Sirolimus Coated Balloon Technologies

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Disclosure 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.

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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

Sirolimus Drug Coated Balloons

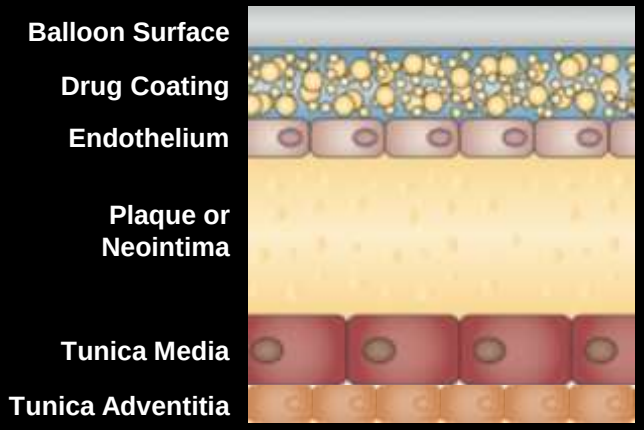
- **Sirolimus offers potential benefits over Paclitaxel:**

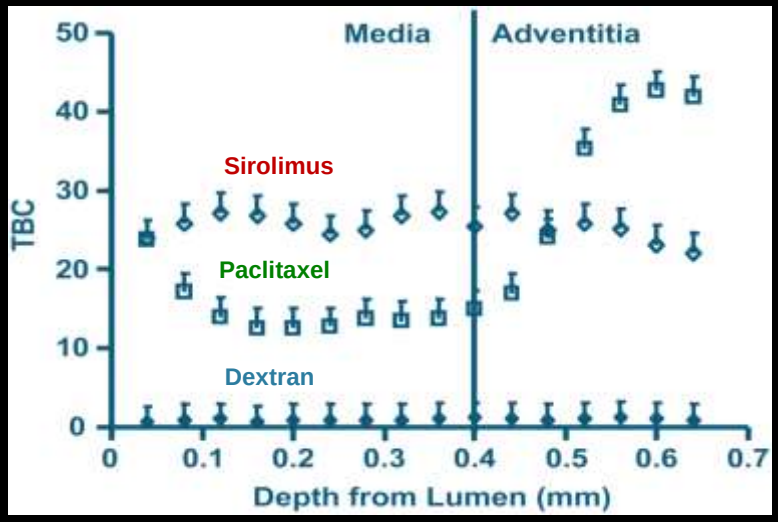
Attribute	Sirolimus (or Analogs)	Paclitaxel
Mode of action	**Cytostatic**	**Cytotoxic**
Margin of safety	**10’000 fold**	**100 fold**
Therapeutic range	**Wide**	**Narrow**
Anti-restenotic	**Yes – lower late lumen loss**	**Yes**
Anti-inflammatory	**Yes**	**No**
Tissue absorption	***Slow***	***Fast***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

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

Sirolimus Coated Balloons – Challenges

- Paclitaxel and Sirolimus act **differently** with tissue:
  - Paclitaxel **absorbs quickly** and tends to localize in sub-intimal space and **partitions significantly** in adventitia
  - Sirolimus **absorbs slowly** and spreads throughout entire artery where it **dilutes down to sub-therapeutic levels**





Tissue Binding Capacity (TBC) of labeled dextran, paclitaxel and sirolimus in 0.040-mm-thick bovine internal carotid tissue segments.
Source: PNAS 2004:101(25);9463–67.

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

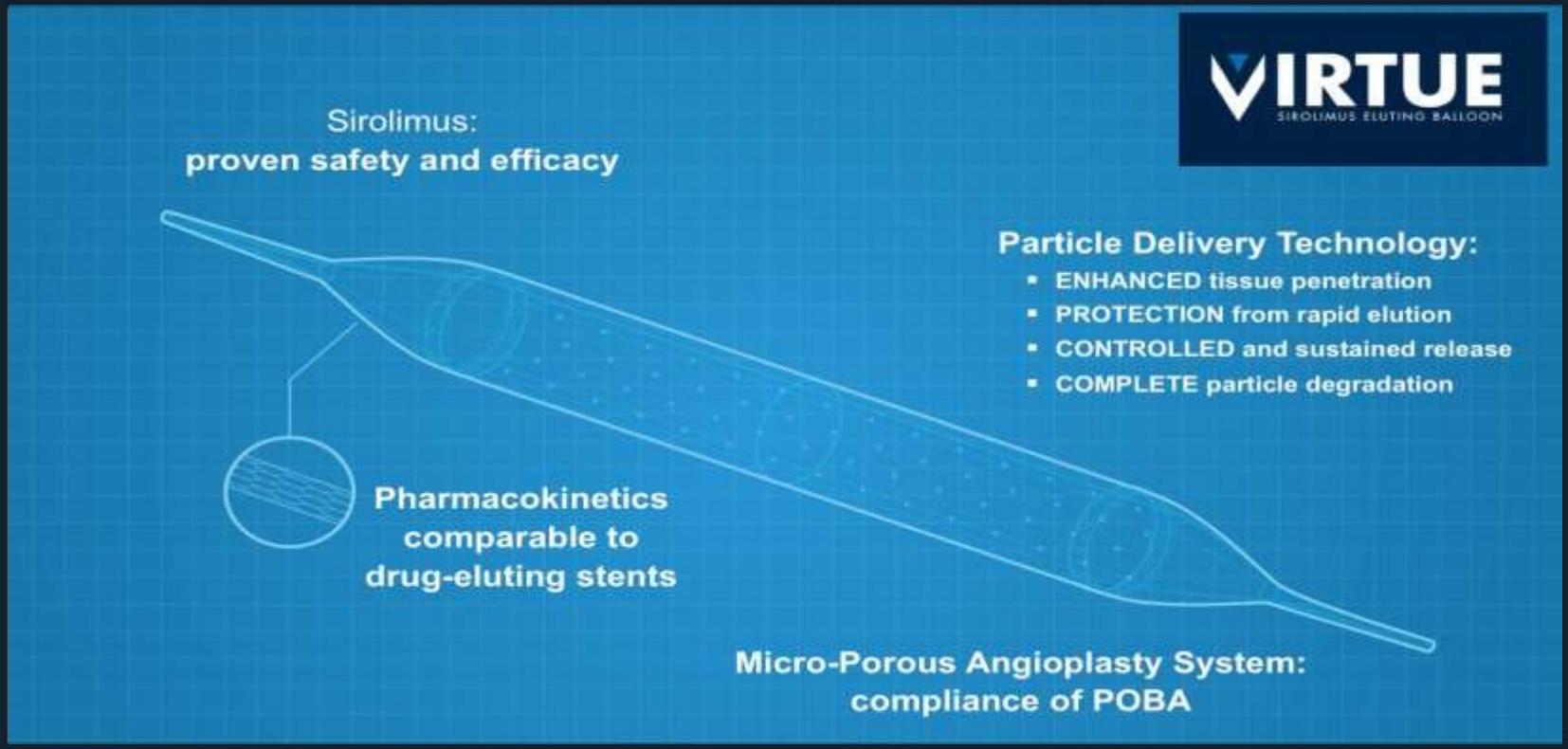
Sirolimus Coated Balloons - Landscape

Company	Product	Drug	Concentration	Delivery Agent
Abbott Vascular	NA	zotarolimus	6-7 μg/mm^2	iopromide matrix
Caliber Therapeutics	Virtue DCB	sirolimus nanoparticles	3 mg	porous balloon
Concept Medical	Magic Touch DCB Xtreme Touch DCB	sirolimus nanoparticles	1.3 μg/mm^2 3.0 μg/mm^2	phospholipid excipient
MedAlliance SA	Selution DCB	sirolimus nanoparticles	1.0 μg/mm^2	CAT-cell adherence technology
Sahajanand Medical Technologies	NA	sirolimus	0.7 μg/mm^2	PLGA/PVP 50-50 coating

VIRTUE Sirolimus Eluting Balloon

Virtue aims to solve DCB Limus delivery challenge of tissue uptake and long-term elution

Sirolimus tissue concentrations > 300-fold higher in coronary artery treatment site and target concentration maintained for 28 days



Granada et al. *In Vivo Delivery and Long Term Tissue Retention of Nano-Encapsulated Sirolimus using a Novel Porous Angioplasty System:* Eurointervention, October 2015.

Granada J TCT 2015

SABRE: Angiographic Results

6 Months Follow Up

	Intent to Treat	Per Protocol Analysis		
	SABRE	SABRE	SABRE BMS	SABRE DES
n	47	35	22	13
RVD+ mm	2.57 ± 0.37	2.58 ± 0.37	2.58 ± 0.32	2.57 ± 0.46
MLD mm	1.75 ± 0.54	1.87 ± 0.45	2.02 ± 0.28	1.62 ± 0.58
% Diameter Stenosis+	30.3 ± 19.9	26.8 ± 16.8	21.7 ± 8.2	35.6 ± 23.4
Change % DS+	12.7 ± 20.6	9.3 ± 15.3	4.9 ± 11.2	16.7 ± 18.7
LLL * mm	0.31 ± 0.52	0.25 ± 0.47	0.13 ± 0.31	0.46 ± 0.60
% Binary Restenosis #	19.1	11.4	0.0	30.8

* Trial primary performance endpoint
\# Trial secondary performance endpoint
\+ RVD reported using inter normal values

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SABRE: Clinical Safety Outcomes

6 Months Follow Up

	Intent to Treat Analysis (ITT)					Per Protocol Analysis (PP)
	In Hospital	30 Days*	6 Months			6 months
n	50	50	All (49)	BMS (32)	DES (17)	36
Cardiac Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CABG	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)
TLR	0 (0.0%)	0 (0.0%)	4 (8.2%)	0 (0%)	4 (23.5%)	2 (5.6%)
MACE	0 (0.0%)	0 (0.0%)	5 (10.2%)	1 (3.1%)	4 (23.5%)	2 (5.6%)

* Primary safety endpoint is 30 day MACE

Values are reported as n (%)

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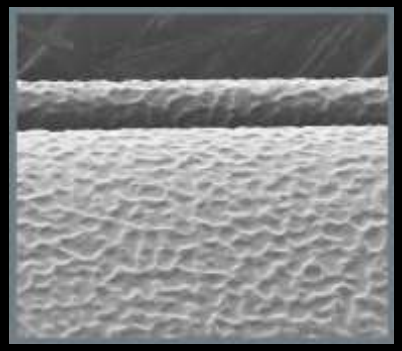
Magic Touch
12-month Clinical Outcomes

Overall Cohort (N=299 lesions)

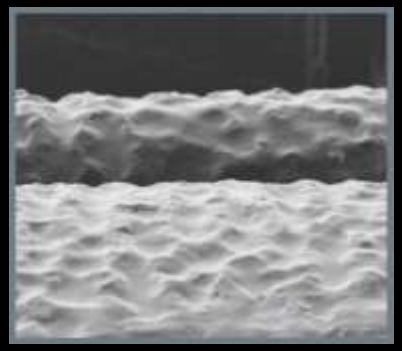
MACE (major adverse cardiac event)	Value, n(%)
Death	1 (0.36%)
Myocardial infarction	0 (0.00%)
TVR/TLR	9 (3.25%)
Total MACE ,n(%)	10 (3.61%)

ISR Subset (N=133 lesions)

*MACE (major adverse cardiac event)	Value, n(%)
Death	0 (0.00%)
Myocardial infarction	0 (0.00%)
TVR/TLR	6(4.84%)
Total MACE ,n(%)	6 (4.84%)

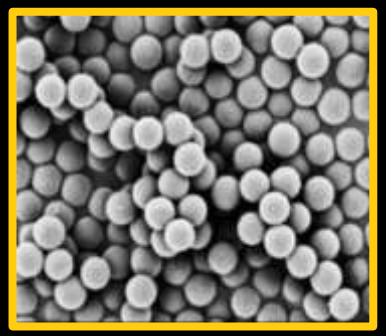


Nanolute™



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

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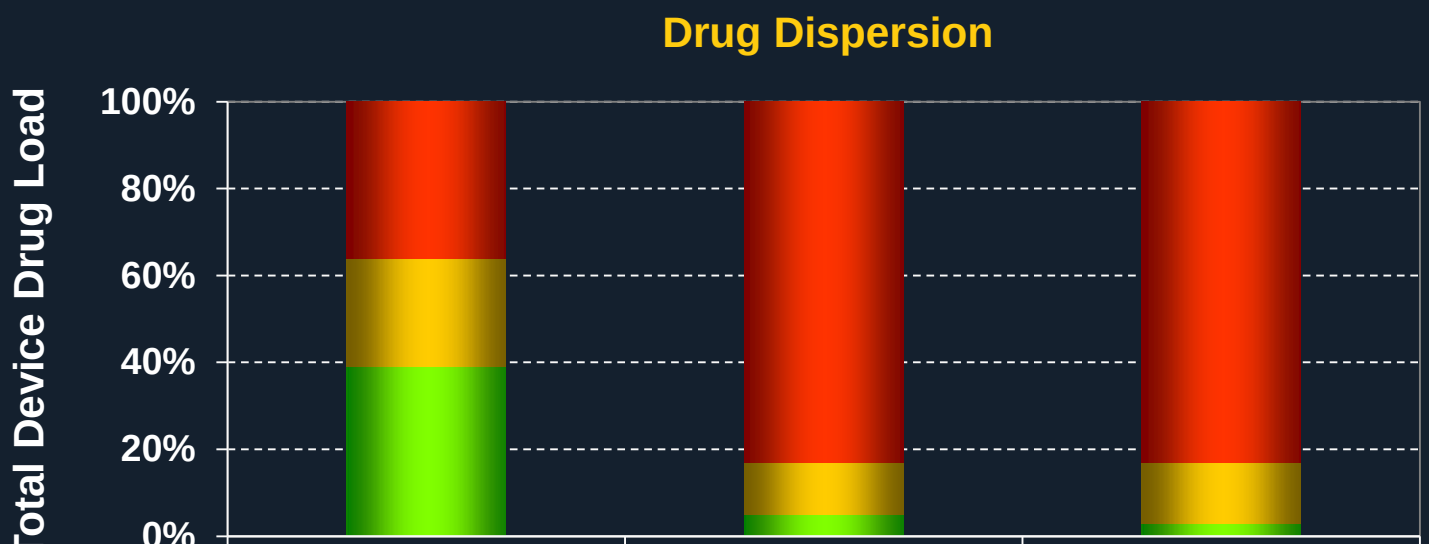
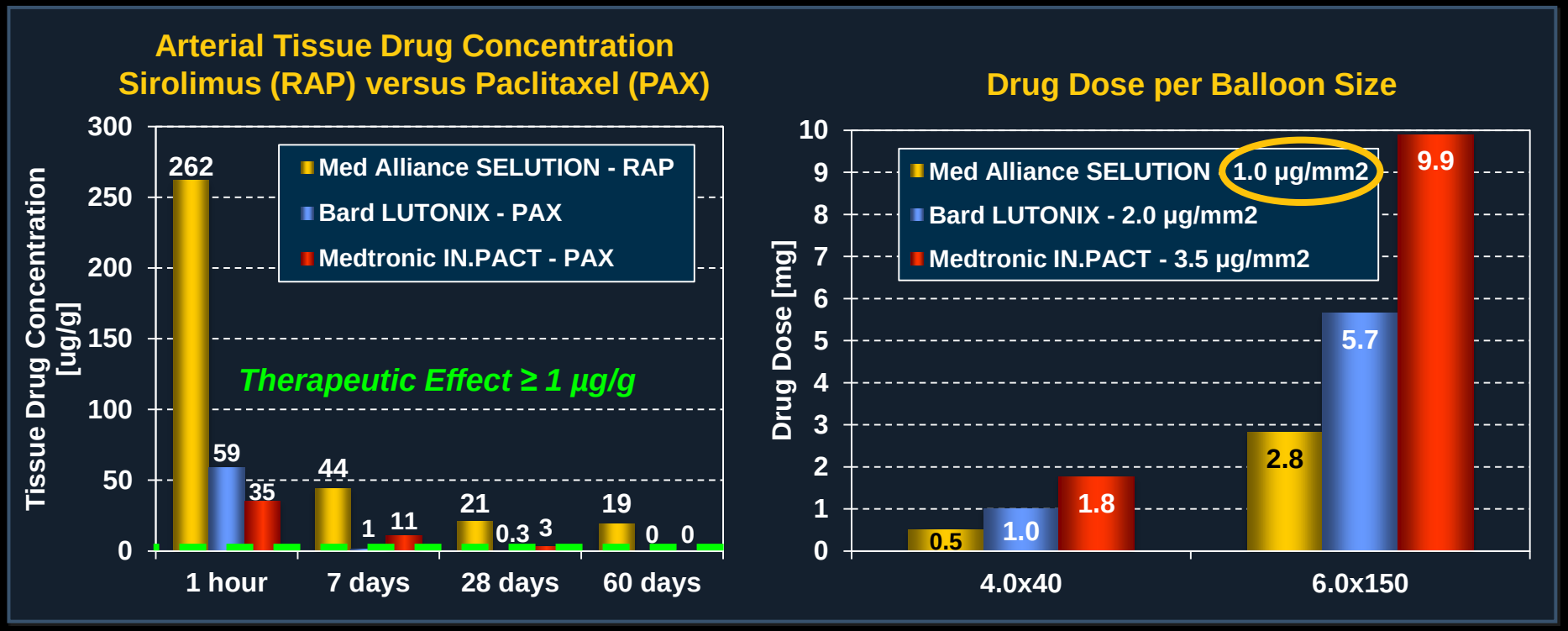
SELUTION™ Sirolimus DCB

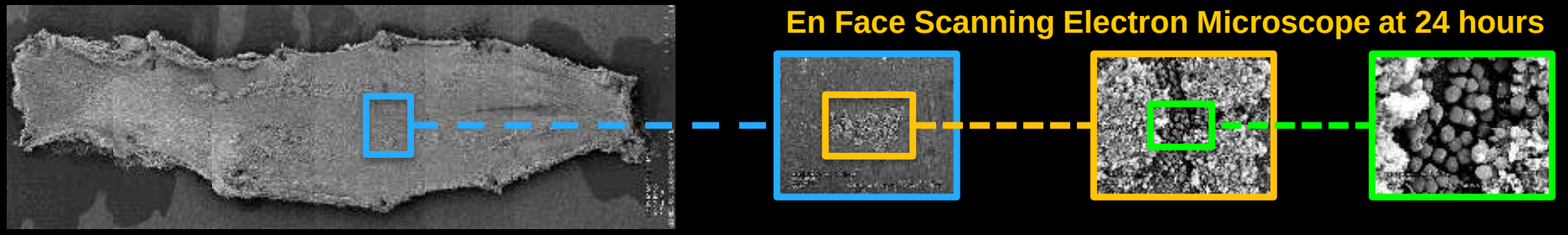


	Med Alliance SELUTION	Bard LUTONIX	Medtronic IN.PACT
Lost during procedure	36%	83%	83%
Retained on balloon	25%	12%	14%
Transferred to vessel (1 hr)	39%	5%	3%

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

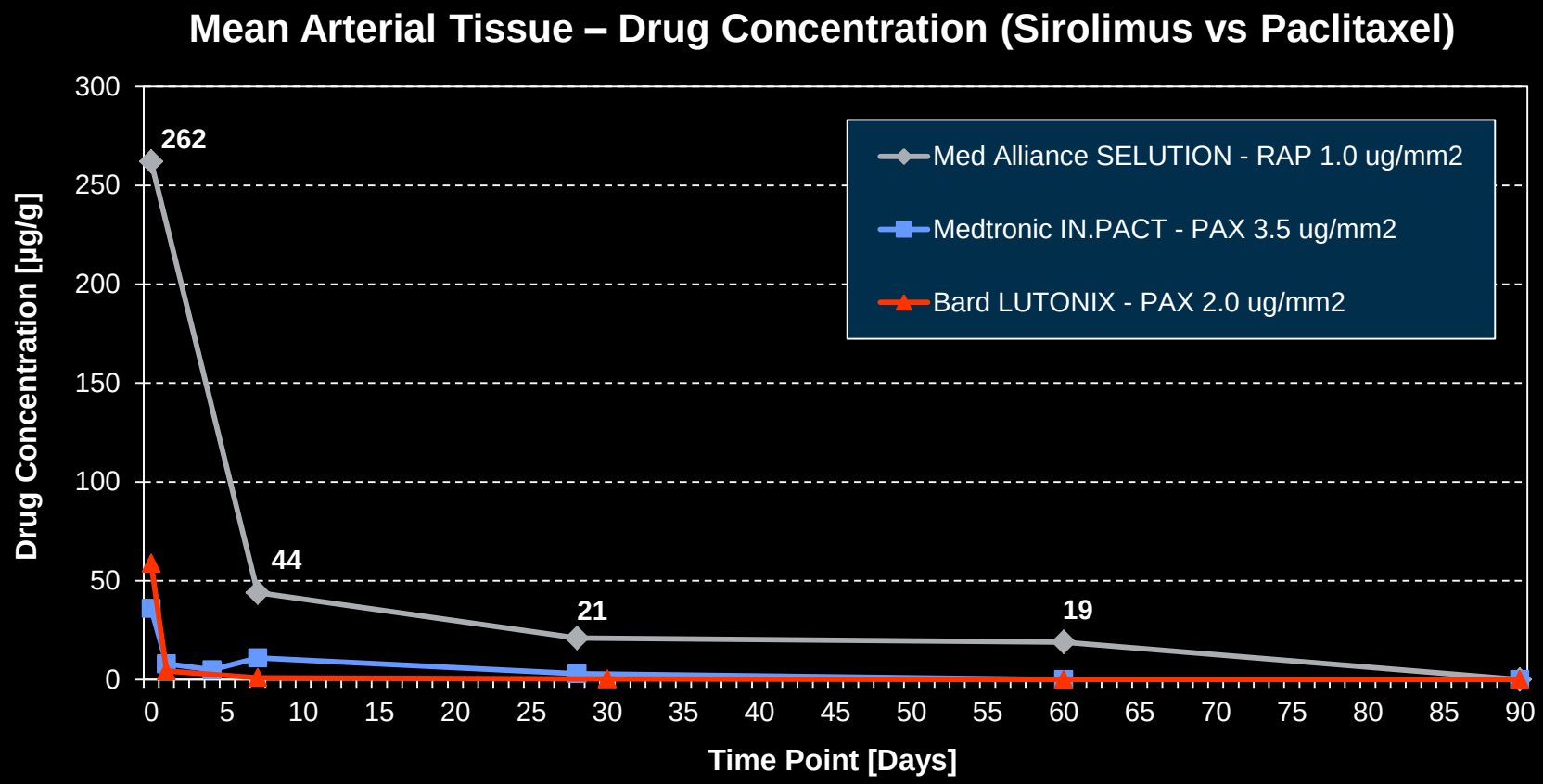
Med Alliance
SELUTION™ Sirolimus DCB





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

Med Alliance SELUTION™ PK Study



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

Peripheral FIH – SELUTION™ Fem-Pop Trial

Objective

To show non-inferiority of **SELUTION™ DCB** vs. **FDA approved DCB** in terms of safety and efficacy for treatment of Superficial Femoral (SFA) or Popliteal (PA) Artery lesions

Design

- Prospective, Multi-Center, Single Blinded, Randomized Controlled
- N=110 (55 in each arm)

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

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Coronary FIH - SELUTION™ ISR Trial

(incl small vessels & side branches)

Investigational Device	▫ SELUTION™ Sirolimus Coated Coronory Balloon (S-DCB)
Design	▫ Assess safety and efficacy of the MedAlliance sirolimus-eluting micro-reservoirs DCB (**SELUTION™**) in comparison with currently **approved paclitaxel DCB** in ISR, side-branch bifurcation lesions, and small (≤2.5 mm) vessels
Other Objectives	▫ Proof of efficacy ▫ Proof of non-inferiority vs. Paclitaxel DCB ▫ Collect data to obtain CE mark approval

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Sirolimus DCBs

- Potential to improve patient outcomes
  - *Efficacy*
    - Sirolimus has potential to reduce late lumen loss
    - Micro-reservoirs provide sustained release of Sirolimus – "*DES like*" but without leaving something behind
  - *Safety*
    - Cytostatic Sirolimus instead of cytotoxic Paclitaxel with higher tissue tolerance
    - Substantially reduced drug dose (especially in case of multiple, longer or overlapping balloons)
    - Reduced wash-off and less harmful to operators
  - *Healing*
    - Less inhibition of healing in target lesion and in distal tissue beds due to lower drug toxicity and reduced embolization of coating (e.g. potentially better wound healing in CLI patients)