iVascular
therapies for living

essential

Paclitaxel-eluting peripheral dilatation balloon

Drug Eluting Balloon (DEB)

The therapy

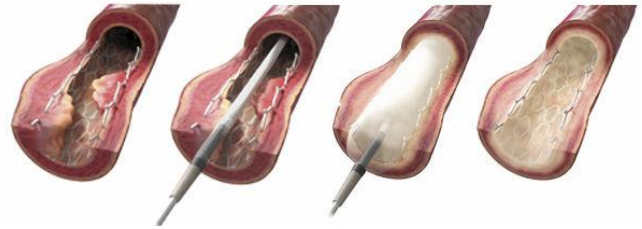
vascular essential

Objective

Inhibition of proliferation of smooth muscle cells and neointimal hyperplasia in the injury under treatment

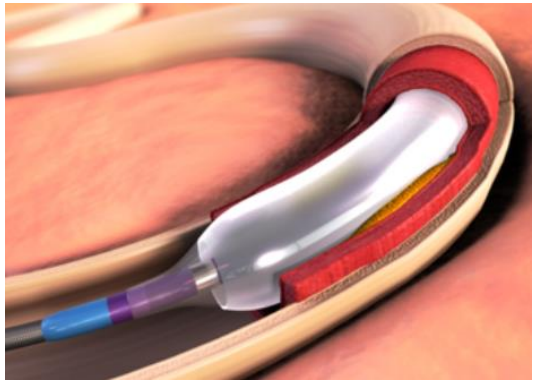
Clinical use

Cases where angioplasty with bare stent or DES is not a feasible alternative



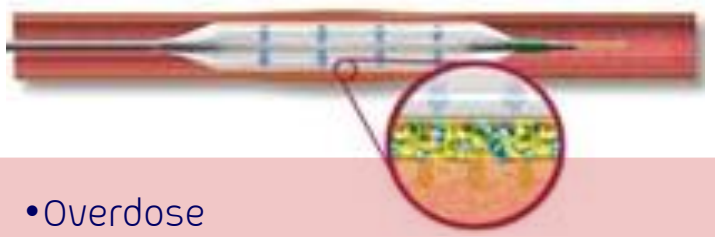
Benefits

- ✓ Prompt drug release without the need of polymer
- ✓ Prevents chronic inflammation
- ✓ After the procedure, nothing remains in the vessel
- ✓ Reduction of the dual antiplatelet treatment
  - Patients allergic to drugs
  - Patients expected to undergo future surgeries
  - Patients at risk of quitting treatment



Drug Eluting Balloon (DEB)

Key features

	NAVIGATION	INJURY	DOWNSTREAM
PROS	•Low profile •Durability •Light solubilization of the coating	•Fast drug absorption •Drug uniformity and dose •Drug retention vs. time •Drug crystallinity	
			
CONS	•Particle release •Delamination	•Overdose •Coating not prepared •High adhesion to balloon •Drug in amorphous state	•Particle loss

Elements

1. Drug
2. Dose
3. Excipient
4. Drug / excipient ratio
5. Balloon shape before coating
6. Crystalline structure
   - Impact on pharmacological efficacy
7. Coating technology
   - Transfertech
8. Catheter design
   - Pushability & trackability
   - Radiopaque markers
   - Tip
9. Inflation time
10. Available sizes and references
11. Safety, Efficacy and Pharmacokinetics
    - Preclinical study

1. Drug: PACLITAXEL

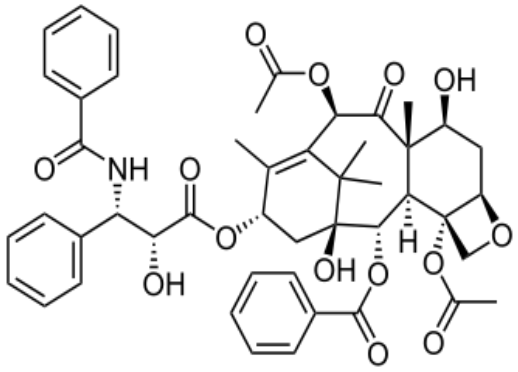
- **Strong inhibition of stenosis:** Blocks proliferation and migration of smooth muscular cells, fibroblasts and inflammatory cells. Blocks secretion of ECM (extracellular matrix).

- **Highly lipophilic**: Fast and high **absorption**. Bonds to the tissue in target locus and remains after washing. (Limus: limited lipophilicity).

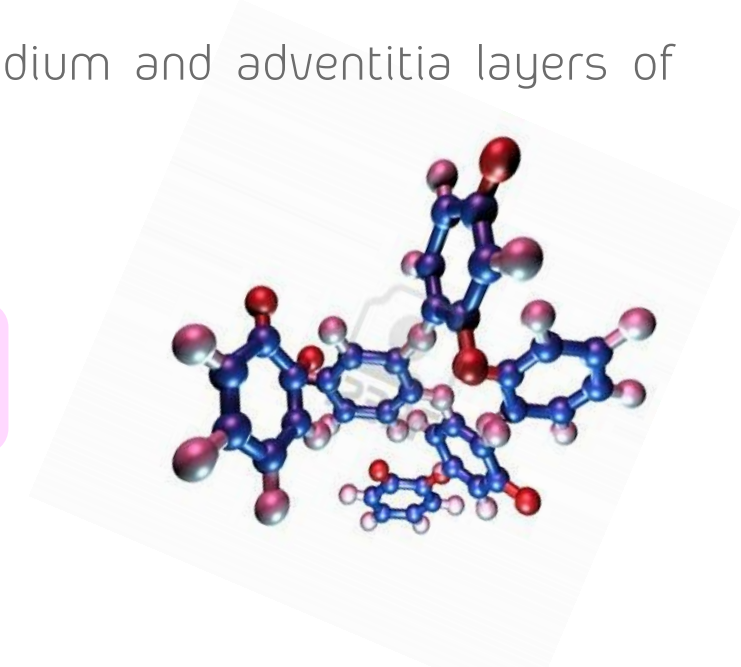
- **Specific cellular receptors. Diffuses** from endothelial surface to medium and adventitia layers of arterial wall. (Limus: low number of receptors)

Paclitaxel

$C_{47}H_{51}NO_{14}$



PACLITAXEL Vascular therapies for living



2. Dose: 3 µg/mm²

Therapeutic window: between **1 – 9 µg/mm²**

iVascular therapies for living

2,5 – 3,5 µg/mm²

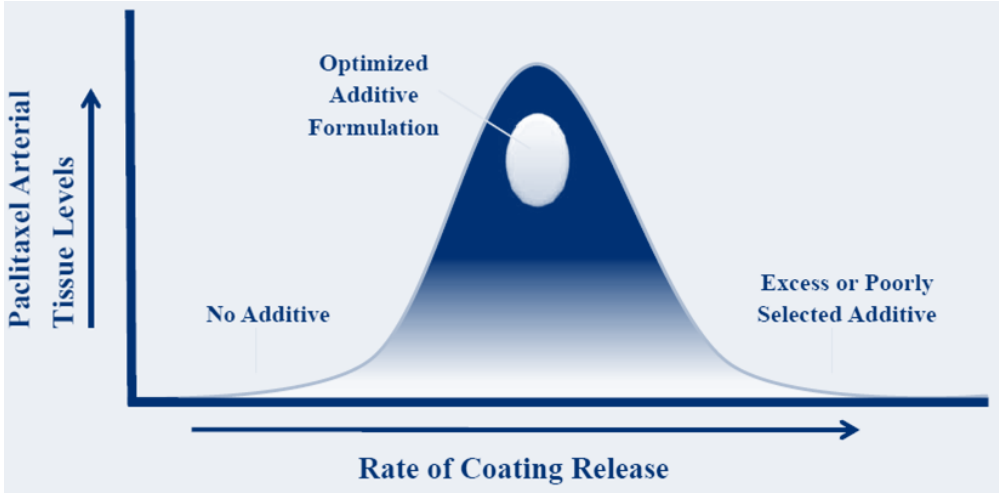
The higher the dose the higher the profile of the coated balloon

3. Excipient

- **Controls coating integrity and drug loss during navigation**
- **Facilitates absorption in tissues:** increases exposition and accelerates drug release and transfer to vessel wall
- **Required to achieve therapeutic dose of drug**

Vascular therapies for living

Water Reduced Ester



4. Drug/excipient ratio

- **DRUG** / excipient — higher risk of drug loss during navigation.
- drug / **EXCIPIENT** — higher risk of blocking drug transfer to arterial wall

The higher the excipient ratio, the larger the amount of coating to achieve the same dose (3 µg/mm2). Higher balloon profile

80/20

5. Coating strategy

Folded- Outside the wings

	PROS	CONS
Folded- Inside the wings	✓ Balloon wings protect the coating ✓ Minimization of losses during navigation	× Micropippeting. Non homogeneous coating × Accumulation in wing corners due to capillarity High profiles × High risk of delamination × No coating preparation before balloon inflation
Folded- Outside the wings	✓ Uniform and homogeneous ✓ Gel effect: light solubilization during navigation ✓ Preparation for optimal transfer	× Little loss during navigation due to solubilization
Expanded	✓ Uniform and homogeneous. ✓ Gel effect: light solubilization during navigation ✓ Preparation for optimal transfer	× Higher risk of distal embolization

6. Crystalline structure

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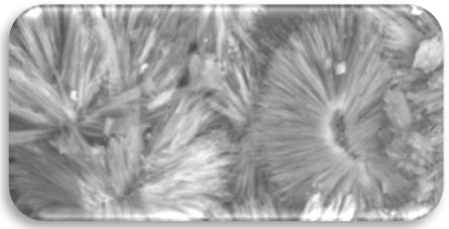
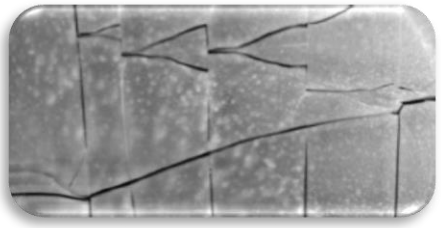
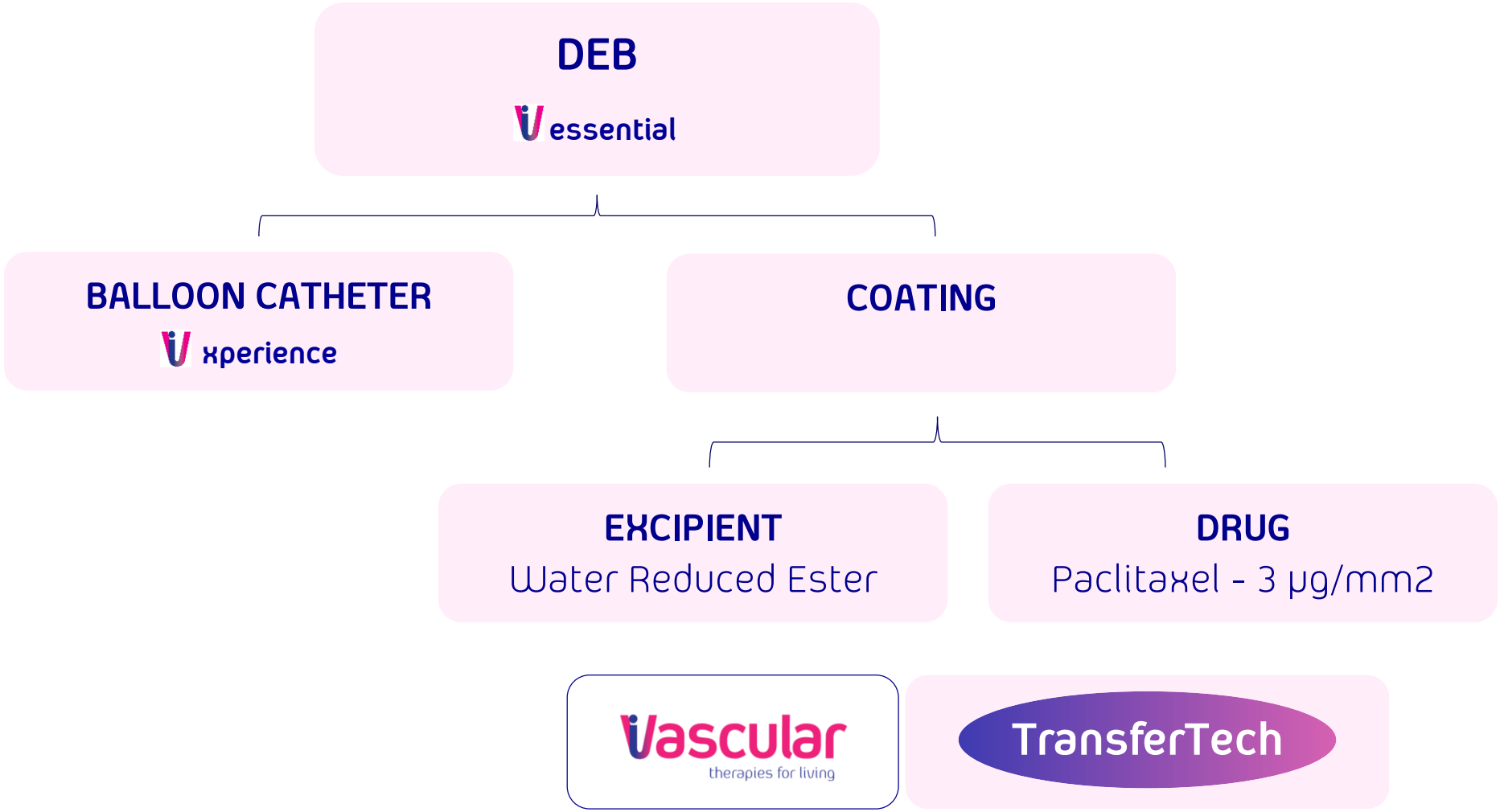
crystalline





	Crystalline	Amorphous
Particle release	●●●	●●
Coating uniformity	●●	●●●
Drug-vessel transfer	●●●	●●
Drug retention vs time	●●●	●
Biological effectiveness	●●●	?

7. Coating technology

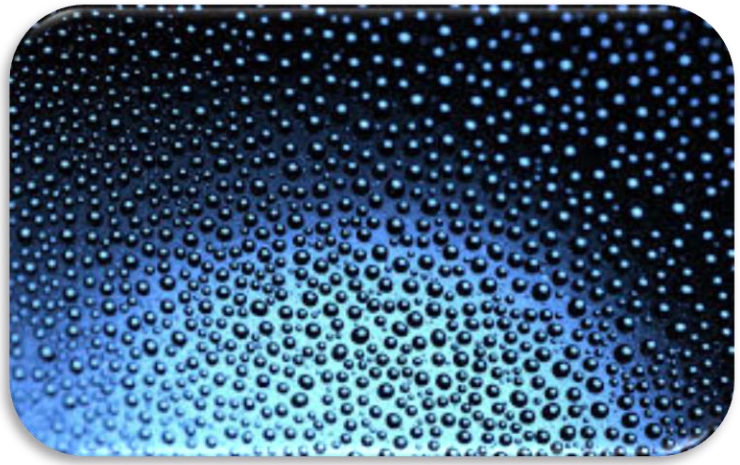


7. Coating technology: technological features

TransferTech

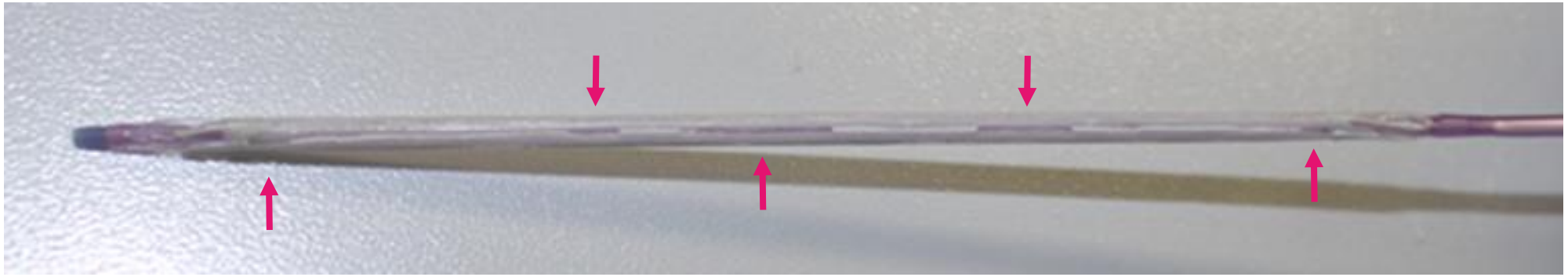
Dosage of uniform diameter nanodrops by direct ultrasonic deposition

- ✓ **Ultrathin multilayer coating:**
  - Increases adhesion to balloon → lower loss related to manipulation
  - Improves durability → lower loss during navigation
  - Improves mechanical properties
- ✓ **Homogeneous distribution of drug**
  - Same dose along the entire length
- ✓ **Repeatable drug load:** 2.5 – 3.5 µg/mm2



7. Coating technology

IN.PACT

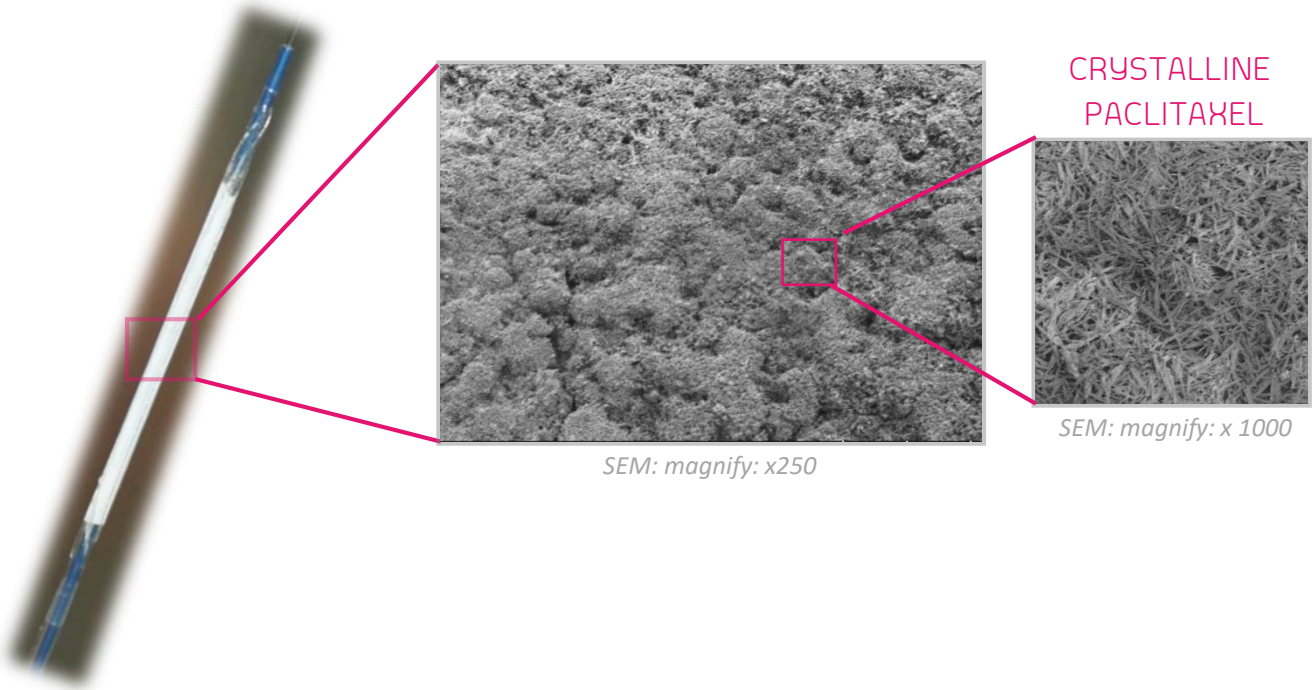


essential TransferTech

7. Coating technology: biological features

TransferTech

Control over drug morphology



- ✓ Paclitaxel **microcrystalline** structure
- ✓ Drug molecules not clumped
- ✓ **Minimum loss** during navigation and inflation
- ✓ **Fast absorption**: 30-60s
- ✓ Excellent drug **transfer** to arterial wall

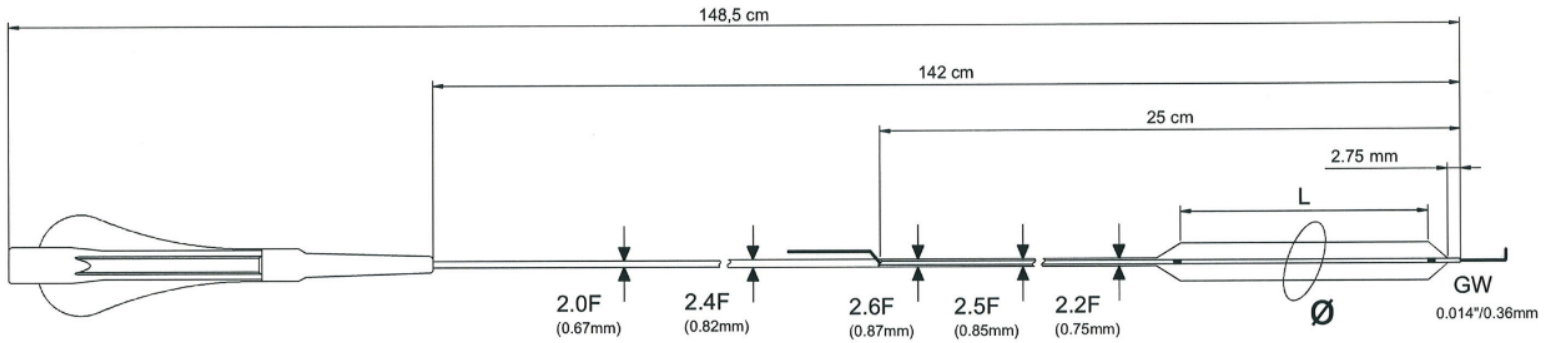
7. Coating technology: benchmark

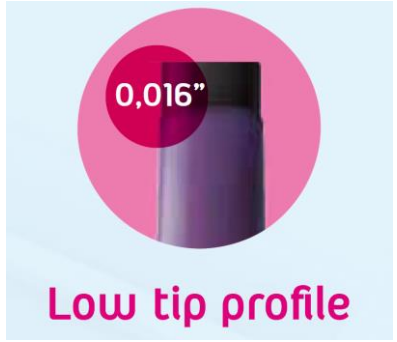
COMPANY	PACLITAXEL	DOSE	EXCIPIENT	RATIO DRUG/EXCIP.	COATING STRATEGY	MORPHOLOGY
Aachen Resonance	✓	3 µg/mm² ✓	No	100/0 ✗	Expanded ✗	Crystalline ✓
B|BRAUN SHARING EXPERTISE	✓	3 µg/mm² ✓	Ultravist 370	67/33 ✗	Outside ✓	Crystalline ✓
BIOTRONIK excellence for life	✓	3 µg/mm² ✓	BTHC	90/10 ✓	Inside ✗	Crystalline ✓
BLUEMEDICAL	✓	3 µg/mm² ✓	?	?	Inside ✗	Amorphous ✗
BARD	✓	3 µg/mm² ✓	Polysorbate and sorbitol	?	Expanded ✗	?
CARDIONOVUM Life deserves the best	✓	3 µg/mm² ✓	Shellac	50/50 ✗	Inside ✗	Amorphous ✗
COOK MEDICAL	✓	3 µg/mm² ✓	No	100/0 ✗	Inside ✗	Crystalline ✓
Eurocor	✓	3 µg/mm² ✓	Shellac	50/50 ✗	Inside ✗	Amorphous ✗
MEDRAD Performance. For life.	✓	3 µg/mm² ✓	Ultravist 370	67/33 ✗	Inside ✗	Crystalline ✓
Medtronic	✓	*4-5 µg/mm² ✗	Urea	80/20 ✓	Outside ✓	Crystalline ✓
MINVASYS	✓	2.5 µg/mm² ✓	BTHC	90/10 ✓	Inside ✗	Crystalline ✓
Vascular therapies for living	✓	3 µg/mm² ✓	Water Reducer Ester	80/20 ✓	Outside ✓	Crystalline ✓

*Data from IVascular

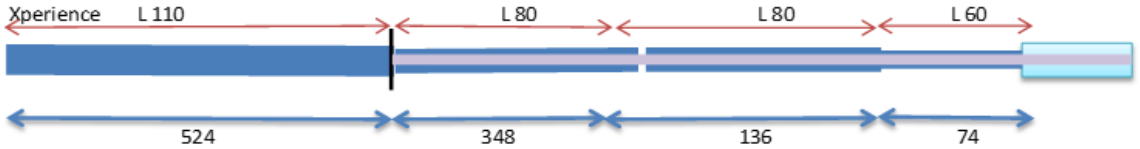
8. Design of the catheter: xperience

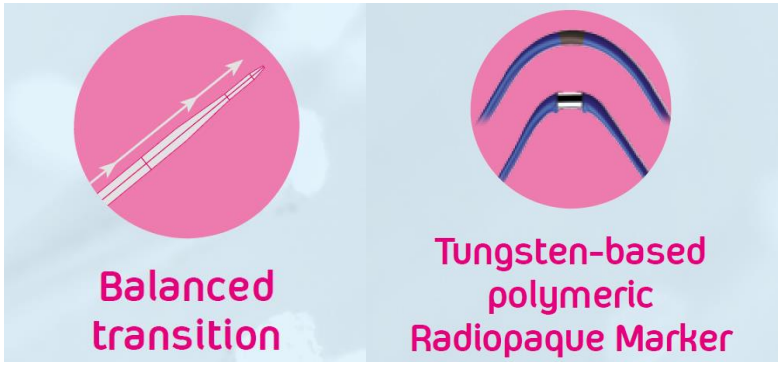
Rapid Exchange (RX)





- ✓ Crossability (penetration to injury)
  - Tip shape and profile
  - Balloon profile
  - Balloon flexibility
- ✓ Pushability and trackability
  - Structure of the catheter
- ✓ Kissing-balloon compatibility
- ✓ Inflation-deflation rates





8. Design of the catheter: xperience


Product 1


Product 2


Product 3


Product 4


Product 5


xperience

Rank	Crossability Tip profile	Crossability Balloon profile	Crossability Balloon flexibility	Proximal Pushability	Trackability Distal Flex.	Kissing balloon	Deflation rates
1	xperience	xperience	xperience	x	xperience	xperience	xperience
2	x	x	x	xperience	x	x	x
3	x	x	x	x	x	x	x
4	x	x	x	x	x	x	x
5	x	x	x	x	x	x	x
6	x	x	x	x	x	x	x

9. Inflation time

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PRODUCT 1	PRODUCT 2	PRODUCT 3	Vascular therapies for living
			
≥ 30 s	30-60 s	30-45 s	30-60 s

✓ Inflation time **comparable to the best in market**

10. Available sizes and references

essential

References Working Catheter Length 142 cm

Ballon diameter (mm)	Ballon length (mm) 10	15	20	25	30	40
1,5	BC DPR14 150 150 010	BC DPR14 150 150 015	BC DPR14 150 150 020		BC DPR14 150 150 030	
2,0	BC DPR14 150 200 010	BC DPR14 150 200 015	BC DPR14 150 200 020	BC DPR14 150 200 025	BC DPR14 150 200 030	BC DPR14 150 200 040
2,5	BC DPR14 150 250 010	BC DPR14 150 250 015	BC DPR14 150 250 020	BC DPR14 150 250 025	BC DPR14 150 250 030	BC DPR14 150 250 040
3,0	BC DPR14 150 300 010	BC DPR14 150 300 015	BC DPR14 150 300 020	BC DPR14 150 300 025	BC DPR14 150 300 030	BC DPR14 150 300 040
3,5	BC DPR14 150 350 010	BC DPR14 150 350 015	BC DPR14 150 350 020	BC DPR14 150 350 025	BC DPR14 150 350 030	BC DPR14 150 350 040
4,0	BC DPR14 150 400 010	BC DPR14 150 400 015	BC DPR14 150 400 020	BC DPR14 150 400 025	BC DPR14 150 400 030	BC DPR14 150 400 040
4,5	BC DPR14 150 450 010	BC DPR14 150 450 015	BC DPR14 150 450 020	BC DPR14 150 450 025	BC DPR14 150 450 030	BC DPR14 150 450 040

10. Available sizes and references

Vascular essential

xperience

References Usable catheter Length 142 cm

Balloon diameter (mm)	Balloon length (mm) 10	15	20	25	30	40
1.50	BC PR14 150 150 010	BC PR14 150 150 015	BC PR14 150 150 020		BC PR14 150 150 030	
2.00	BC PR14 150 200 010	BC PR14 150 200 015	BC PR14 150 200 020	BC PR14 150 200 025	BC PR14 150 200 030	BC PR14 150 200 040
2.50	BC PR14 150 250 010	BC PR14 150 250 015	BC PR14 150 250 020	BC PR14 150 250 025	BC PR14 150 250 030	BC PR14 150 250 040
3.00	BC PR14 150 300 010	BC PR14 150 300 015	BC PR14 150 300 020	BC PR14 150 300 025	BC PR14 150 300 030	BC PR14 150 300 040
3.50	BC PR14 150 350 010	BC PR14 150 350 015	BC PR14 150 350 020	BC PR14 150 350 025	BC PR14 150 350 030	BC PR14 150 350 040
4.00	BC PR14 150 400 010	BC PR14 150 400 015	BC PR14 150 400 020	BC PR14 150 400 025	BC PR14 150 400 030	BC PR14 150 400 040
4.50	BC PR14 150 450 010	BC PR14 150 450 015	BC PR14 150 450 020	BC PR14 150 450 025	BC PR14 150 450 030	BC PR14 150 450 040

Key selling points

1. Drug: **Paclitaxel**
2. Proprietary coating technology
   - ✓ Coating: **Multilayer, ultrathin, uniform**
   - ✓ Increases: **mechanical properties, adhesion, durability**
   - ✓ Reduces: **thickness, losses, delamination**
   - ✓ Drug with crystalline structure
     - Less **detachment**
     - Better **transfer** (quick and quantitative)
     - Higher **retention**
     - Biological **efficacy**
3. **Inflation** times like the best in the market
4. Extra fast **deflation** rates

Key selling points

5. **Conical design** of the catheter optimizes pushability in proximal section
6. Progressive increase in **flexibility** towards distal section contributes to a better **trackability**
7. Non-traumatic conical tip for more **safety** during intervention
8. Low tip profile for better **crossability of severe injuries**
9. **Tungsten radiopaque markers**: more flexibility, same visibility
10. **Wide size range**
11. Preclinical data proves **higher efficacy** than a control and up to 23% more than other commercial DEBs

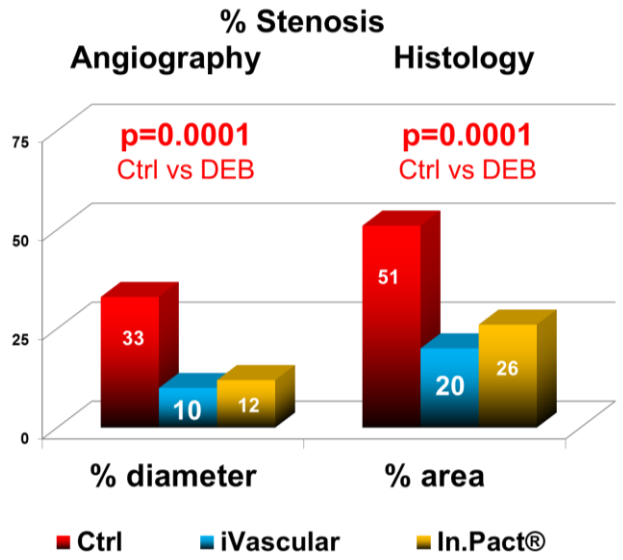
Method

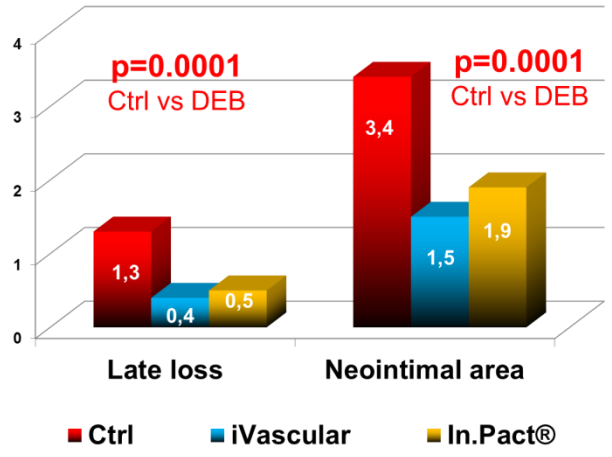
- **Healthy arteries, swine model**

- **Domestic pigs: 25 ± 3 kg; n = 17**
  - **CoCr Stent: architect, n=51**
  - **Post-dilatation Stent (balloon-artery ratio 1,21 ± 0,14) with:**
    - Control: Bare balloon oceanus and xperience
    - DEB: luminor 14, luminor 35, essential 3 µg/mm² paclitaxel, TransferTech
    - Commercial DEB (In.Pact®): 3µg/mm² paclitaxel, FreePac® tech

- **28-day follow-up: Angiography & Histology**
  - Restenosis: % diameter and area of stenosis, late-loss and neointimal area
  - Vascular healing parameters: injury score, inflammation, fibrin and endothelization

Efficacy: restenosis





- >50% less restenosis than control
- 23% less restenosis than commercial DEB In.Pact

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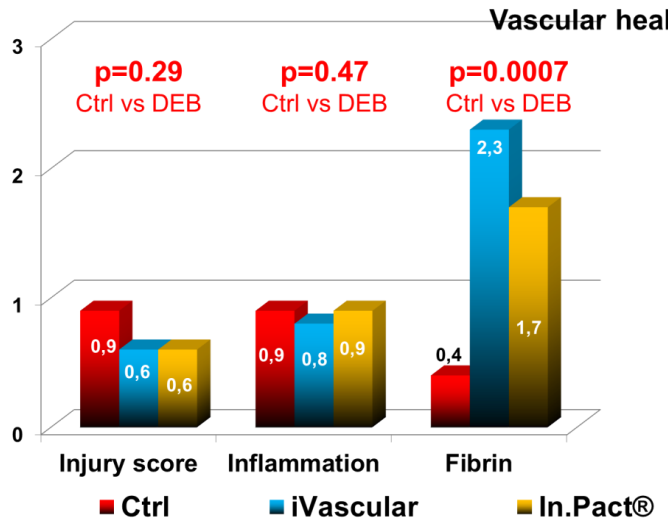
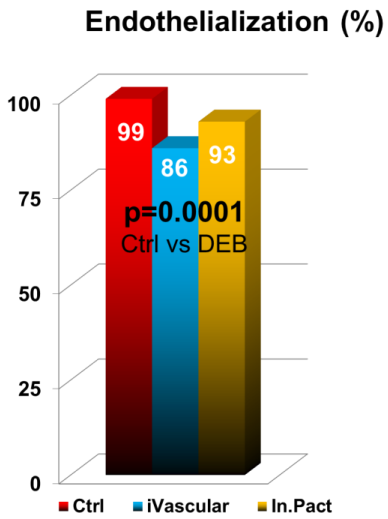
Safety: vascular healing

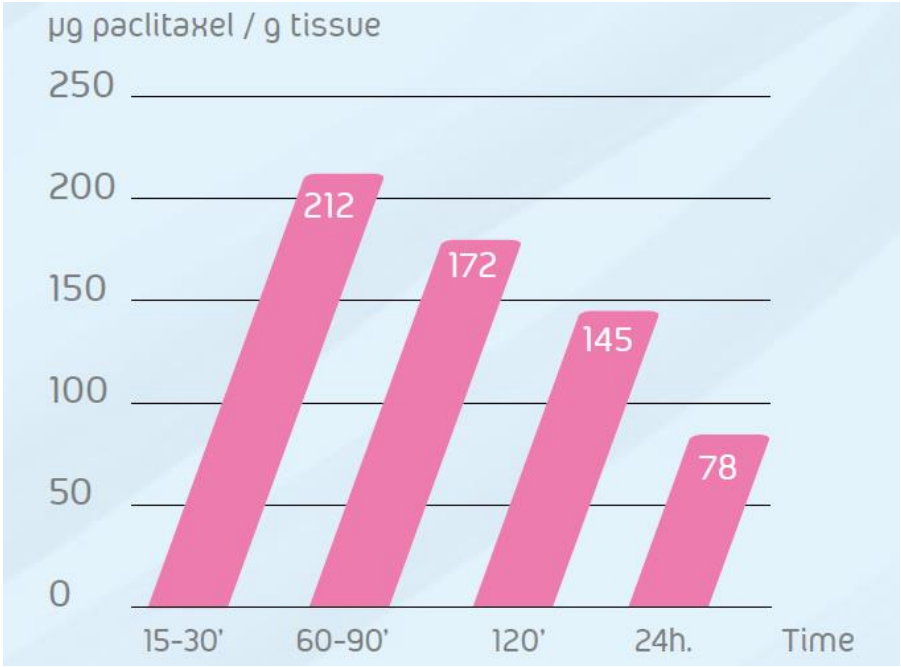




- Inflammation is uniformly low in all groups
- Less endothelization and more fibrin than control → pharmacological effect
- No differences between DEBs

Pharmacokinetics

- 3 extra pigs
- Sampling:
  - n= 2, 15 - 30'
  - n= 2, 60 - 90'
  - n= 2, 120'
  - n= 2, 24h
- HPLC analysis of µg paclitaxel / g tissue



- **Inflammation is uniformly low** in all groups
- Less **endothelization** and more **fibrin** than control → **pharmacological effect**
- **No differences between DEBs**

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DES observational registry by J.Benezet

Treatment of de novo coronary lesions with a novel second generation paclitaxel coated balloon catheter: 5 - month clinical results

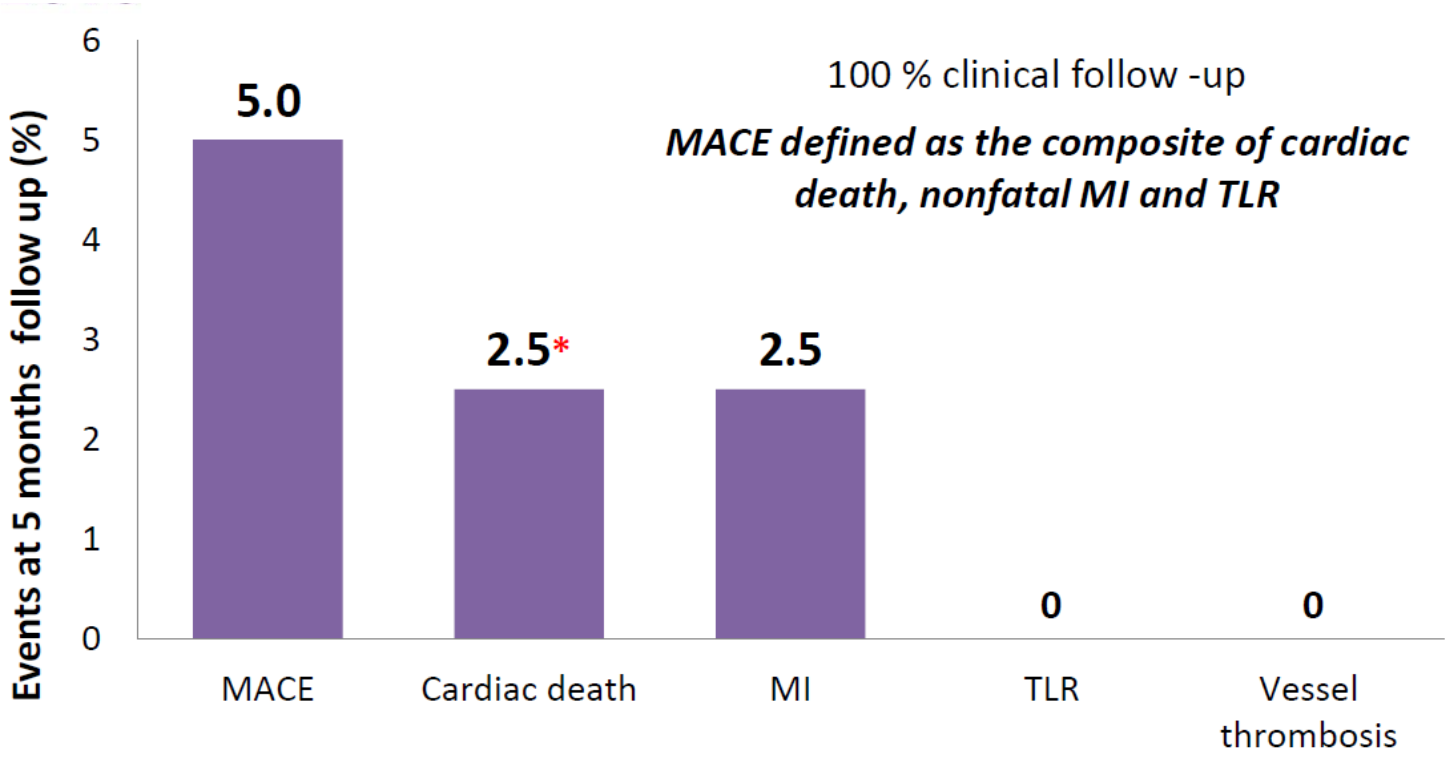
Coronary Dissection	**2 (5%)**
Recoil	**3 (7.5%)**
Abrupt Closure	**0**
Additional Stent Implantation "Bailout"	**5 (12.5%)** ***BMS* 3 (7.5 %)** ***DES* 2 (5%)**
Device Success (single PCB strategy)	**87.5 %**
Angiographic success *Residual stenosis < 20 % in the target vessel with TIMI 3 flow*	**100 %**
Procedural success *Angiographic success without the occurrence of MACE during the hospital stay*	**100 %**

PATIENTS	38	FOLLOW UP	5m

iVascular
therapies for living

Essential 5-month follow-up

5- month clinical results (n=38)



The treatment of de novo coronary lesions with the Essential® PCB had high procedural success.

The Essential® PCB system demonstrated:

- ✓ **Safety** (2.5% death / 2.5% MI)
- ✓ **Efficacy** (0 % TLR) at 5 month follow-up

*One patient with atrial fibrillation died after 41 days follow up due to intracranial hemorrhage associated with antithrombotic therapy.

Thank you