Are all DCB equal?
IN.PACT Admiral™ Drug Coated Balloon

**Platform**
- Invatec®
- Admiral™ PTA balloon
- 4 - 7 mm diameters
- 40, 60, 80, 120 mm lengths

**Drug**
- Paclitaxel
- Hydrophobic, lipophilic, proven anti-proliferative drug, 3.5 µg/mm²

**Excipient**
- Urea
- Hydrophilic, naturally occurring, nontoxic

**Coating process**
- Medtronic
- Uniformity + stability + release
- Controlled and scalable
DCB mechanism of action facilitates the transfer of PTX deep into vessel

IN.PACT balloon matrix coating:
- Paclitaxel
- Urea - excipient that controls drug release

DCB inflation:
- Matrix coating contact with the blood
- Urea hydrates causing the release of paclitaxel
- Paclitaxel binds to the wall due to its hydrophobic and lipophilic properties

Paclitaxel penetration:
- Through vessel wall deep into the media and adventitia
- Interferes with the causes of restenosis
- Can remain in the vessel wall for over 180 days at therapeutic levels

1Melder, Robert. DEB Science Presentation in Brazil 2012.
Paclitaxel prevents cellular division and replication, providing a strong anti-restenotic effect

Paclitaxel (Cytotoxic)  
*Interferes with cell division*

Rapamycin (Cytostatic)  
*Interferes with cell growth*

Cytotoxic drugs halt cellular replication cycle, inducing apoptosis

Cytostatic drugs hold a cell in G₀ phase, arresting growth
Paclitaxel concentrations following treatment suggest both safety and efficacy

Tissue
- Detectable levels of drug up to 180 days in both arms (therapy dose and safety margin)

Plasma
- Drug concentrations drop 50% within the first 30 min
- No drug quantified after 48 h at nominal dose

Safety Margin=3x dose

**Porcine ilio-femoral model**
Histology images show sustained retention of low drug levels for extended neointimal inhibition.

Paclitaxel crystals are released as urea hydrates.

Crystals are embedded into arterial wall and sequestered by tissue.

Embedded crystals provide extended drug release to surrounding tissue.

Sections shown are stained by Hematoxylin & Eosin (H&E).
Paclitaxel offers a wide therapeutic window

- Dose dependent response up to ~ 3-4 µg/mm² (effective dose) and wide stable therapeutic window hereafter up to 10 µg/mm²
- Neither prolonged inflation times (2x60 seconds) nor overdosing up to 10 µg/mm² have led to statistically significant (and clinically relevant) differences in neointimal inhibition or local toxic effects.
- Uniform endothelialization of stent struts has been shown to be similar to control benchmark (std PTCA)

Therapeutic range 2-4 µg/mm²

An excipient supports the uptake of drug by vessel tissue

1. Acts as a molecular spacer to increase paclitaxel surface exposure
2. Facilitates paclitaxel transfer through its hydrophilic properties
3. IN.PACT Admiral DCB uses Urea as the excipient
Medtronic’s proprietary coating technology provides reliable and uniform drug delivery

**DURABLE**
Balloon coating in semi-inflated shape:
~ 60-70% of dose protected within balloon folds¹

**UNIFORM**
Longitudinal Coating Thickness Uniformity+/- 6%
Circumferential Coating Uniformity +/- 2%

¹experimental data on file at Medtronic
IN.PACT: Site specific therapeutic dose drug delivery

- DCB advancement
- DCB inflation
- DCB retrieval

~ 20% of drug lost during DCB delivery to the target lesion (in-vitro/in-vivo studies)*

~ 20% of Drug delivered to the vessel wall (in-vitro studies)*

~ 20% found on balloon surface after removal (in-vitro / in-vivo studies)*

~ 40-50% wash-out

*Data on file at Medtronic (GLP Study FS208; In Vitro Report RE-11050-001; GLP Study PS516)
IN.PACT DCB Technology Summary

- DCB design objective: restenosis inhibition while preserving future therapeutic options
- Paclitaxel/excipient formulation can enhance rapid paclitaxel transfer to the vascular wall with sustained levels
- Excipient balances paclitaxel’s hydrophobic properties and facilitates arterial wall drug transfer
- Coating technologies with specific excipients jointly support transfer efficiency
- Differences in any/all of these attributes can affect DCB clinical performance