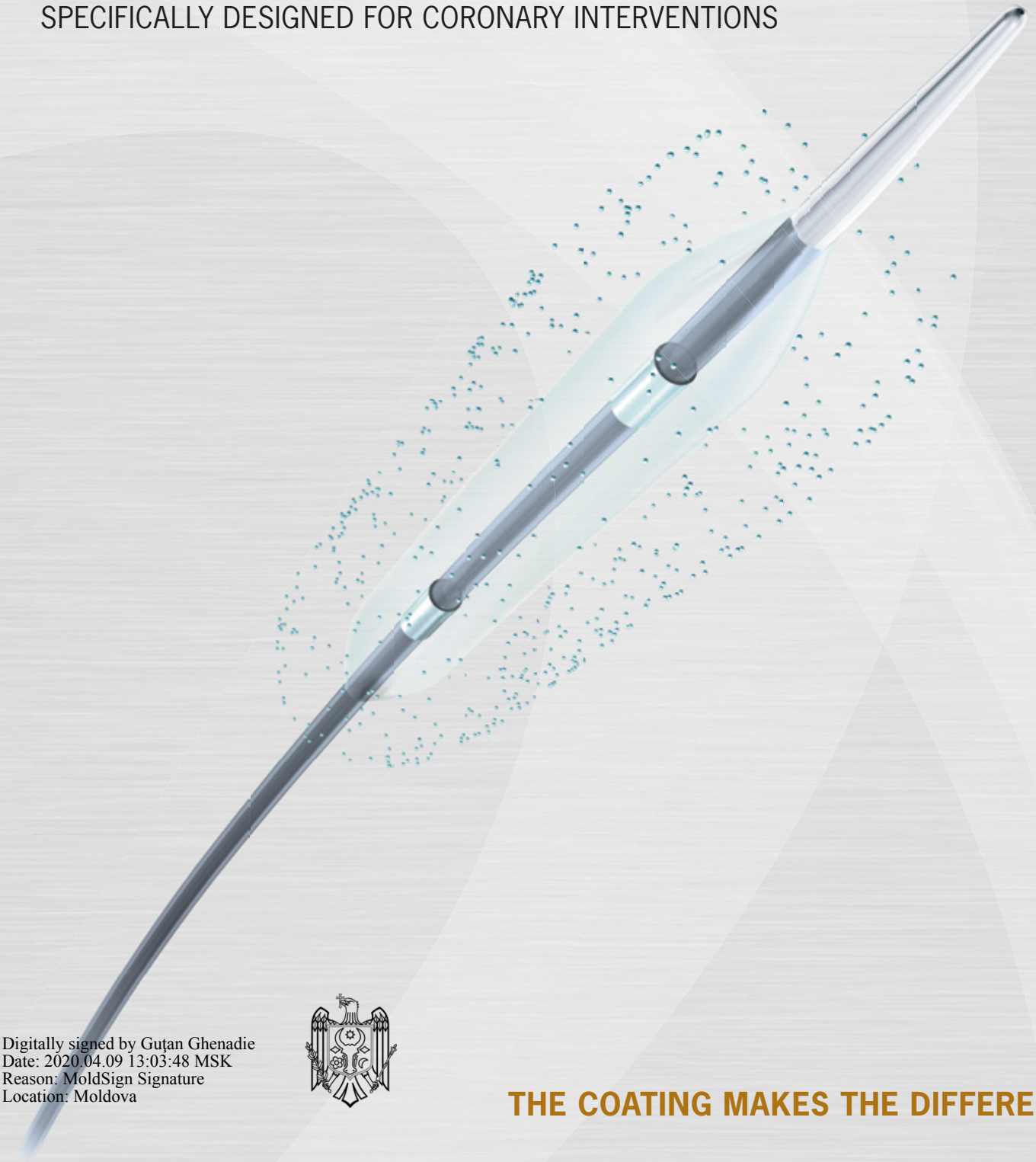
DIOR®

DRUG-ELUTING PTCA BALLOON TECHNOLOGY

SPECIFICALLY DESIGNED FOR CORONARY INTERVENTIONS



THE COATING MAKES THE DIFFERENCE

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DIOR® – DRUG-ELUTING PTCA BALLOON TECHNOLOGY

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DIOR® – COATING CHARACTERISTICS

Paclitaxel

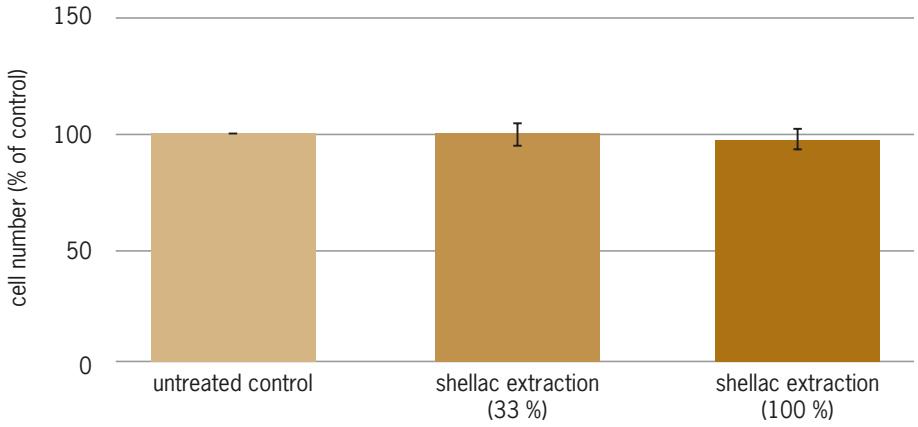
Paclitaxel is an active ingredient that inhibits the cell replication; thus blocking the microtubules decomposition during the metaphase and anaphase stages of mitosis.

By selectively inhibiting the proliferation of smooth muscle cells, paclitaxel does not influence non-proliferating cells.

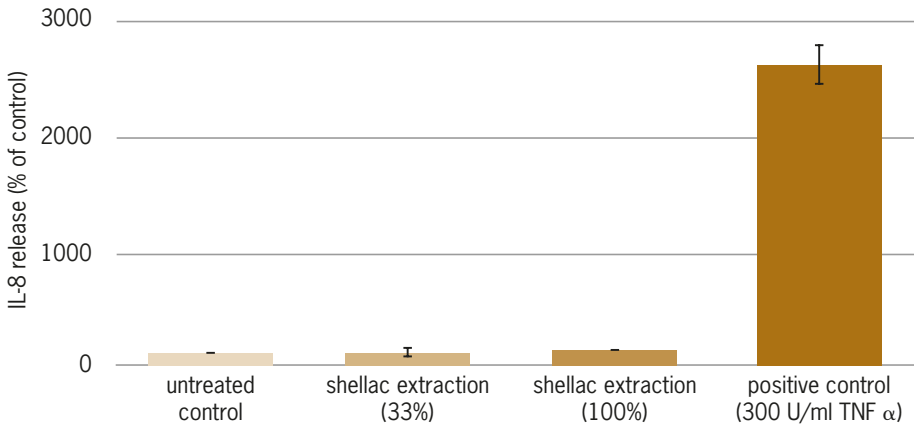
Shellac

Shellac is a natural resin composed of shellolic and alleuritic acid. The excellent film forming properties of shellac are used to coat pharmaceutical products and in the food industry.

Investigation of cytotoxicity



Shellac extracts do not impair viability and metabolic activity of EC & SMC[1]



Shellac extracts show no signs of pro-inflammatory activation[1]

SHELLAC DOES NOT SHOW ANY CYTOTOXICITY – SHELLAC IS SAFE.

[1] Peters K et al. "In Vitro Evaluation of Cytocompatibility of Shellac as Coating for Intravascular Devices." Trends Biomater Artif Organ 2012 26(2): 110-11.

DIOR® – COATING CHARACTERISTICS

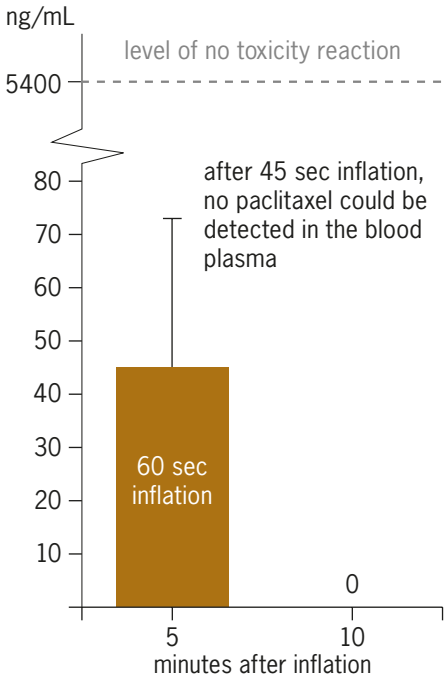
Amorphous Coating

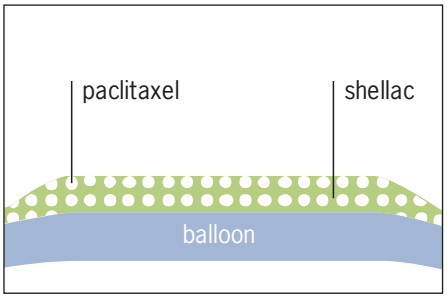
The durable non-crystalline bioshell coating homogenously covers the balloon surface and protects the drug from mechanical abrasion and early wash off, resulting in a low paclitaxel blood plasma concentration.

Paclitaxel blood plasma concentrations at 5 and 10 minutes after inflation (60 sec) with DIOR® DEB. After inflations of 45 sec or less no paclitaxel could be detected in the blood plasma.[2] Level of toxicity for paclitaxel plasma concentration calculated with a human body surface area of 1.9 m² and blood plasma content of 3.5l.[3]

[2] Pósa A., et al. Optimization of drug-eluting balloon use for safety and efficacy: Evaluation of the second generation paclitaxel-eluting DIOR-balloon in porcine coronary arteries. CCI 2010; 76(3):395-403

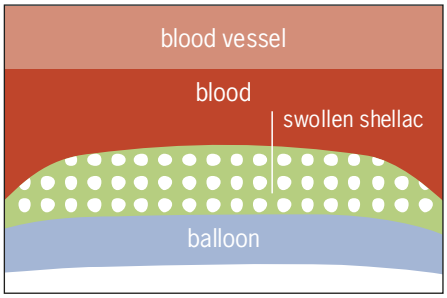
[3] Margolis J et al. "Systemic nanoparticle paclitaxel (nab-paclitaxel) for in-stent restenosis I (SNAPIST-I): a first-in-human safety and dose-finding study." Clinical cardiology, 2007 30(4), 165-170.





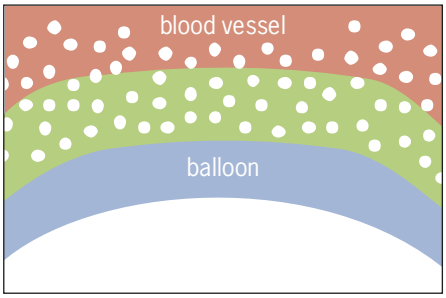
coated balloon deflated

The DIOR® amorphous bioshell coating matrix consists of a 1:1 mixture of paclitaxel with shellac applied to the balloon surface by a micro-pipetting procedure in a clean room under sterile conditions. Paclitaxel is applied in a final concentration of 3 µg/mm².



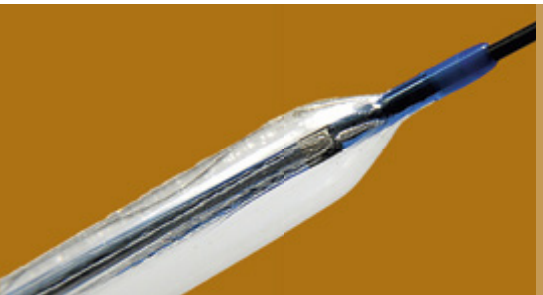
in contact with blood

In contact with body liquid the hydrophilic shellac matrix of the composite swells and opens the structure for the pressure-induced fast release of paclitaxel from the inflated balloon.



inflated balloon allows freed paclitaxel to enter the vessel wall

After balloon dilatation, injuries to the arterial wall stimulate inflammatory reaction, the excretion of growth factors and the onset of vascular smooth muscle cell division and migration to the intima. The DIOR® Paclitaxel-eluting PTCA balloon catheter delivers a proper concentration of paclitaxel to the arterial wall, thus prevents restenosis and enhances a smooth re-endothelialization process after balloon dilatation.



EFFECTIVE BIOSHELL COATING [2, 4–11]

THE COATING MAKES THE DIFFERENCE

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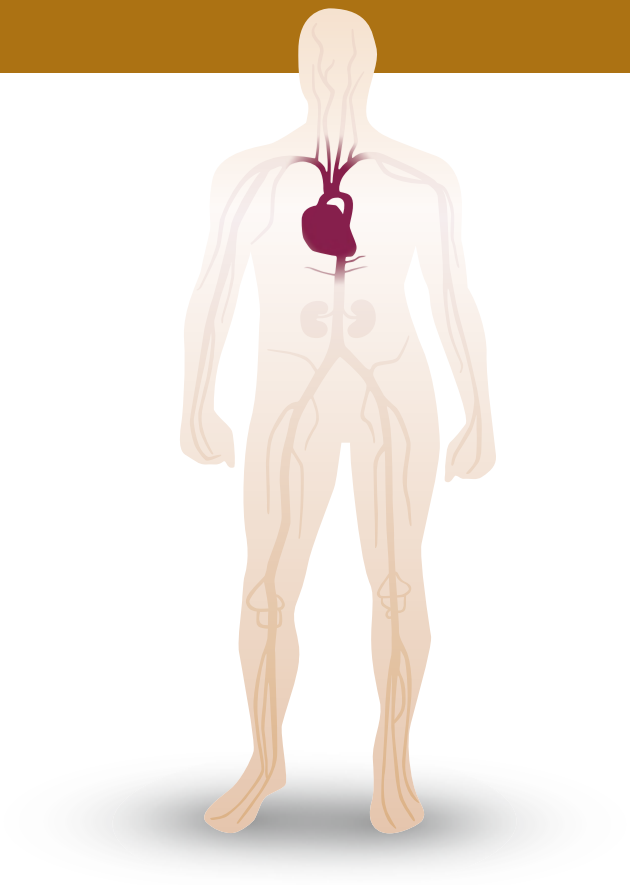
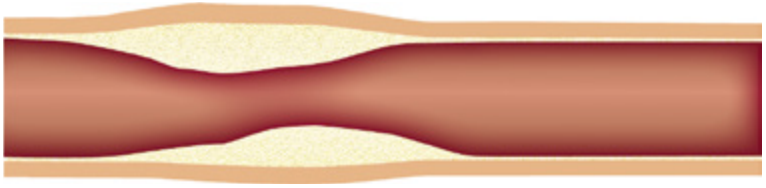
HOW IT WORKS

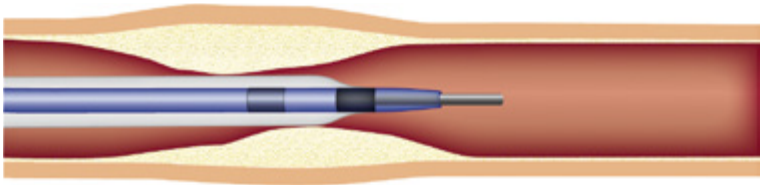


DIOR®, coronary PTCA balloon catheter –
An innovative concept with many benefits:

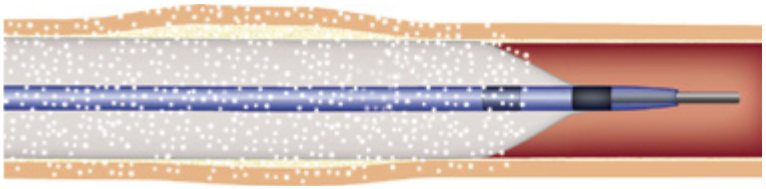
- **Delivers** drug locally over a short period of time
- **Safety** due to non-crystalline coating
- **Crosses** lesions smoothly due to the low profile
- **Treats** lesions where stents are not a viable solution
- **Enables** re-intervention



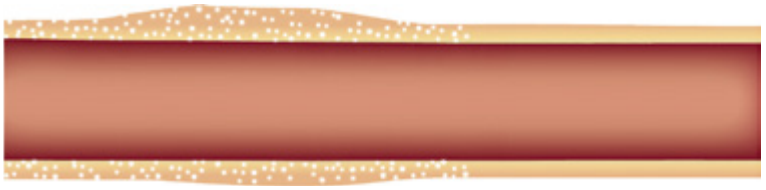
PTCA causes vessel wall injury. Hyperplasia of the inner vessel wall resulting in lumen narrowing is the natural reaction to this injury.



After predilatation, the DIOR® Paclitaxel-eluting PTCA balloon is advanced to the lesion site.



With the balloon well positioned, inflation for at least 45 seconds releases an optimal amount of the anti-proliferative drug.



The balloon is withdrawn as the drug penetrates into the artery wall. Paclitaxel will act immediately, over a short term, to inhibit cell re-growth. The shellac coating remains on the balloon.

DIOR® – PRECLINICAL PROGRAM

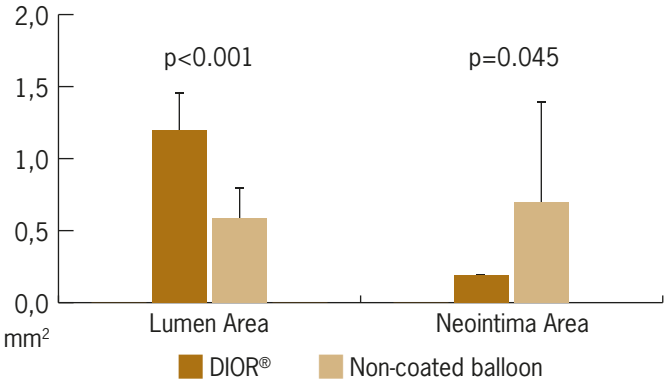
DIOR® DEB

Coronary arteries of 33 domestic pig were treated with the DIOR drug eluting balloon in a time-dependent matter. Arteries were dissected and sent to a blinded laboratory for paclitaxel determination. Histomorphometry and histopathology were performed two weeks after dilatation.

- No delay in endothelialization, no disadvantages in injury and inflammation score compared to standard balloon dilatation coronary arteries two weeks after dilatation.
- DIOR® DEB demonstrated safety and efficacy in a preclinical model of overstretch injury in coronary arteries.
- Reaching the effective concentration of paclitaxel in the arterial wall with DIOR® DEB inflation.

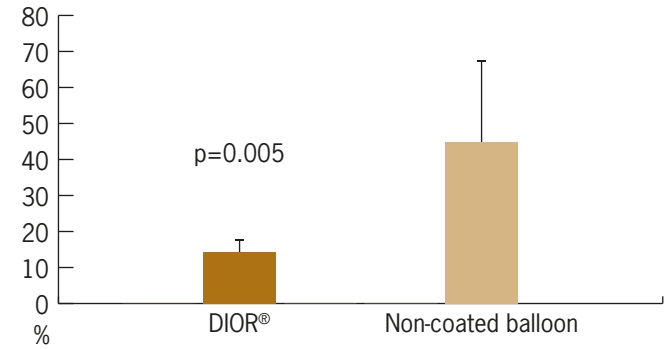
Lumen Area and Neointima area (mm²) at FU

Vessels treated with DIOR® DEB show **significantly higher lumen** area and **significantly lower neointima area** two weeks after dilatation compared to uncoated balloon treatment.[2]



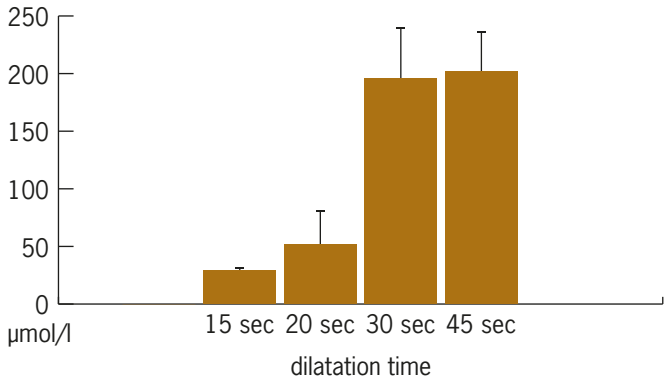
Area Stenosis (%) at FU

Vessels treated with DIOR® DEB show **significantly lower area of stenosis** after two weeks follow-up compared to uncoated balloon treatment.[2]



Tissue paclitaxel concentration (µmol/l)

Inflation of **45s** with DIOR® DEB leads to long presence and **high concentration of paclitaxel** in the arterial wall[2] – crucial for inhibition of neointimal proliferation and restenosis.



[2] Pósa A., et al. Optimization of drug-eluting balloon use for safety and efficacy: Evaluation of the second generation paclitaxel-eluting DIOR-balloon in porcine coronary arteries. CCI 2010; 76(3):395-403

DIOR® – CLINICAL PROGRAM

Evidence for the safety and efficacy of the DIOR® DEB

DIOR® in in-stent restenosis (ISR)[4,5,6]

Valentines Trial

- International prospective multicenter registry
- 250 patients with coronary DES and BMS in-stent restenosis (ISR)
- 8 months follow-up
- Clinical safety and low MACE rate at follow-up in a real world ISR population.

Spanish Registry

- Prospective multicenter registry
- 126 patients with coronary DES and BMS in-stent restenosis (ISR)
- 12 months follow-up
- Clinical safety and low MACE rate at follow-up in a real world ISR population.

[4] Stella PR et al. "The Valentines Trial: results of the first one week worldwide multicentre enrolment trial, evaluating the real world usage of the second generation DIOR paclitaxel drug-eluting balloon for in-stent restenosis treatment." EuroIntervention 2011 7(6): 705-710.

[5] Loh JP et al. "Paclitaxel-coated balloon for the treatment of drug-eluting stent restenosis: subanalysis results from the Valentines I trial." Cardiovasc Revasc Med 2014 15(1): 23-28.

[6] Vaquerizo B et al. "1-year outcomes with angiographic follow-up of Paclitaxel eluting balloon for the treatment of in-stent restenosis: insights from Spanish Multicenter Registry." JOIC 2011 24(6):518-528

DIOR® in small vessels[7]

Spanish Registry

- Prospective multicenter registry
- 104 patients with native coronary small vessel lesions
- 12 months follow-up
- Clinical safety and very low MACE rate in real small vessels (< 2.0 mm).

[7] Vaquerizo B et al. "Treatment of small vessel disease with the paclitaxel drug-eluting balloon: 6-Month angiographic and 1-Year clinical outcomes of the Spanish Multicenter Registry." J INTERV CARDIOL 2015 28(5): 430-438.

DIOR® – CLINICAL PROGRAM

DIOR® in bifurcation lesions[8,9]

001 Trial

- Prospective multicenter registry
- 49 patients with coronary *de novo* Medina 001 bifurcation lesions
- 12 months follow-up
- DIOR® as a safe and technically easy option for treatment of sidebranch ostial lesions (001 bifurcations).

DEBIFU Registry

- Prospective multicenter registry
- 100 patients with coronary bifurcation lesions
- 12 months follow-up
- DIOR® is a safe alternative in complex bifurcation lesion with low MACE rate at follow-up.

[8] Vaquerizo B et al. "Second-Generation Drug-Eluting Balloon for Ostial Side Branch Lesions (001-Bifurcations): Mid-Term Clinical and Angiographic Results." Journal of interventional cardiology 2016 29(3): 285-292.

[9] von Korn et al. "Interventional therapy of bifurcation lesions: a new approach using drug-eluting balloons for the main branch and/or for the side branch the DEBIFU Registry" Presentation at EuroPCR Paris 2016

DIOR® in *de novo* lesions[10,11]

Valentines Trial II

- International prospective multicenter registry
- 103 patients with coronary *de novo* lesions
- 8 months follow-up
- Clinical safety and low MACE rate at follow-up in a real *de novo* lesion population (2.40 mm mean reference vessel diameter) with low bail-out stenting rate.

DEAR Registry

- Prospective multicenter registry
- 91 diabetic patients with *de novo* lesions
- 12 months follow-up
- Significantly lower MACE rate for DIOR® vs. BMS comparison group.

[10] Waksman R et al. "Drug-coated balloons for de novo coronary lesions: results from the Valentines II trial." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 2013 9(5): 613-619.

[11] Mieres J et al. "One-year outcome of patients with diabetes mellitus after percutaneous coronary intervention with three different revascularization strategies: results from the Diabetic Argentina Registry (DEAR)." Cardiovasc Revasc Med 2012 13(5): 265-271.

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TECHNICAL DATA

DIOR® – PACLITAXEL-ELUTING CORONARY BALLOON DILATATION CATHETER	
Design	Rapid exchange
Balloon diameter	2.0 / 2.25 / 2.50 / 2.75 / 3.00 / 3.50 and 4.00 mm
Balloon length	15 / 20 / 25 and 30 mm
Usable catheter length (tip to strain relief)	140 cm
Recommended guide wire	0.014" (0.36 mm)
Minimum guiding catheter	5F
Tip profile	0.016" (0.41 mm)
Proximal shaft diameter	1.8 F
Shaft coating	Hydrophilic
Ballon coating	Paclitaxel (3µg/mm²) within a shellac matrix (1:1 ratio)
Balloon material	PA, Polyamid/Nylon
Balloon folding	3-fold
Balloon characteristics	Semi-compliant
Recommended inflation time	45 sec
Nominal pressure	6 bar
Rated burst pressure	Balloon length 15 / 20 / 25 / 30 mm Dianeter 2.00 - 3.50 mm: 16 bar
	Balloon length 15 / 20 mm Diameter 4.00 mm: 16 bar
	Balloon length 25 / 30 mm Diameter 4.00 mm: 14 bar
Packaging unit	1

PRODUCT ORDERING INFORMATION

Balloon Diameter (mm-Ø)	Balloon length (mm)			
	15	20	25	30
2.00	DIOR 2.00-15	DIOR 2.00-20	DIOR 2.00-25	DIOR 2.00-30
2.25	DIOR 2.25-15	DIOR 2.25-20	DIOR 2.25-25	DIOR 2.25-30
2.50	DIOR 2.50-15	DIOR 2.50-20	DIOR 2.50-25	DIOR 2.50-30
2.75	DIOR 2.75-15	DIOR 2.75-20	DIOR 2.75-25	DIOR 2.75-30
3.00	DIOR 3.00-15	DIOR 3.00-20	DIOR 3.00-25	DIOR 3.00-30
3.50	DIOR 3.50-15	DIOR 3.50-20	DIOR 3.50-25	DIOR 3.50-30
4.00	DIOR 4.00-15	DIOR 4.00-20	DIOR 4.00-25	DIOR 4.00-30

Eurocor

Eurocor Tech GmbH
In den Dauen 6a, 53117 Bonn, Germany
Phone: +49 (0)228/20 15 0-0
Fax: +49 (0)228/20 15 0-5
info@eurocor.de, eurocor.de

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