The Evolution of SFA Treatment Strategy with IN.PACT DCB

JOS VAN DEN BERG, MD
OSPEDALE REGIONALE DI LUGANO
LUGANO, SWITZERLAND

RAPHAEL COSCAS, MD
HÔPITAL AMBROISE PARÉ
BOULOGNE BILLANCOURT , FRANCE

ROBERTO FERRARESI, MD
HUMANITAS GAVEZZENI
BERGAMO, ITALY

CONTROVERSIES & UPDATES IN VASCULAR SURGERY

Medtronic
Further, Together

Industry Symposium Supported by Medtronic

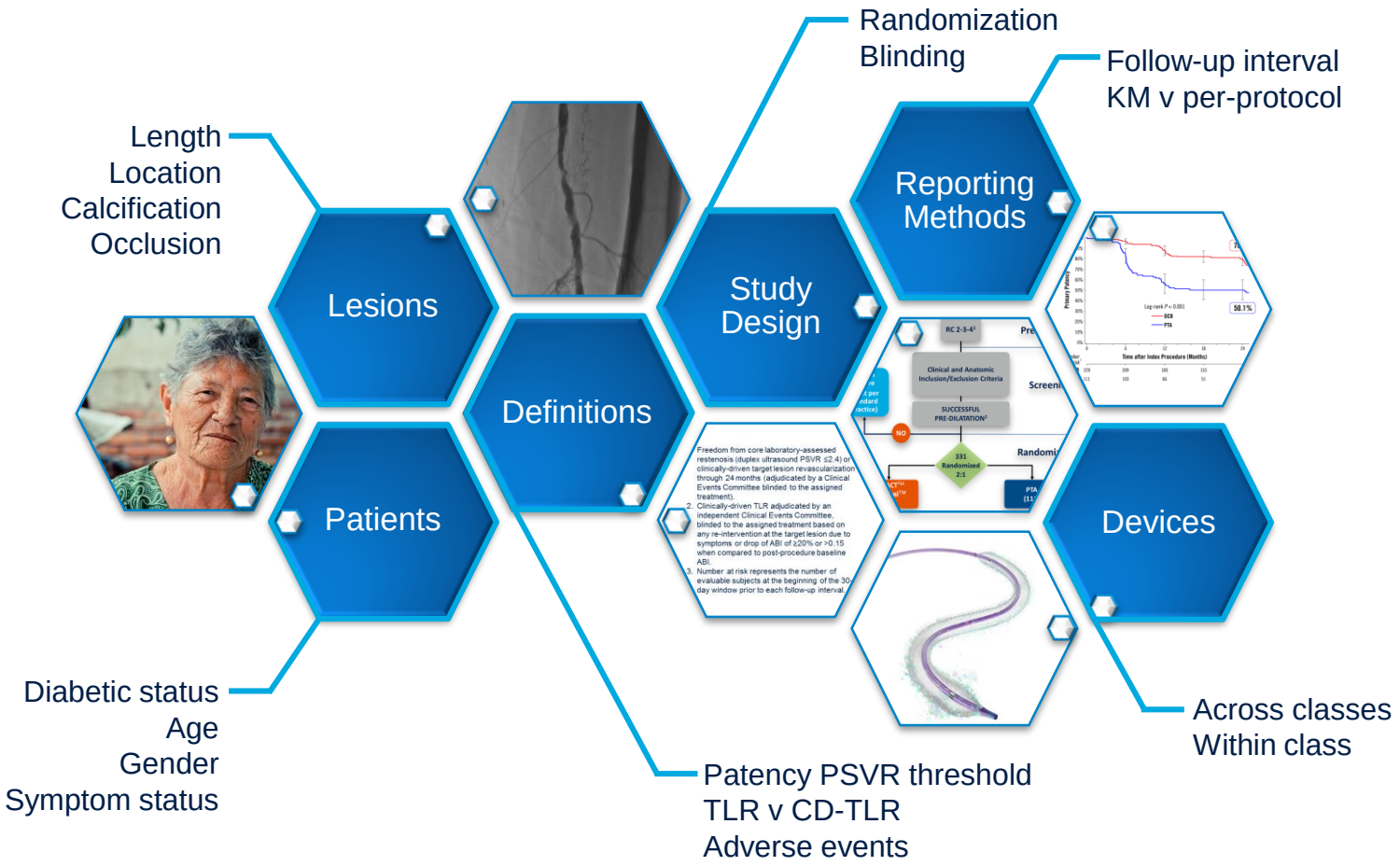
Drug-Coated Balloons

Seeing the Differences through the Mechanisms of Action

RAPHAEL COSCAS, MD
HÔPITAL AMBROISE PARÉ
BOULOGNE BILLANCOURT , FRANCE

Medtronic
Further, Together

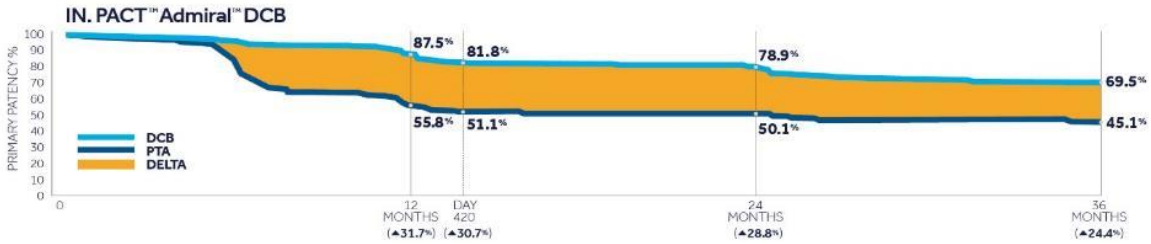
The Challenge in Interpreting Data:
Variables Obscure Comparisons of Trials and Devices



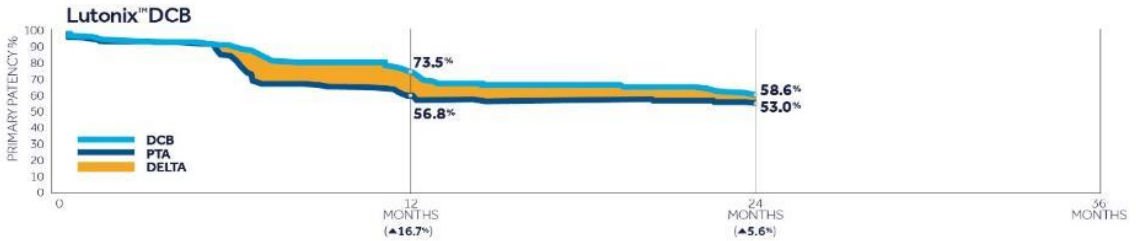
DCB Pivotal Trial Comparisons:

Primary Patency of FDA-Approved DCBs[1]

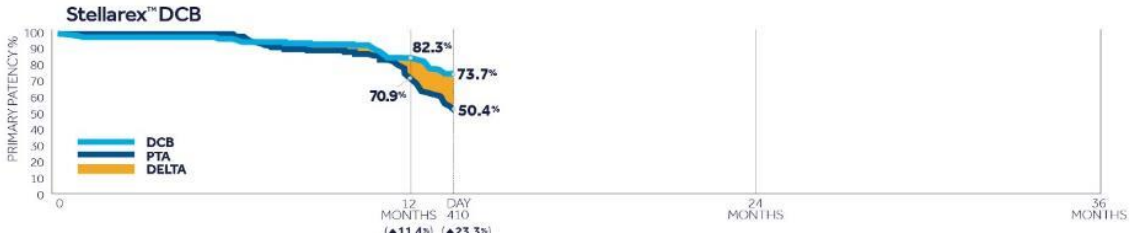
IN.PACT SFA



LEVANT II



ILLUMENATE Pivotal RCT



How does DCB design influence mechanism of action?

1. Primary patency and target lesion revascularization (TLR) rates may be calculated differently, and therefore may not be directly comparable; chart is for illustration only.
2. IN.PACT SFA Trial values represent IN.PACT™ Admiral™ DCB arm as evaluated by 36-mo Kaplan-Meier, patency defined as PSVR ≤ 2.4 and freedom from TLR defined here as clinically-driven TLR; IN.PACT Admiral Instructions for Use M052624T001 Rev 1F.
3. LEVANT II values represent Lutonix 035 arm as evaluated by 730-day Kaplan-Meier, patency defined as PSVR ≤ 2.5 and freedom from TLR defined here as all TLR; Lutonix 035 Instructions for Use BAW1387400r3..
4. ILLUMENATE RCT Pivotal values represent Stellarex as evaluated by 410-day Kaplan-Meier, patency defined as PSVR ≤ 2.5 and freedom from clinically-driven TLR; Stellarex Instructions for Use No. P011966-C Rev 07/2017.

Design Summary of the FDA-Approved DCBs

Excipient is critical in delivering and sustaining paclitaxel in the tissue.

- All three devices use paclitaxel dosing significantly lower than other medical applications[1]
- Excipient is unique to each DCB

	Drug (Dose)	Excipient
IN.PACT™ Admiral™ DCB	**Paclitaxel (3.5µg/mm²)**	**Urea**
Lutonix™* 035 DCB	Paclitaxel (2.0µg/mm²)	Polysorbate-Sorbitol
Stellarex™* DCB	Paclitaxel (2.0µg/mm²)	Polyethylene Glycol

1. Ng, Vivian. Eur J Clinical Investigation 2015;45(3):333-345

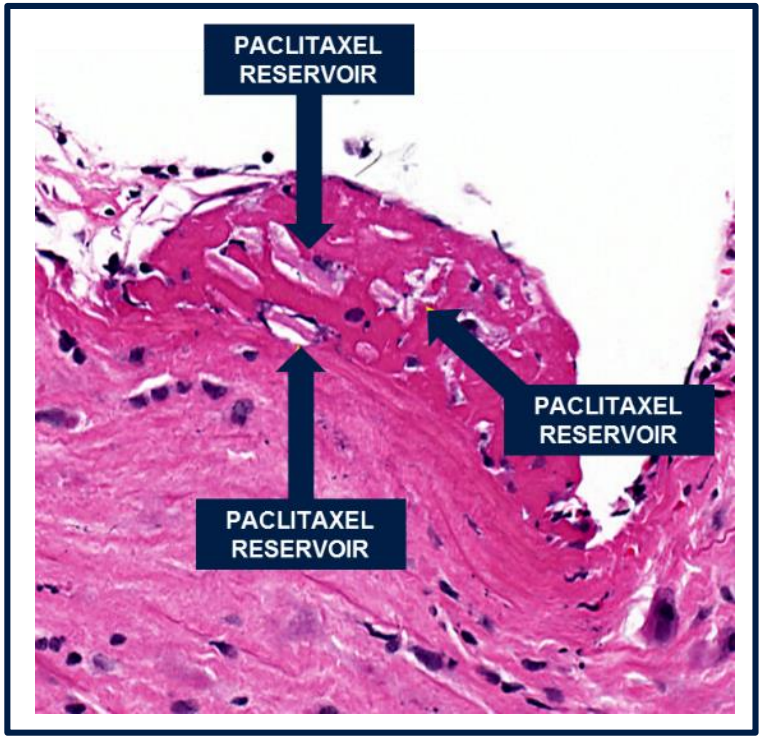
Solid-Phase Drug Enables Sustained Effect

Without a permanent scaffold like DES, DCB must transfer drug to the tissue in a manner that enables a long-term effect on restenosis.

1. **Solid-phase drug delivery**
   The DCB delivers solid-phase paclitaxel to the vessel, establishing reservoirs of drug

2. **Sustained drug availability**
   These reservoirs provide a source of soluble drug which is available to exert an anti-proliferative effect on tissue

3. **Prolonged anti-proliferative effect**
   With extended drug availability, the anti-proliferative effect of paclitaxel is prolonged



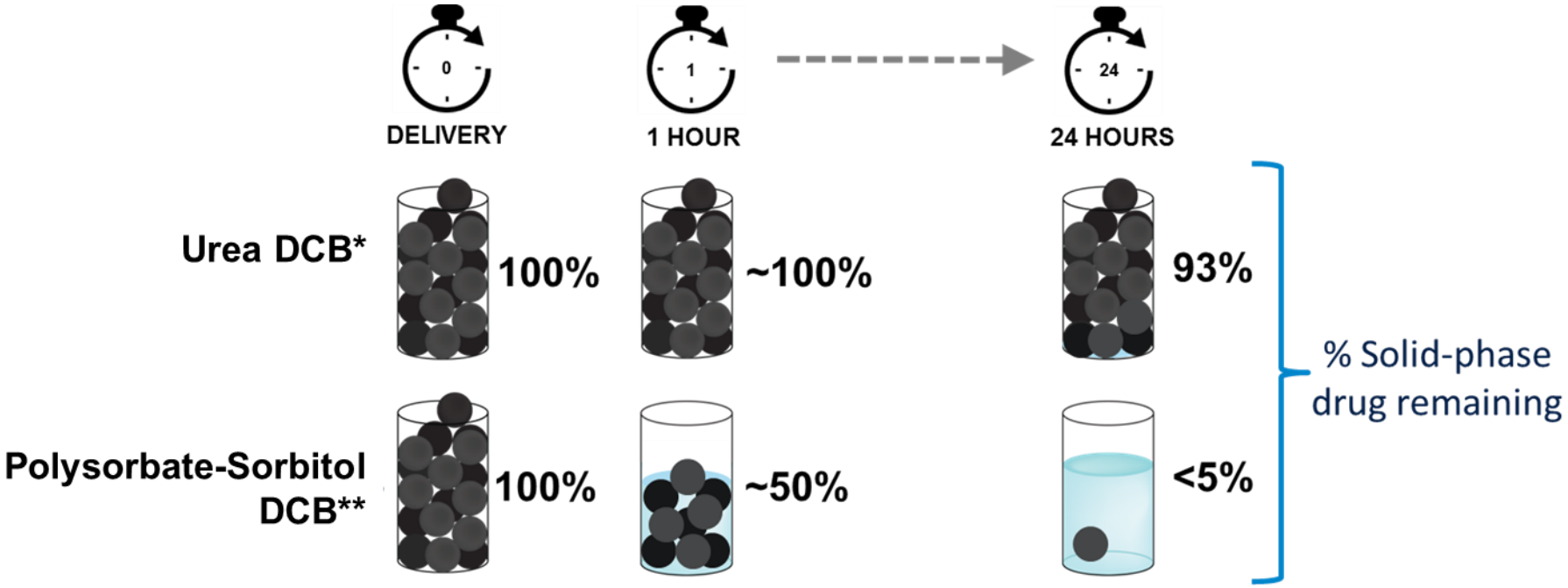
Representative micrograph 28-days post drug delivery.[1]

1. Data on file at Medtronic.

1 Solid-Phase Drug Transition

Transition from solid- to soluble-phase is different through 24 hours.[1-2]

- Bench-top porcine plasma model reveals that both devices transfer solid-phase paclitaxel from the DCB
- Subsequent transition from solid-phase to soluble-phase occurs at different rates
- At 24 hours, IN.PACT™ Admiral™ DCB retains more drug in solid-phase than Polysorbate-Sorbitol DCB**

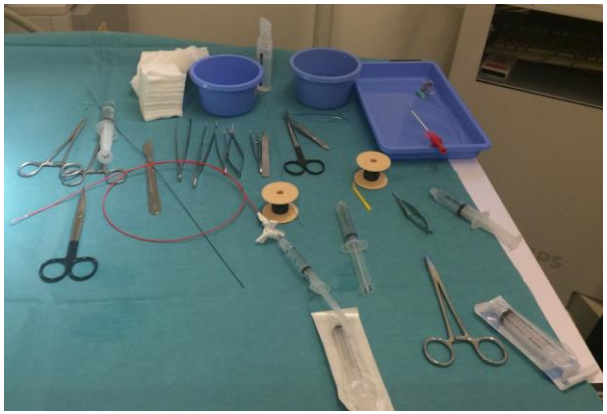


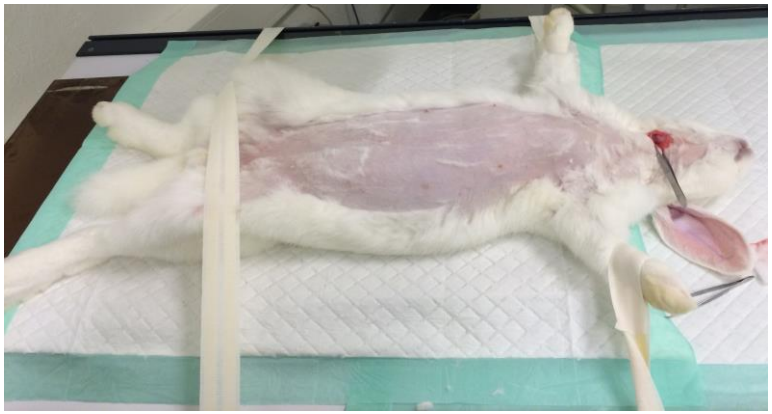
1. Data on file with Medtronic.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.

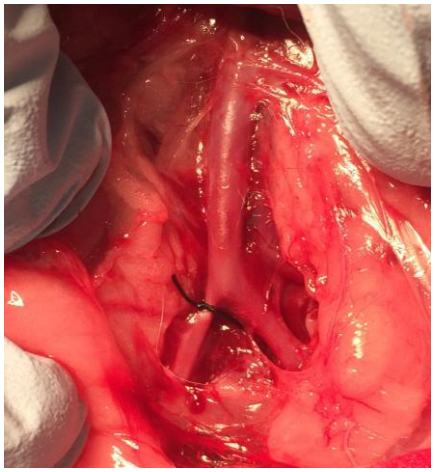
* IN.PACT™ Admiral™ DCB

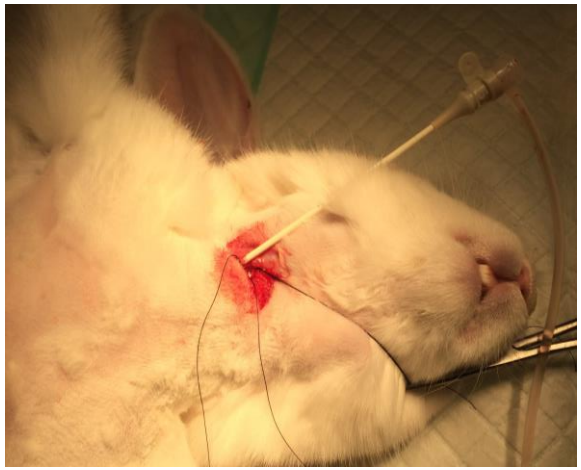
** Lutonix™* 035

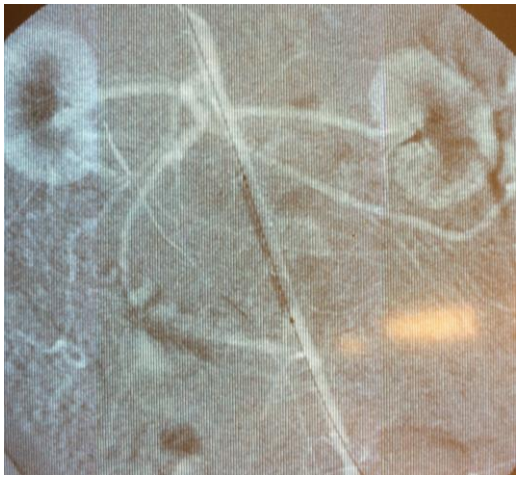
Personal experimental approach







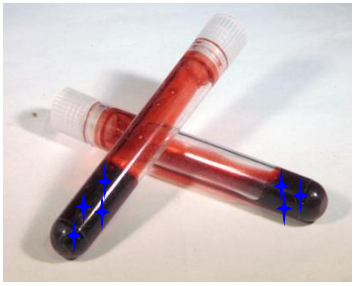


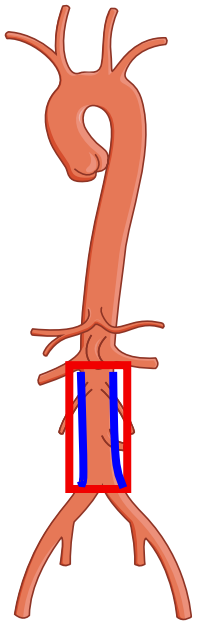


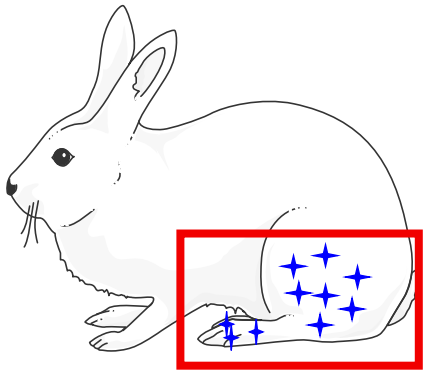
Boitet A (Master of Science), Coscas R. Unpublished data 2017

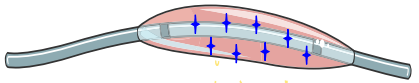
Personal experimental approach

- Sacrifice H2
- Samples
  - Aorta
  - Plasma
  - DCB
  - Muscles
    - Thigh: TFL, Vastus lateralis
    - Leg: Tibialis cranialis





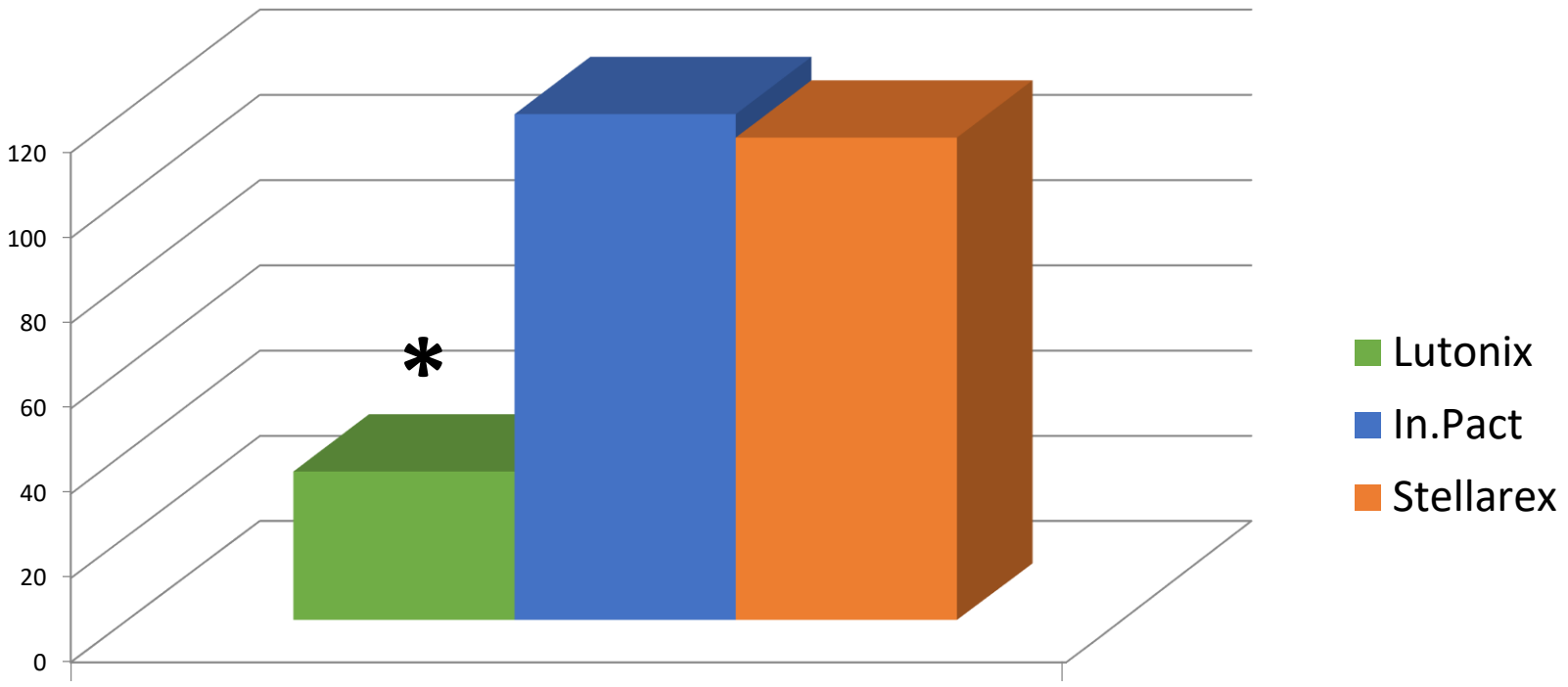




- Blinded dosage PTX by high pressure liquid chromatography

Boitet A (Master of Science), Coscas R. Unpublished data 2017

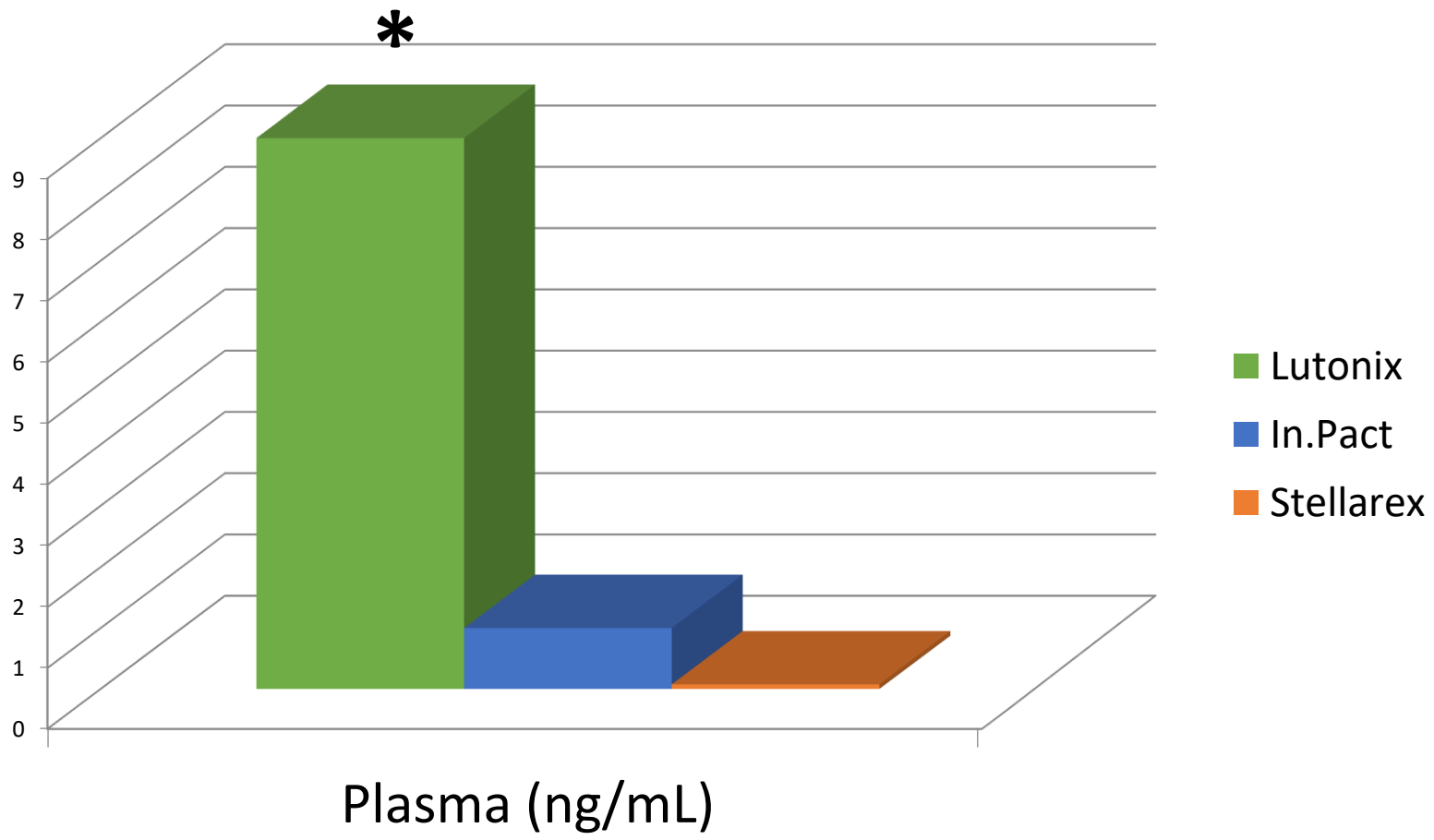
PTX in the aortic wall



Aorte (ng/mg)

Boitet A (Master of Science), Coscas R. Unpublished data 2017

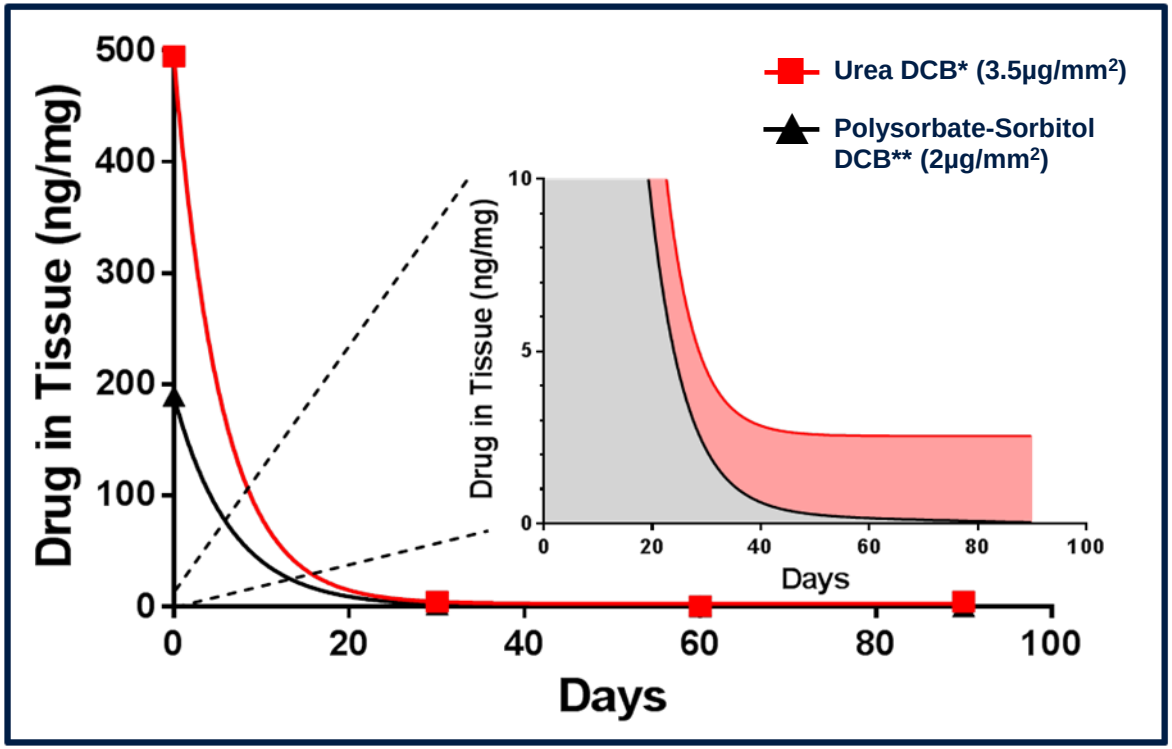
PTX in the Plasma



Boitet A (Master of Science), Coscas R. Unpublished data 2017

2 Sustained Drug Availability

Higher percentage of solid-phase drug is associated with higher drug tissue concentration through 90 days.[1-2]



In vivo porcine model used to quantify sustained drug residence in tissue

1. Data on file with Medtronic; Study PS747.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.

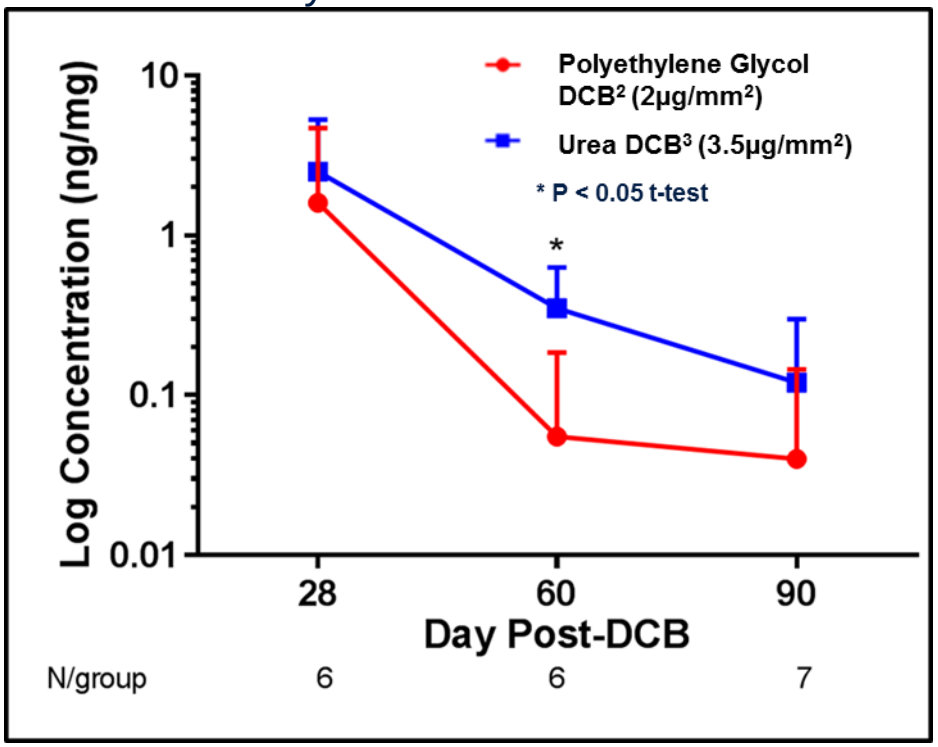
* IN.PACT™ Admiral™ DCB

** Lutonix™* 035

2 Sustained Drug Availability

Different tissue drug concentrations also demonstrated in a similar head-to-head experiment between devices of different drug dosage.[1]

Healthy Porcine Arterial Model



In vivo porcine model used to quantify sustained drug residence in tissue.

1. Data on file with Medtronic; Study PS767.
2. Stellarex™* DCB
3. IN.PACT™ Admiral™ DCB

2 IN-STENT Restenosis Animal Study Plan

Purpose

To compare efficacy of IN.PACT™ Admiral™ DCB to Stellarex™* drug coated balloons (DCBs) with in-stent restenosis (ISR) lesions in a Yucatan swine model

Objective

Execute a controlled restenotic model, treat with DCB and assess qualitative vascular angiography (QVA) and optical coherence tomography (OCT) imaging at 60 and 90 day post DCB treatment with drug in tissue determination at 90 days

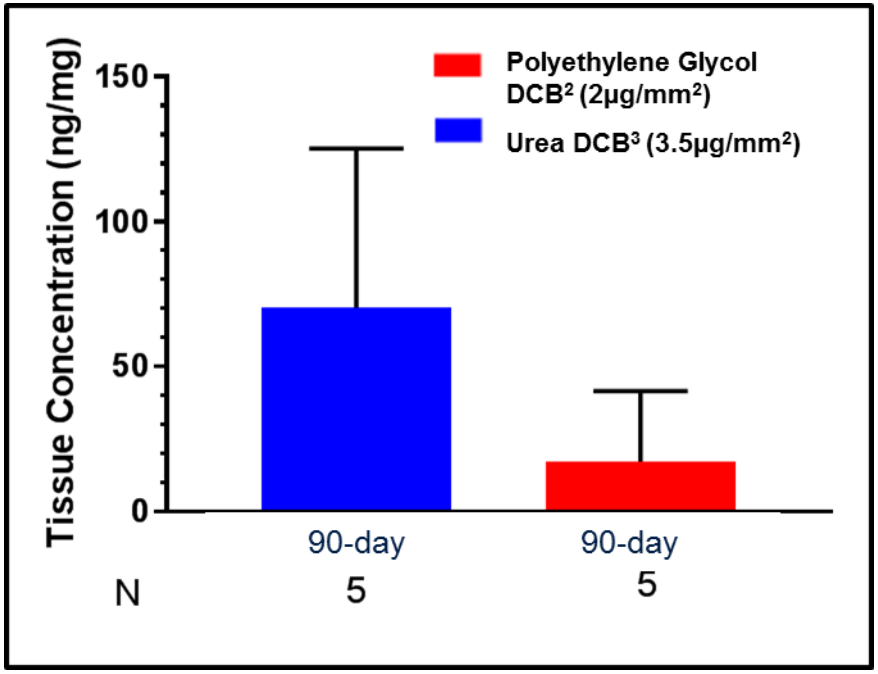
Methods

- Creation of ISR model in swine peripheral vasculature by injuring the target artery with angioplasty and stenting.
- 28 days post-stent implantation, treat the target vasculature with DCB, (Treatment Day 0)
- Image treated site at Day 0, Day 60 and Day 90
- Sample tissue for drug content at 90 days post treatment

2 Sustained Drug Availability

Different tissue drug concentrations also demonstrated in similar head-to-head experiment between devices of different drug dosage.[1]

Healthy Porcine Arterial Model

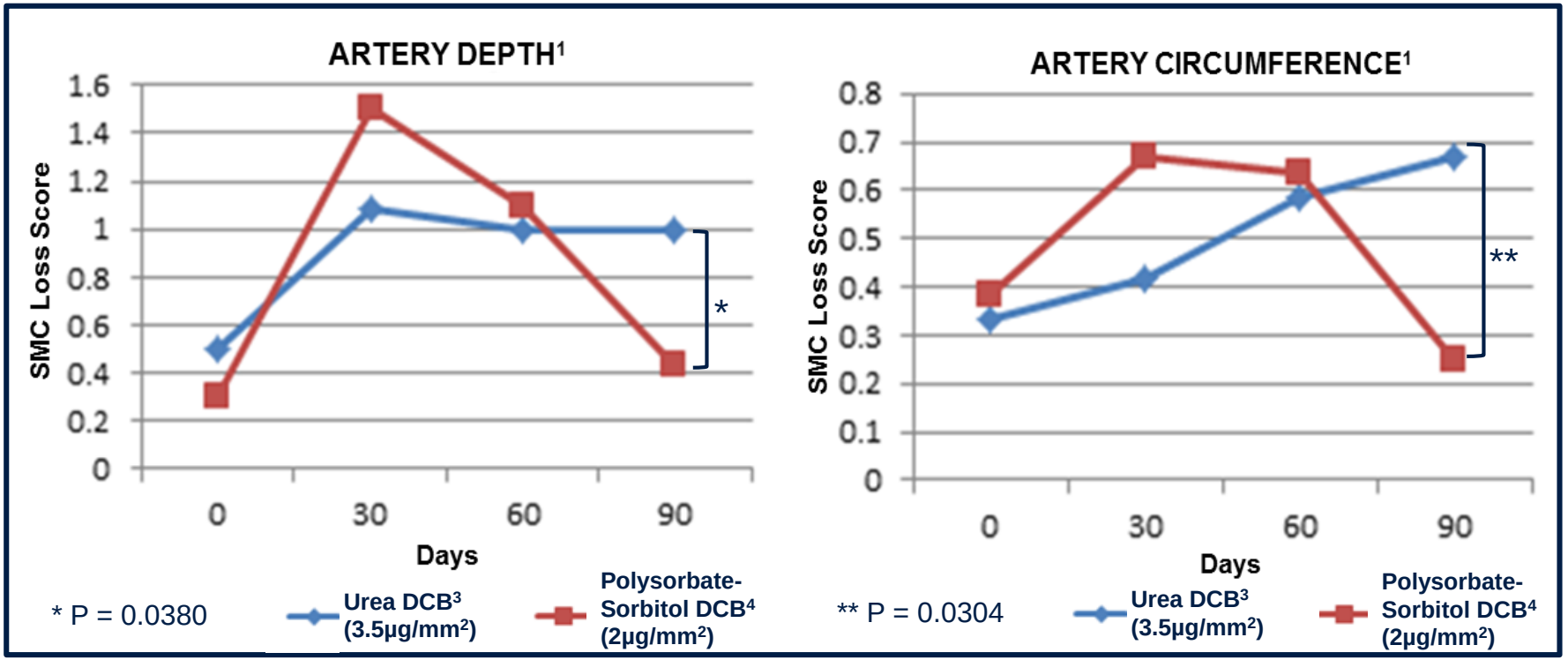


Higher input drug concentration facilitates greater long-term concentrations.

1. Data on file with Medtronic; Study PS781.
2. Stellarex™* DCB
3. IN.PACT™ Admiral™ DCB

3 Prolonged Anti-Proliferative Effect

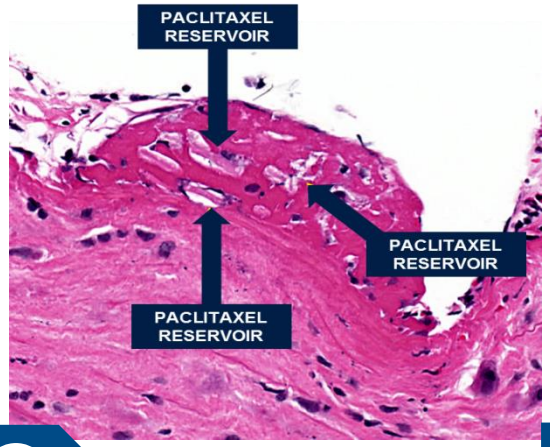
Higher percentage of solid-phase drug is associated with continued trend of smooth muscle cell loss through 90 days.[1-2]



In vivo porcine model used to quantify smooth muscle cell loss through 90 days

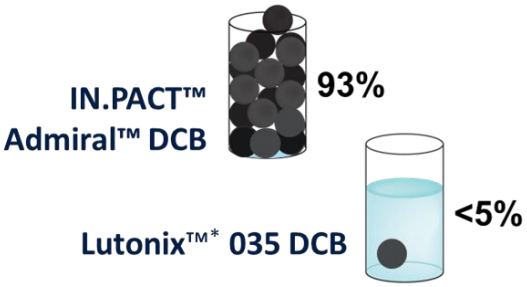
1. Data on file with Medtronic; PS747.
2. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.
3. IN.PACT™ Admiral™ DCB
4. Lutonix™* 035

Keys to Sustained Effect



1

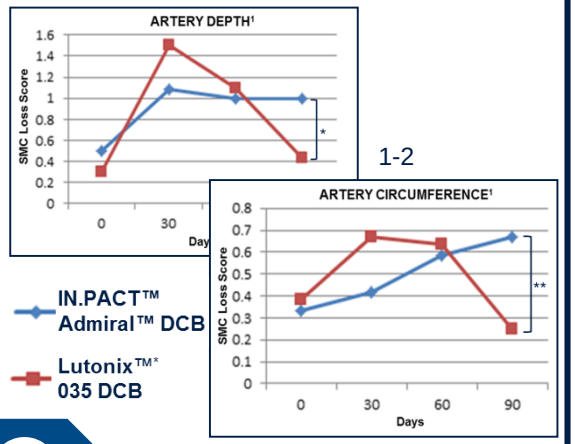
Solid-phase drug delivery



Solid-phase paclitaxel at 24h[1-2]

2

Sustained drug availability



3

Prolonged anti-proliferative effect

1. Data on file with Medtronic. Ninety-day differences in artery depth delta and artery circumference demonstrate p=0.0380 and p=0.0304, respectively (right panel).
2. Virmani R, “Arterial wall response to drug-coated balloon use” presented at Charing Cross, London 2016.

Conclusions

- IN.PACT™ Admiral™ DCB demonstrates durable results through three, and now, four years, and consistent results across numerous clinical scenarios[1]
- DCBs as a class demonstrate promising results, though clinical observations suggest performance is device-specific[2-4]
- Performance of IN.PACT™ Admiral™ is a product of its unique design which enables transfer of solid-phase paclitaxel to sustain an anti-proliferative effect[5]

1. Presented by Schneider, P, VIVA Las Vegas, USA 2017.
2. Tepe G, et al. Circ 131:495-502 (2015).
3. Rosenfield K, et al. NEJM 373:145-53 (2015).
4. Schroeder H, et al. Circ 2017;135:2227-2236.
5. Virmani R, "Arterial wall response to drug-coated balloon use" presented at Charing Cross, London 2016.