Below the knee DCB
Where are we and what do we know?

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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.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott, Covidien/Medtronic
• Consulting (non-compensated)	• Covidien/Medtronic, Boston Scientific, Abbott
• Major Stock Shareholder/Equity	• Arsenal, Primacea, TissueGen, CV Ingenuity, Spirox, Scion Cardiovascular, Syntervention, Essential Medical
• Royalty Income	• None
• Ownership/Founder	• Innovation Vascular Partners, Consulting
• Intellectual Property Rights	• None
• Other Financial Benefit	• None

Primary IN.PACT DEEP Outcomes

Primary Efficacy	DEB	PTA	*p*
12-month LLL (mm) [1]	0.61 ± 0.78	0.62 ± 0.78	*0.950*
12-month CD-TLR [2]	9.2% (18/196)	13.1% (14/107)	*0.291*

Primary Safety	DEB	PTA	*p*
6-month Death Major Amputation or CD TLR	17.7% (41/232)	15.8% (18/114)	*0.021* (non-inferiority) *0.662 (superiority)*

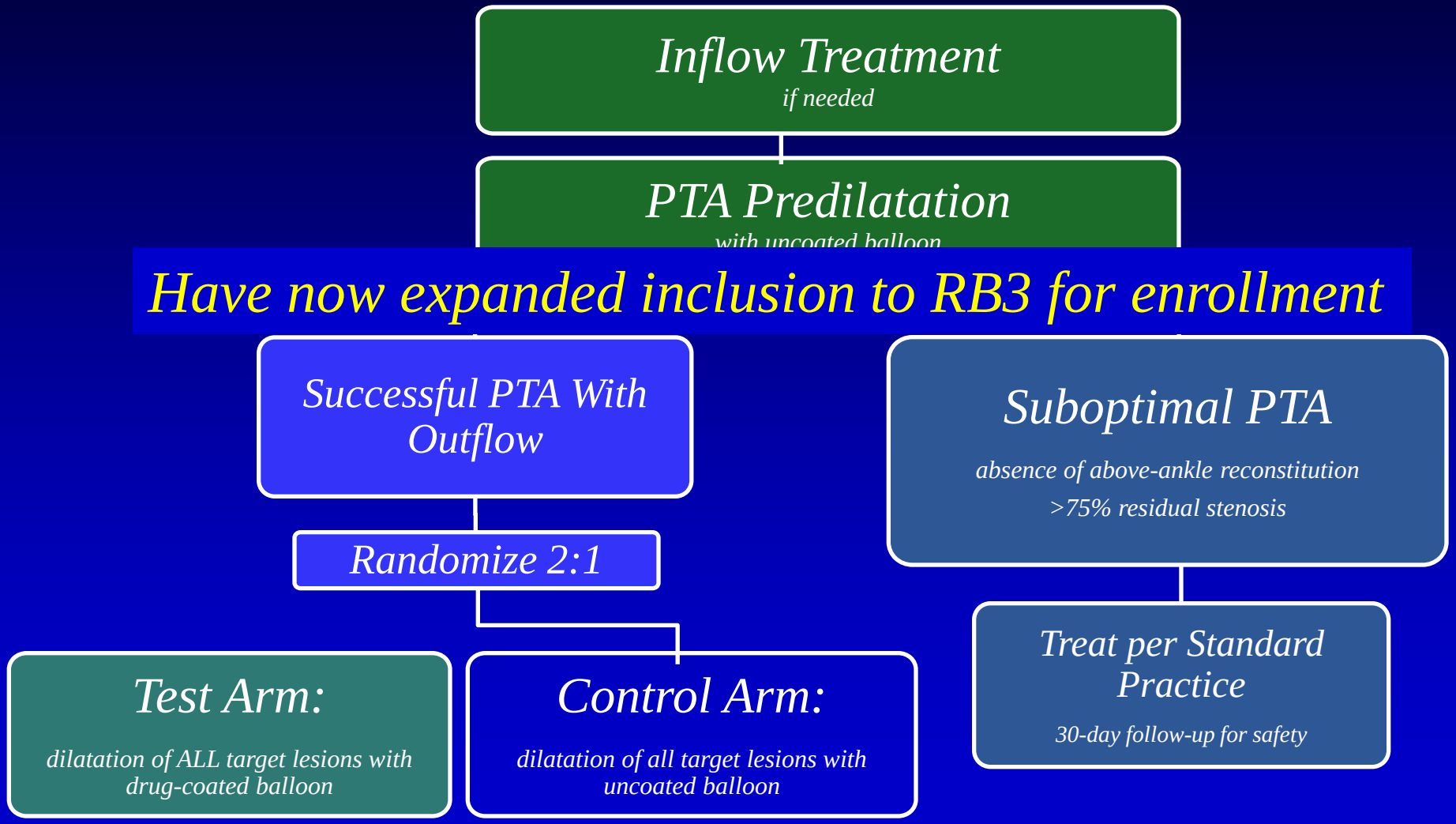
1. *Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)*
2. *Clinically driven TLR of the target lesion in the (major) amputation free surviving subjects at 12 months. "Clinically driven TLR" defined as any TLR of the target lesion associated with: a) deterioration of RC and / or b) Increase in size of pre-existing wounds and / or c) occurrence of a new wound(s), with b) and c) adjudicated by the Wound Healing Core lab*

Angio Cohort Outcomes

12-month Outcomes [1]	DEB	PTA	*p*
Mean Lesion Length (mm±SD)	59.1 ± 41.7	79.7 ± 74.6	*0.060*
Binary (50%) Rest. Rate (%)	41.0% (25/61)	35.5% (11/31)	*0.609*
Occlusion Rate (%)	11.5% (7/61)	16.1% (5/31)	*0.531*
Longitudinal Restenosis (%) [2]	62.7 ± 56.2	93.2 ± 60.8	*0.167*
Revalidated Lumen Loss [3]	**DEB**	**PTA**	***p***
12-month LLL (mm, mean ± SD)	0.51 ± 0.66	0.60 ± 0.97	*0.654*

1. *Angio Cohort, Corelab adjudicated. Angiogaphic Imaging 12-month FU compliance = 70.9% (DEB) vs. 71.4% (PTA)*
2. *Mean % of stenosis length vs. treated lesion length± SD (Angiographic Cohort, ITT)*
3. *As evaluated by additional angiographic core laboratory (Beth Israel Deconess Medical Center, Boston, MA) to confirm earlier analysis*

LEVANT BTK


Inflow Treatment
if needed
PTA Predilatation
with uncoated balloon
Have now expanded inclusion to RB3 for enrollment
Successful PTA With Outflow
Suboptimal PTA
absence of above-ankle reconstitution
>75% residual stenosis
Randomize 2:1
Treat per Standard Practice
30-day follow-up for safety
Test Arm:
dilatation of ALL target lesions with drug-coated balloon
Control Arm:
dilatation of all target lesions with uncoated balloon

Current Status of Lutonix 014 BTK IDE Study

- *48 Active Sites—Completed enrollment*
- *382 Randomized Subjects*
  - *287 have completed 6 month follow-up*
  - *222 have completed 12 month follow-up*
- *12 subjects with a Major Amputation (3.2%)*
- *The Data Monitoring Committee (DMC) has met over 11 times and unanimously recommended continuation of the study with no modifications.*

Information current as of 03.06.2017

BIOLUX

- RCT 1:1 Paseo DCB to Paseo PTA
  - 72 patients
- Endpoints 30 day, 6 month (angio) and 12 MAE
- 6 month patency DCB 82.9% vs PTA 73.9% (p=NS)

Zeller T, et al JACC Cardio Interv 2015 Oct 8 (12) 1614-22

Calcification†			—
None	19 (55.9)	31 (81.6)	0.018
Mild	6 (17.6)	4 (10.5)	0.501
Moderate	1 (2.9)	0 (0.0)	0.472
Moderate/severe	3 (8.8)	1 (2.6)	0.338
Severe	5 (4.7)	2 (5.3)	0.243
Moderate to severe	9 (26.5)	3 (7.9)	0.056
Thrombus present	0 (0.0)	0 (0.0)	>0.999
Treated lesion length, mm	113.1 ± 88.1, 24–351	115.0 ± 86.9, 39–295	0.960

Time-To-Event Estimates of Clinical Outcomes at Follow-Up

365 Days	DEB	PTA	p Value
MAE	13 (41.1)	14 (39.1)	0.957
Death	3 (9.4)	2 (6.0)	0.575
In CLI patients only	2 (8.6)	2 (7.9)	0.917
Amputation target extremity	8 (23.7)	9 (25.7)	0.988
Major	1 (3.3)	2 (5.6)	0.631
In CLI patients only	1 (4.3)	2 (7.1)	0.696
TLR			
Lesion based	12 (30.1)	15 (30.6)	0.805
Subject based	10 (34.9)	10 (30.0)	0.817
Clinically driven	9 (31.3)	9 (26.9)	0.805
TLR, subject based	5 (16.8)	6 (17.5)	0.881
TVR			
Target lesion thrombosis	0 (0.0)	1 (2.8)	>0.999
Patency loss (lesion based)*	7 (17.1)	13 (26.1)	0.298

180 Days	DEB	PTA	p Value
MAE	8 (24.8)	9 (25.0)	0.944
Death	2 (6.1)	1 (2.9)	0.499
In CLI patients only	1 (4.0)	1 (3.7)	0.921
Amputation target extremity	8 (23.7)	7 (19.6)	0.619
Major	1 (3.3)	2 (5.6)	0.631
TLR lesion based	6 (14.6)	10 (19.7)	0.460
Subject based	5 (16.8)	6 (17.5)	0.881
TVR	5 (16.8)	6 (17.5)	0.881
Target lesion thrombosis	0 (0.0)	1 (2.8)	>0.999
Patency loss (lesion based)*	7 (17.1)	13 (26.1)	0.298

IDEAS

- Small RCT DES vs DCB
- Primary endpoint angio patency at 6 months
- DES PP 28% vs DCB 42%

TABLE 3 Angiographic and Clinical Outcomes: QVA and Outcome Measures at 6 Months (ITT Analysis)

	DES Group	PCB Group	p Value
QVA analysis			
Post-procedure stenosis, %	9.6 ± 2.2	24.8 ± 3.5	<0.0001
6-month vessel stenosis, %	50.6 ± 6.6	54.3 ± 8.1	0.73
Late lumen loss, mm	1.35 ± 0.2	1.15 ± 0.3	0.62
Length of >50% restenosis, cm	3.6 ± 1.5	4.3 ± 1.6	0.16
Outcome measures			
Binary restenosis >50%	7/25 (28)	11/19 (57.9)	0.0457
Positive remodelling, late lumen loss <0 mm	0/25 (0)	3/19 (15.8)	0.07
Target lesion revascularization	2/26 (7.7)	3/22 (13.6)	0.65
Rutherford class at 6 months	1 (1, 2.75)	1 (1, 3.5)	0.87

Values are mean ± SD, n/n (%), or median (interquartile range).

Siablis D, et al JACC Cardio Interv 2014 Sep 7 (9): 1048-56

Future trials

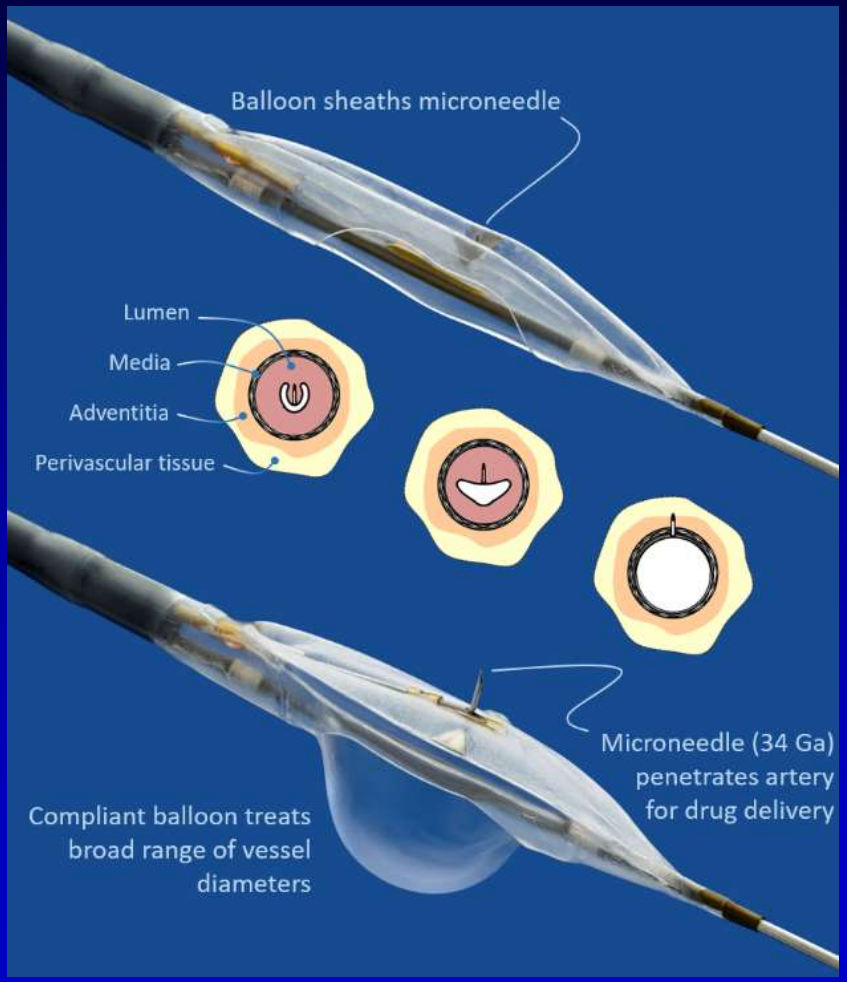
- BSC Ranger BTK
  - FDA approaved IDE Fem-pop study
- Spectranetics Stellarx BTK
- Interest in limus driven therapy

Possible Reasons for Failed Trials for DCB in BTK

- Drug does not work in BTK lesions
- Insufficient drug dosing in BTK studies
- Improper DCB sizing or insufficient duration of therapy
- PTX delays wound healing
- Loss of drug due to transit time
- Calcification impedes drug delivery
- Recoil effect in small vessels >>>Drug effect
- Endpoints have not been validated
- Heterogeneity of treatment in multi-center studies
  - Procedural differences
  - Differences in post-procedural wound care

Injection platforms

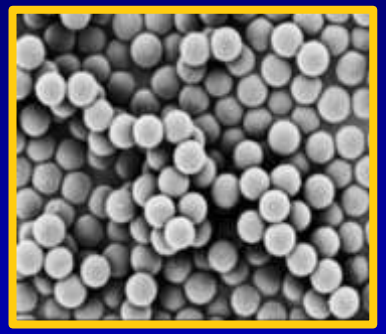
- Bullfrog device (Merkatur, USA)
- TANGO
  - 60 pt CLI
    - 20 low/20high/20 control
  - 6 mo clinical and angiographic
  - 12 mo clinical and DUS outcomes
- LIMBO
  - 120 pt CLI
  - 6 mo clinical and angiographic endpoint



- Proteon (Waltham, MA)
- Vonapanitase (elastase)
- Injection through Bullfrog device
- Destroys elastase thereby halting vaso-motor function
- Theory no recoil may have positive impact on clinical outcome
- Currently in Phase III study

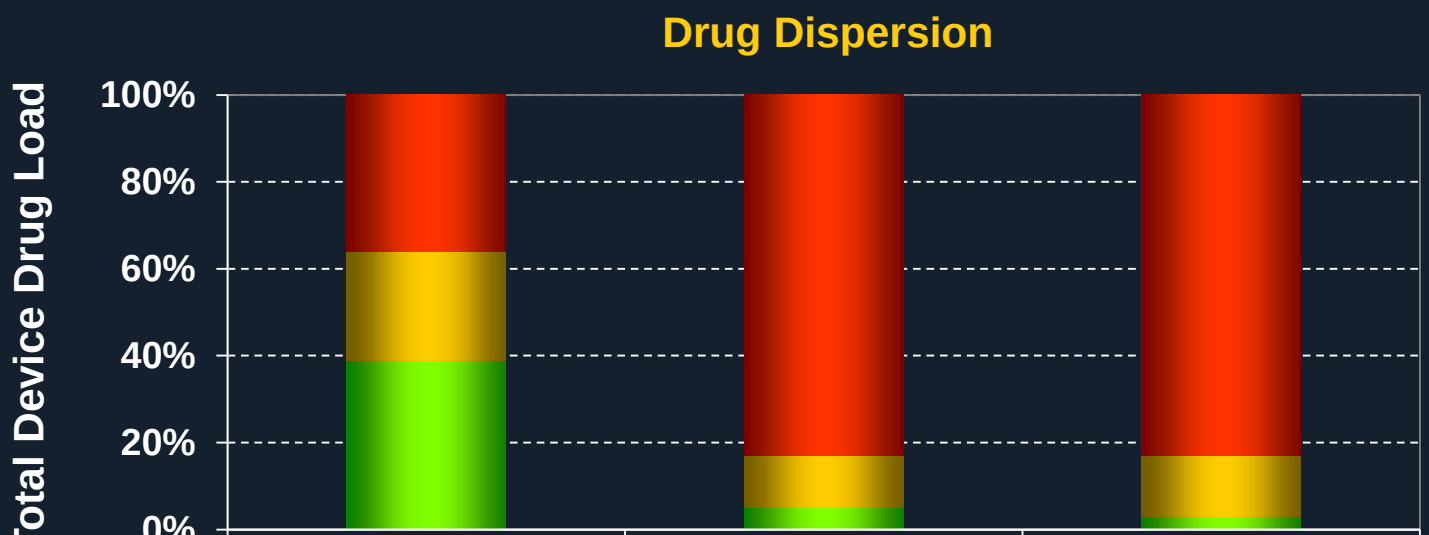
Med Alliance
SELUTION™ Sirolimus DCB

- *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*

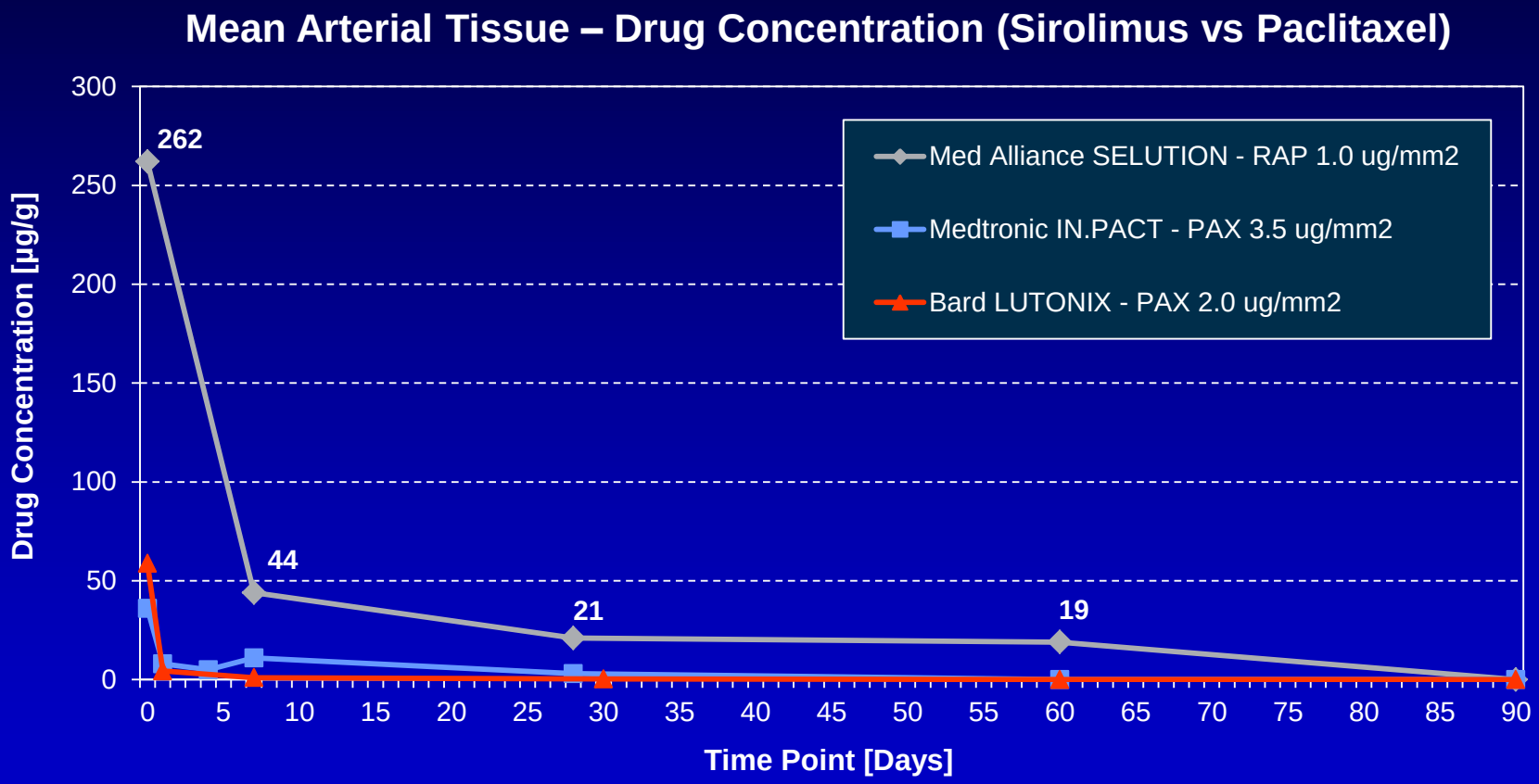
Med Alliance
SELUTION™ Sirolimus DCB



	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™ PK Study



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

Areas For Improvement

- Vessel preparation
- Improved balloon platform for optimal drug delivery
- Optimal Drug Dosing
- Optimal Drug Application
  - Crystalline>>Amorphous??
  - Nanoparticles??
  - Limus vs taxol
- Appropriate trial design
  - Primary Endpoint - Patency vs Wound healing?
  - Patency easier to measure and reflects device performance
  - Wound healing is true desired outcome, but influenced by several factors not related to device being studied

What should we choose?

- All interventions afford AFS in short focal lesions
  - BMS primary patency poor
  - Focal DES excellent primary patency compared with BMS
- DCB (IN-Pact DEEP)failed in largest trial for below knee use
  - Principal studies using DCB still may be appealing but given the data?
- Current review of data supports revascularization for infra-popliteal disease though choice is at discretion
  - All DCB BTK data remain mired in the definitions and endpoints
  - Till this is well defined and accepted, seems PTA alone is best option
- Limus drugs appealing in early stage evaluations