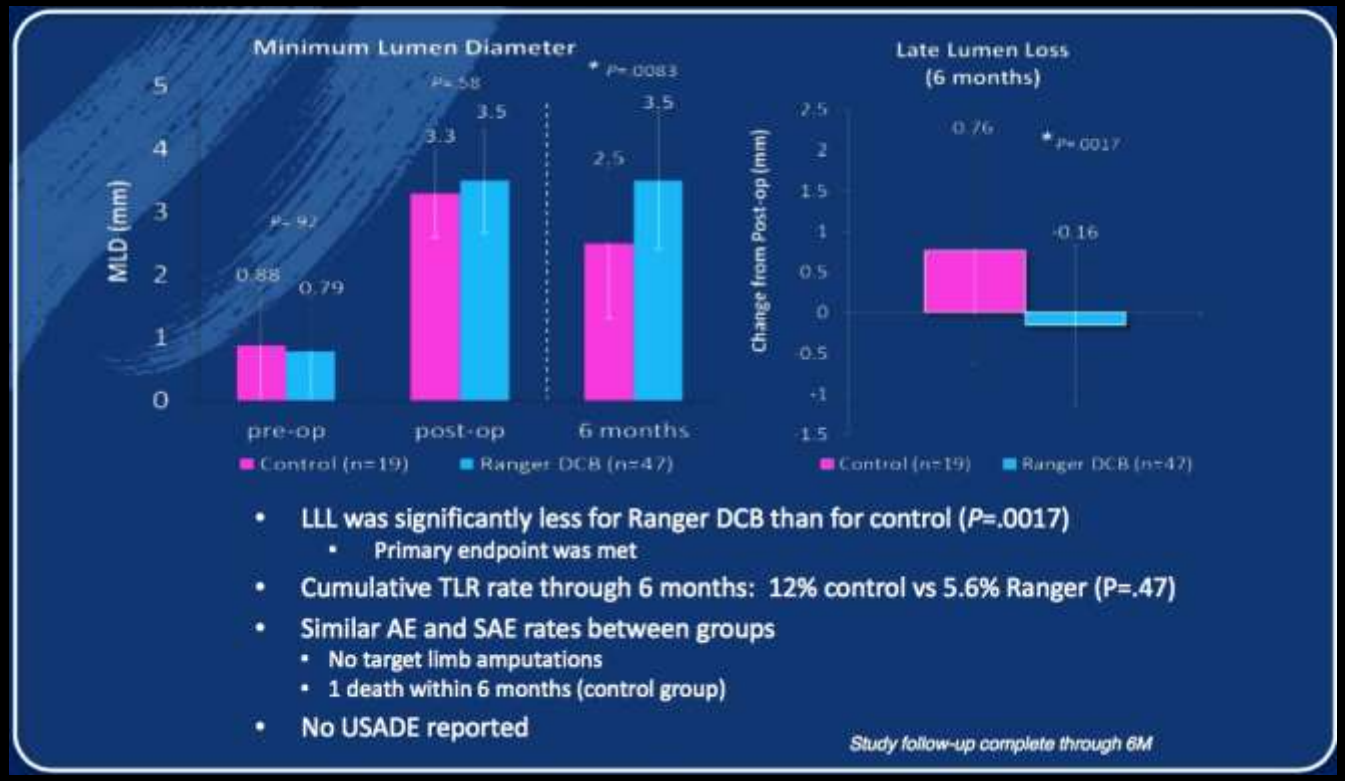
- Paclitaxel 2 µg/mm^2
- Citrate ester (acetyl tributyl citrate – ATBC)
- Balanced hydophyllic/hydrophobic excipient enhances drug retention and transfer





RANGER-SFA Trial

Prospective 2:1 randomized trial in 105 patients

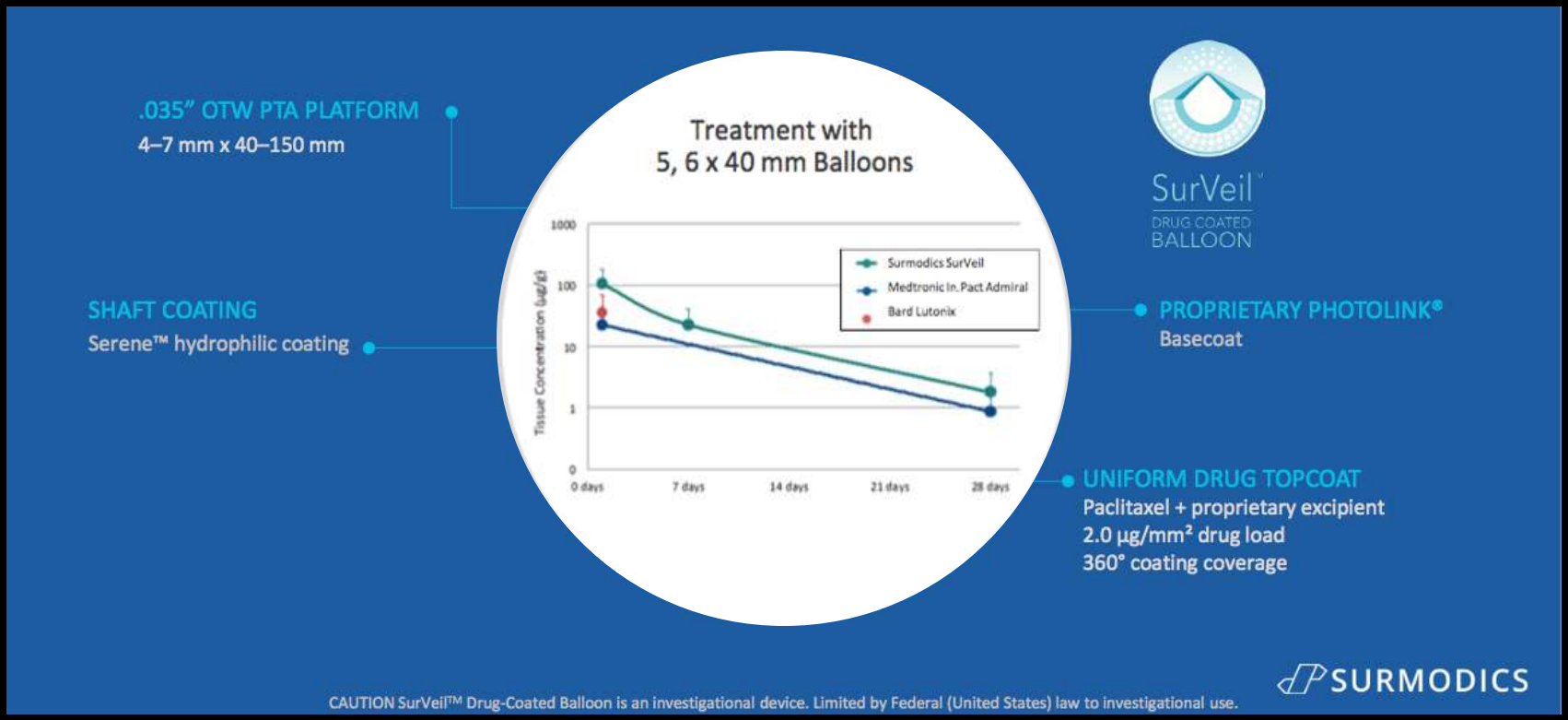


SFA: 4-8mm; 30-100mm
BTK: 2-4 mm; up to 150 mm

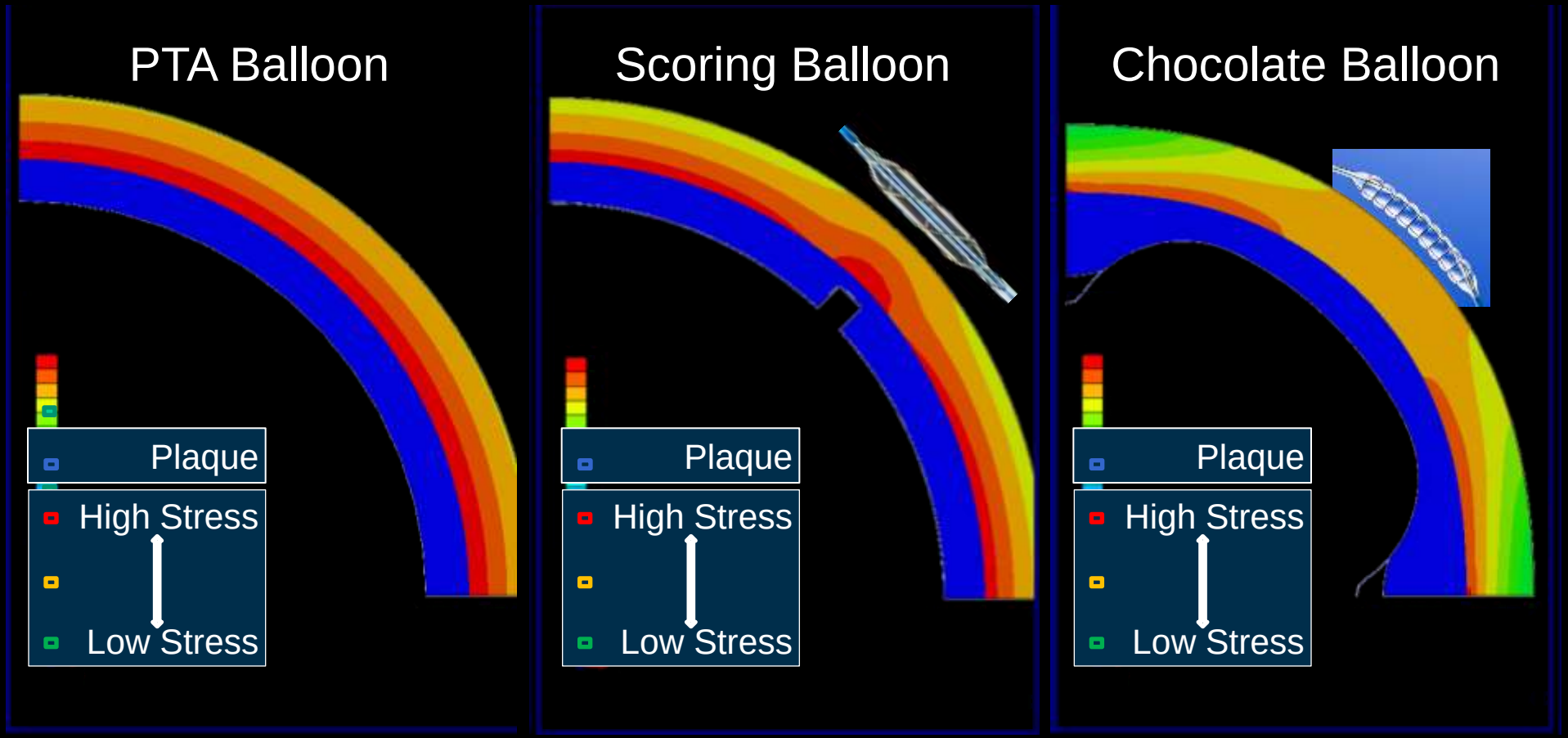
Sheinert D CIRSE 2016

Surveil™ DCB

2 µg/mm^2 paclitaxel DCB
PREVEIL FIH trial enrolling in US



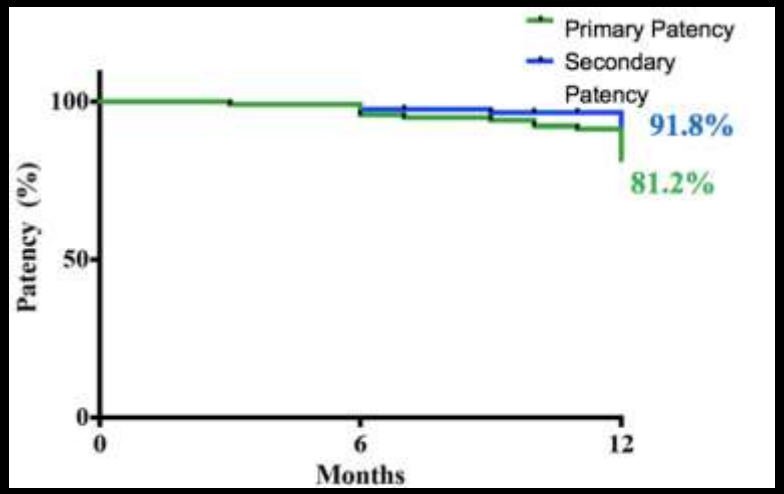
Focal Balloon Technologies



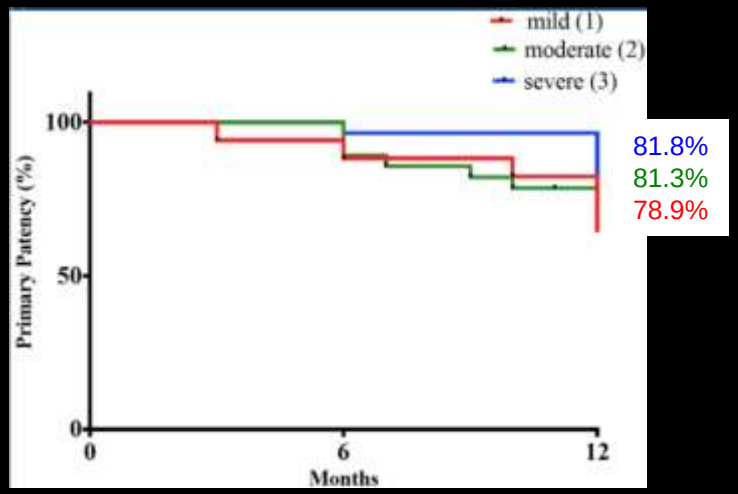
AngioSculpt DCB

PANTHER Registry (N=121 patients, 124 lesions)

- 37.1% Angiosculpt alone (N-46)
- 32.3% Angiosculpt plus DCB (N=40)
- 30.6% Angiosculpt plus stent (N=38)



Overall results



PP by extent of calcification

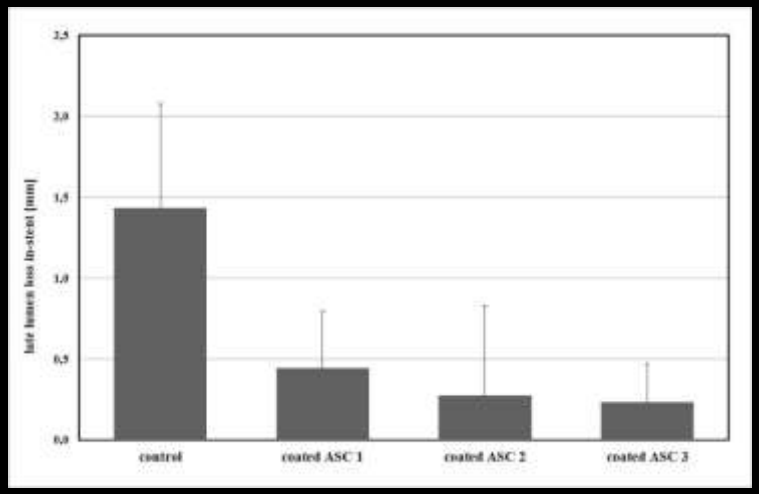
BIOTRONIK
excellence for life

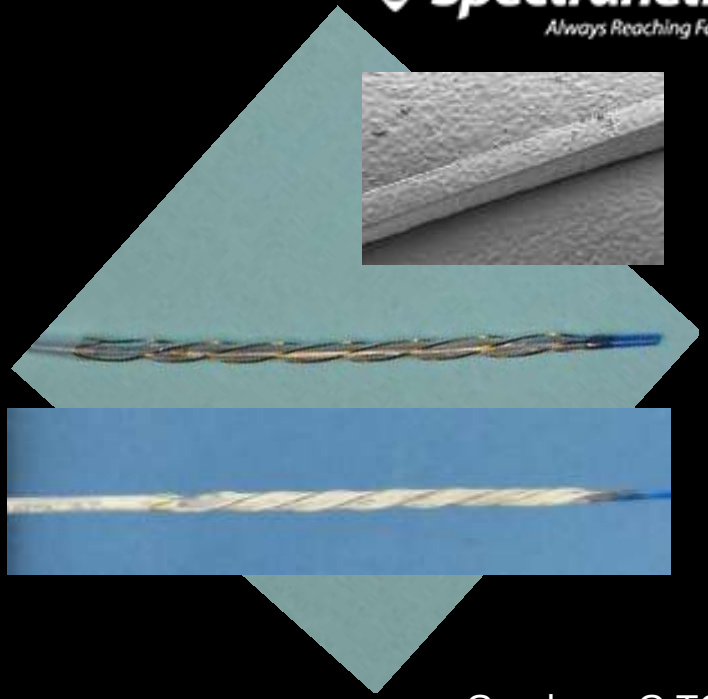
Pantera LUX™ DCB

Blessing E LINC 2014

AngioScore DCB

- 60 patient single-arm registry (4 sites)
- 3 µgr/mm2 paclitaxel with Ultravist excipient (switch to PEG?)
- Coronary ISR (endovascular application now being considered)



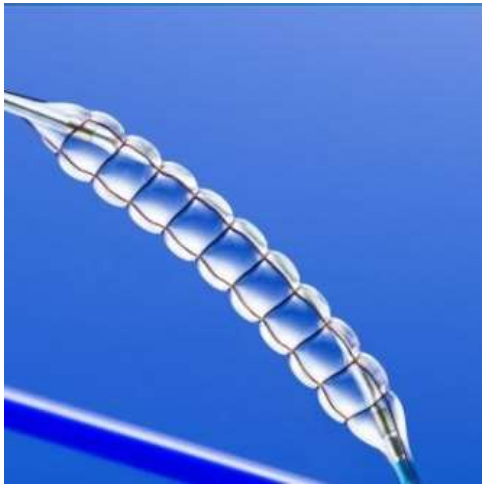


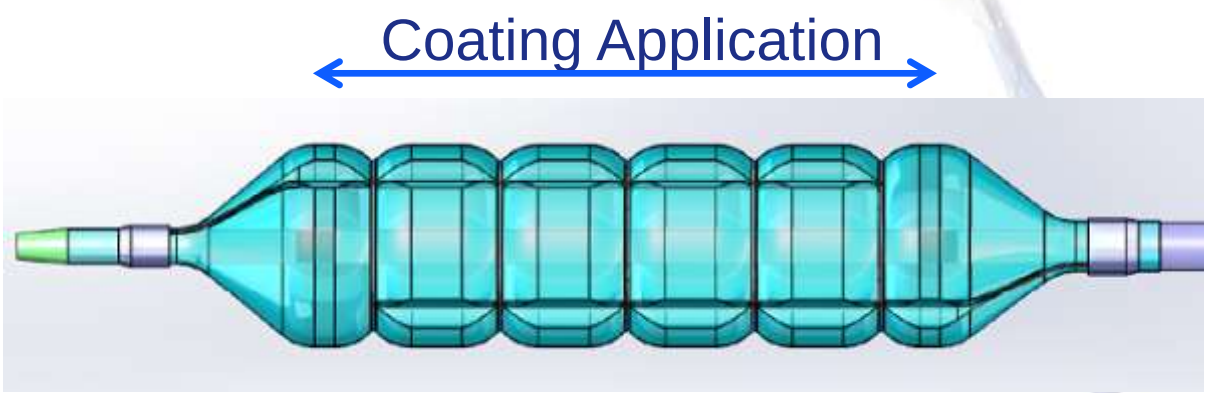
30-day LLL porcine overstretched BMS model (N=30)

Gershony G TCT 2012

Chocolate Touch DCB

- Nominal dose density of paclitaxel on Chocolate Touch is 3µg/mm^2, similar to other drug coated balloons.
- Excipient is a GRAS substance used in the pharmaceutical and in the food industry for 65yrs.



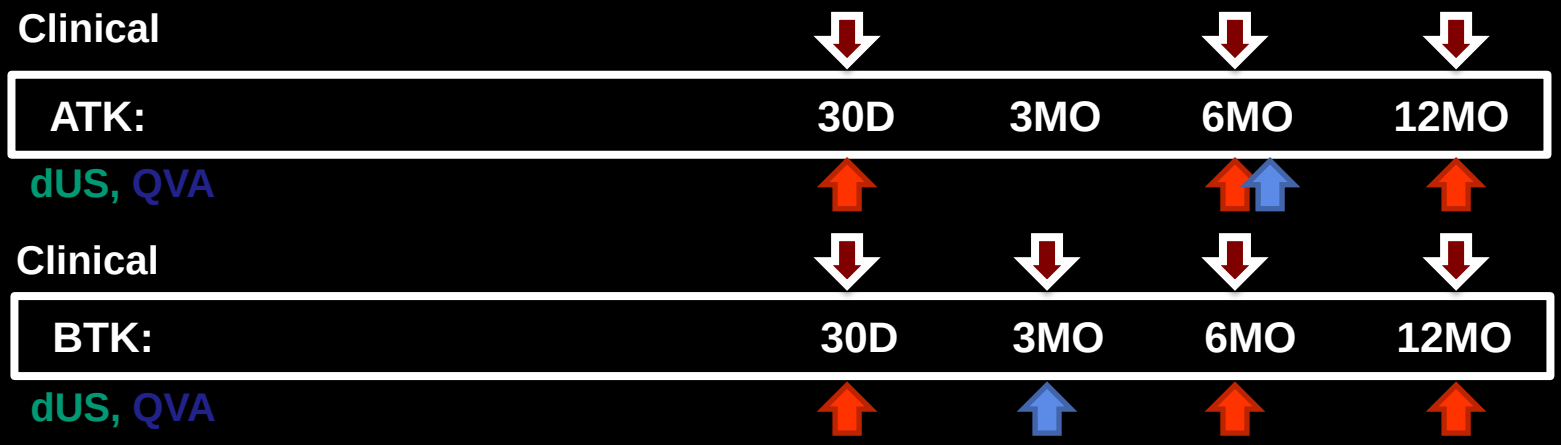


GRAS: Generally Recognized as Safe
Investigational device. Not approved for human use.

ENDURE Study Design

Up to 80 patients; Single-Arm Trial

- Single or Tandem *de novo* lesion
- Total lesion length ≤ 150 mm
- RVD 2.0 – 6.0 mm
- Rutherford Grade 3-5



Study Endpoints

- Late Lumen Loss – Angiography (QVA Core Lab)
- Patency Rate – Duplex Ultrasound (dUS Core Lab)
- TLR Rate
- Amputation Rate
- Clinical Improvement (Rutherford Grade change)

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***

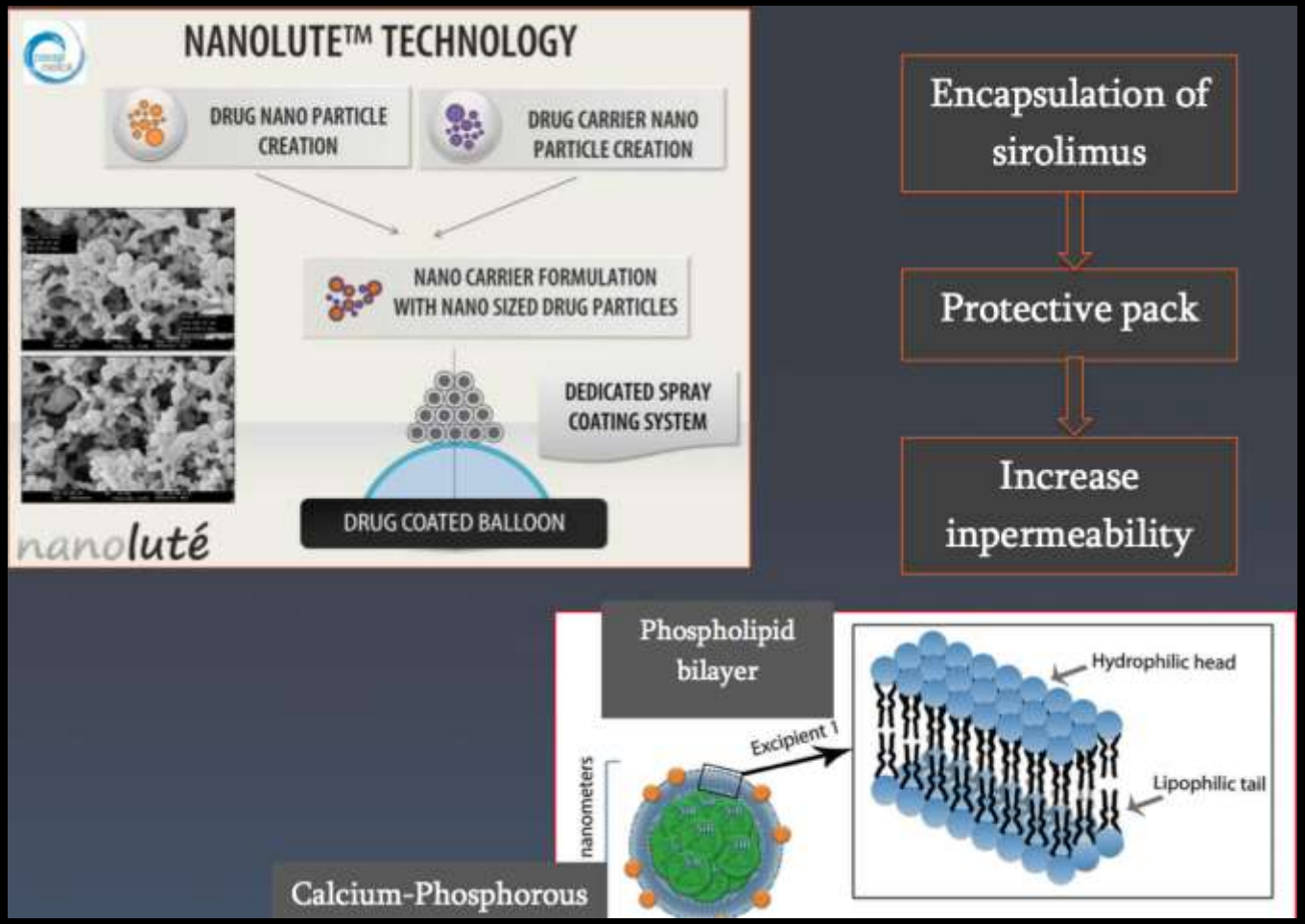
- **Sirolimus is *drug of choice* for coronary DES supported by solid clinical based evidence**

Sirolimus Coated Balloons – Challenges

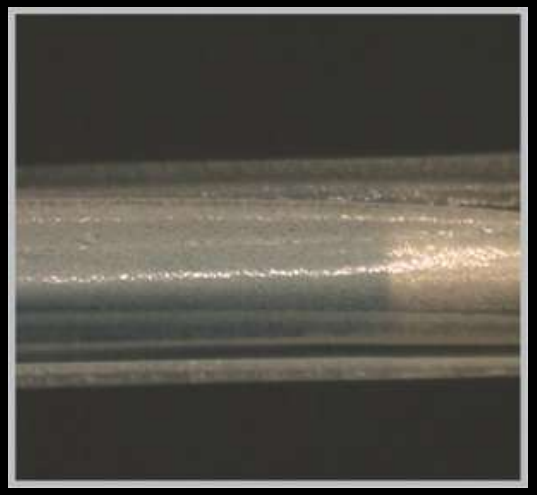
- **Enhance** tissue absorption
  - Difficult to get sirolimus to enter into arterial tissue within 30 to 180 seconds of balloon dilatation; hence some kind of "**instant glue**" is required to transfer the drug from the balloon to the tissue efficiently

- **Extend** tissue retention
  - Sirolimus must be continuously delivered over time, so some form of "**time release mechanism**" must be employed to maintain therapeutic levels

Magic Touch
Nanolute Technology



Xtreme Touch Neo Endovascular DCB

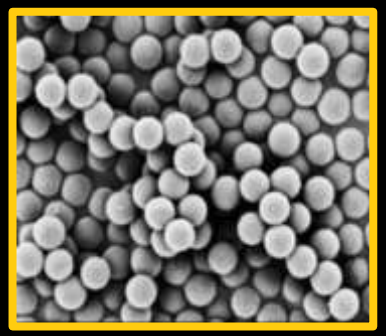


Catheter Configuration	Over-The-Wire (OTW)
Available Balloon Lengths	Up to 150 mm
Available Balloon Diameters	Up to 12.00 mm
Effective Catheter Length	130 cm (1300 mm) and 150 cm (1500 mm)
Radiopaque Marker Bands	2
Guide wire compatibility (max)	0.014" / 0.018" / 0.035"
Coating Formulation	Active Pharmaceutical Ingredient: Sirolimus Drug Excipients: Phospholipid
Drug Dose	3µg/mm^2

Concept Medical Product Brochure

Med Alliance
SELUTION™ Sirolimus DCB

- Micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus:
  - Controlled and sustained drug release mechanism
  - Maintains therapeutic effect in tissue over long period of time

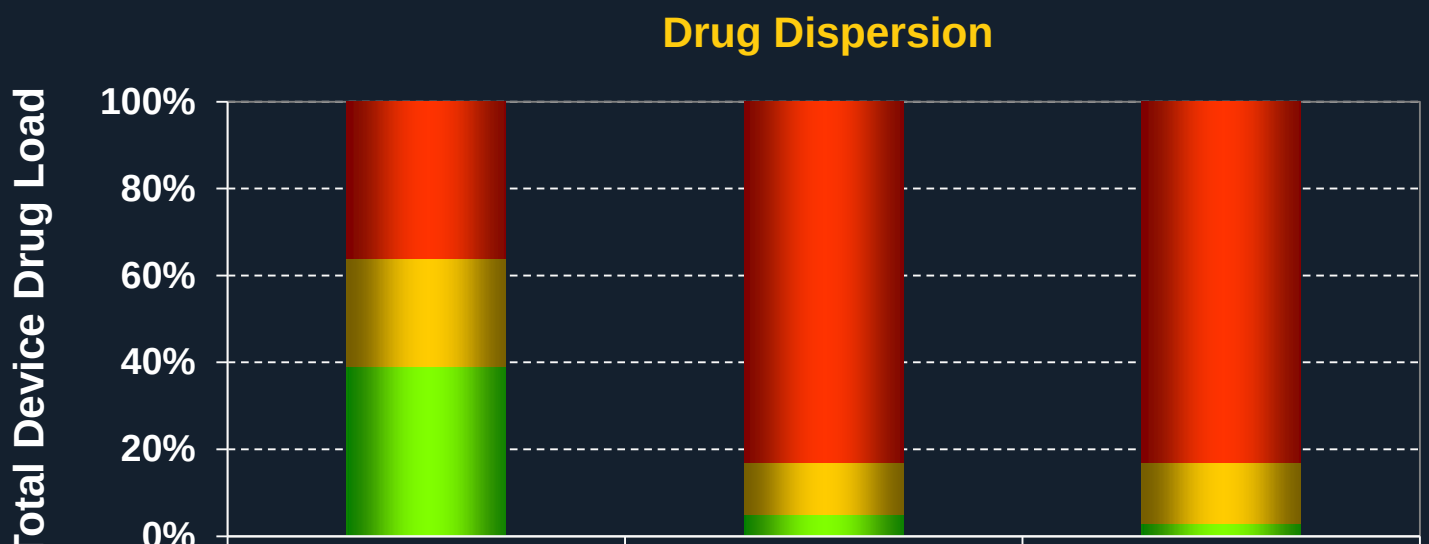


- Novel Cell Adherent Technology – CAT™:
  - CAT™ transfer membrane houses and protects micro-reservoirs during balloon insertion, lesion crossing and expansion
  - CAT™ transfer membrane with embedded micro-reservoirs releases from balloon delivery system and adheres to vessel lumen with short balloon inflations

Med Alliance SELUTION™ vs. Competition

Med Alliance
Swiss. Medical. Technology.

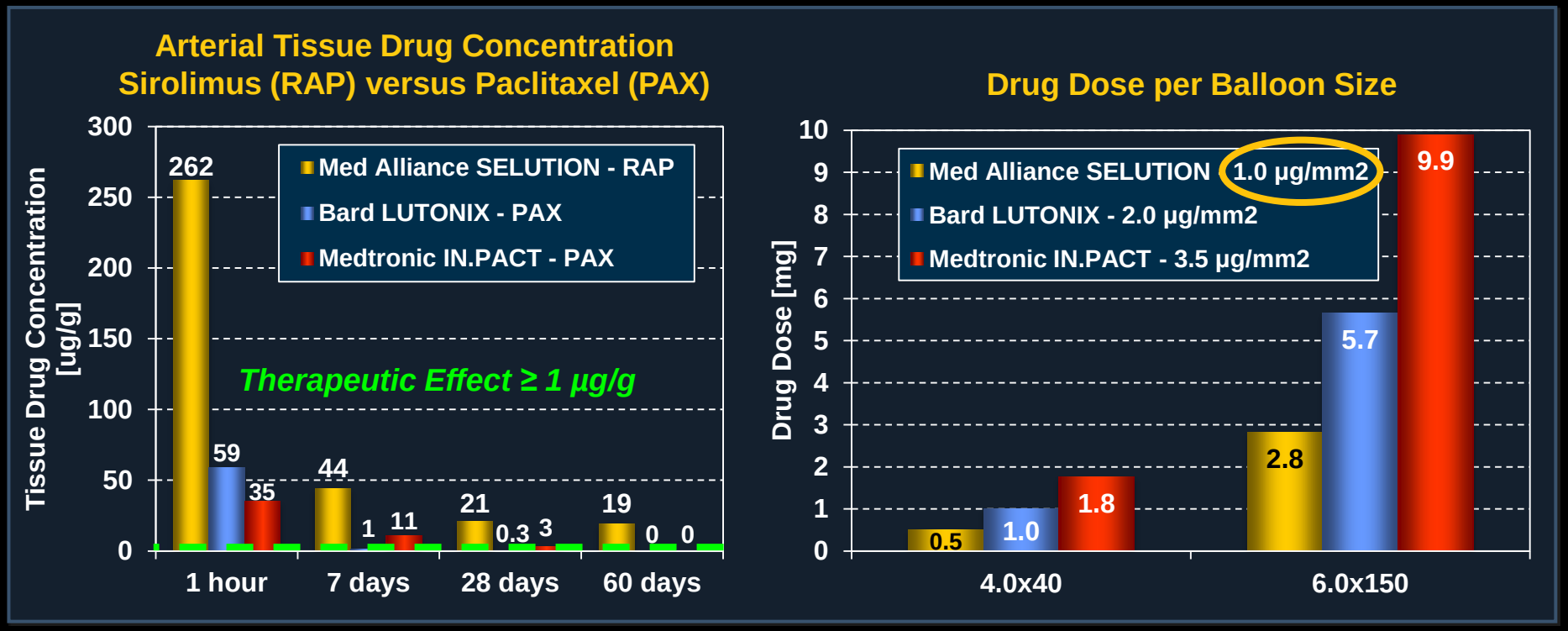
Med Alliance
SELUTION™ Sirolimus DCB

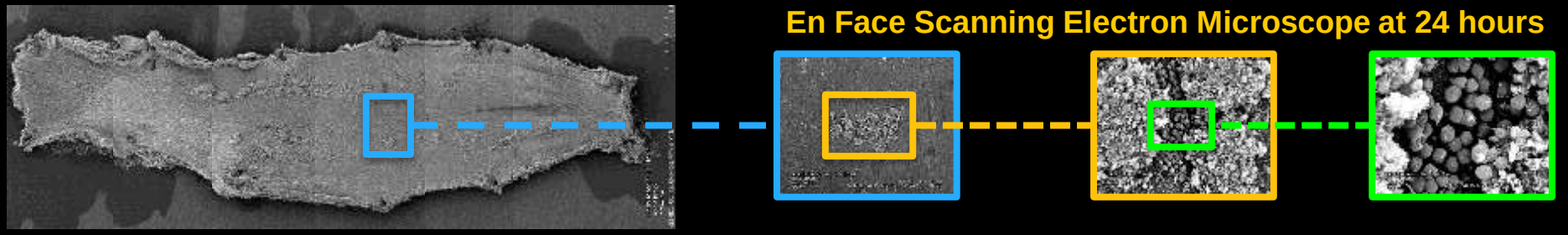


	Med Alliance SELUTION	Bard LUTONIX	Medtronic IN.PACT
Lost during procedure	36%	83%	83%
Retained on balloon	25%	12%	14%
Transferred to vessel (1 hr)	39%	5%	3%

Med Alliance – In vitro test data on file
Bard & Medtronic – Presentation J.F. Granada (TCT 2014)

Med Alliance
SELUTION™ Sirolimus DCB





Med Alliance – PK Study (2014-004)
Medtronic – Presentation R.J. Melder (LINC 2012)
Bard – *Catheterization and Cardiovascular Interventions* 83:132–140 (2014)

SELUTION™ FIH Fem-Pop Trial

Objective	To show non-inferiority of **SELUTION™ DCB** in terms of safety and efficacy for treatment of Superficial Femoral (SFA) or Popliteal (PA) Artery lesions
Design	▫ Prospective, Multi-Center, Single Blinded, Single Arm Controlled ▫ N=50
Primary Endpoint	▫ **Angiographic Late Lumen Loss (LLL) by QVA** ▪ **6 months**
Secondary Endpoints	▫ Major Adverse Events (Death, TLR, Thrombosis, 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

Endovascular DCB Conclusions

1. Endovascular DCB has been proven to reduce late loss in SFA-popliteal lesions with paclitaxel (Thunder, Fem-Pac, LEVANT I, BIOLUX P-I and PACIFIER) and to reduce restenosis/TLR in SFA-popliteal lesions with paclitaxel (Thunder, Fem-Pac and PACIFIER).
2. All current research with DCB has focused on the use of paclitaxel with a dosing of 2-3 $\mu g/mm^2$.
3. The use of DCB is particularly attractive in long lesions where DES is problematic and expensive, but lesion preparation will be increasingly important to achieve acceptable acute outcomes with PTA.
4. The role of lesion preparation with atherectomy and focal/scoring balloons is currently under investigation, and the preliminary data suggests this may be particulary beneficial in calcified and long lesions.
5. Sirolimus DCBs have been proven to be effective in coronary applications and are now being developed for SFA applications.