Clinical Evaluation Report
According to MEDDEV 2.7.1 Rev. 4

for

FREEWAY™
PACLITAXEL ELUTING PTA BALLOON CATHETER

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Statement of Confidentiality

The information contained in this Clinical Evaluation Report is intended for authorized competent authorities and notified bodies of the manufacturer Eurocor Tech GmbH. It must not be disclosed to third parties without written permission to be given by Eurocor Tech GmbH.

Abbreviations

PAD	=	Peripheral Arterial Disease
BMS	=	Bare Metal Stent
DCB / DEB	=	Drug-Coated Balloon / Drug-Eluting Balloon
DES	=	Drug-Eluting Stent
LLL	=	Late Lumen Loss
MAE	=	Major Adverse Events
PTA	=	Percutaneous Transluminal Angioplasty
PTCA	=	Percutaneous Transluminal Coronary Angioplasty
TLR	=	Target Lesion Revascularization
TVF	=	Target Vessel Failure
TVR	=	Target Vessel Revascularization
ISR	=	In-Stent Restenosis
SFA	=	Superficial Femoral Artery
PMCF	=	Post Market Clinical Follow-up

Revision	Date	Changes (PSUR changes not included)
1	06/2013	new
2	08/2015	Addition of preclinical data FREEWAY, addition of clinical data: Pacuba study Freeway Stent Study, Freeride Study, complaint & sales update, literature update
3	04/2018	Publication of Freeway preclinical data, update: Freeride study, Freeway Stent study, addition Freeway AV clinical data, complaint & sales update, literature update
4	07/2019	Addition subgroup analyses Freeway Stent study, addition topic of late mortality signal, paclitaxel mortality topic in chapter 4.5 Appraisal of clinical data and 5.; complaint & sales update, literature update
5	11/2019	Update paclitaxel mortality topic in chapter 4.5 Appraisal of clinical data and 5. Conclusion risks / benefits evaluation, added clinical literature paclitaxel mortality topic, annual PSUR update, literature update
6	11/2020	Addition subgroup analyses stent type Freeway Stent study; complaint & sales update, literature update
7	11/2021	Addition clinical literature, Yildiz FREEWAY in AV, annual PSUR update, literature update
8	11/2022	Addition preliminary results of Freeway longterm study to Safety, risk, performance evaluation and conclusion part, annual PSUR update, literature update
9	11/2023	Addition new chapter 2. Clinical Evaluation Plan, updated Chapter 3. Scope of clinical evaluation, update and re-worked topic of paclitaxel

		mortality, deleted topic from literature section, updated Safety, risk, performance evaluation and conclusion part updated of that topic with latest clinical data and FDA evaluation, annual PSUR update, literature update
10	10/2024	Addition final data of Freeway Long-term study and publication reference, added Freeway China RCT data and reference; revision history table, annual PSUR update, literature update

Table of contents

Abbreviations 2

Table of contents 3

1. Summary 5

2. Clinical Evaluation Plan 5

3. Scope of the clinical evaluation 6

4. Device description 6

4.1 Product sales volumes 7

a) FREEWAY 014 7

b) FREEWAY 035 7

5. Clinical background and state of the art 8

5.1 Clinical background 8

5.2 Data from Literature - Search and Review 9

5.3 Data from Literature Preclinical and Clinical data 13

6. Device under evaluation 17

6.1. Type of evaluation 17

6.2. Predicate devices 17

6.2.1 Identification and evaluation of predicate devices 17

6.3 Data generated by the manufacturer / Data with the device under evaluation 19

6.3.1. Pre-clinical data 19

6.3.2. Clinical trials using the device under evaluation 21

6.3.3. Complaints of device under evaluation FREEWAY™ 26

6.3.4 Field safety corrective actions 28

6.4 Summary and appraisal of clinical and pre-clinical data 29

6.4.1 Appraisal plan 29

6.5 Safety, risk, performance and essential requirement analysis of the device under evaluation 30

6.5.1. Requirement on safety 30

6.5.2. Requirement on acceptable benefit/risk profile 30
6.5.3. Requirement on performance 30
6.5.4. Requirement on acceptability of side-effects 30
6.5.5. FDA evaluation of the meta-analysis on paclitaxel device late mortality signal 31
7. Conclusion risks / benefits evaluation 31
8. Date of next clinical evaluation 32
9. Dates and signatures 32
10. Qualification of the responsible experts 33
11. References 33

1. Summary

This report evaluated scientific data from journals, the results from finalized and ongoing randomized trials (post market clinical follow-up studies) and registry studies with the FREEWAY™ Paclitaxel eluting PTA catheter as well as expert's consultation reports and technical results of the present device. It is concluded that the product can be expected to exhibit the claimed medical and technical performance and that potential undesirable clinical effects and risks seem well controlled and acceptable, when weighed against their benefits in interventional procedures. Therefore, a positive risk versus benefit ratio can be stated by the Expert for the FREEWAY™ Paclitaxel eluting PTA catheter, provided that the FREEWAY™ Paclitaxel eluting PTA catheter is applied in accordance with its intended use as outlined in the manufacturer's instructions for use. A continued marketing of the product can be supported.

2. Clinical Evaluation Plan

In accordance with the requirements outlined in Annex XIV Part A(1) of Regulation (EU) 2017/745/EEC, manufacturers are mandated to establish and continually update a comprehensive Clinical Evaluation Plan for our medical device. This plan serves as the foundation for our clinical evaluation process and includes the following critical components:

(a) Identification of Safety and Performance Requirements: We shall identify and specify the general safety and performance requirements that necessitate support from relevant clinical data. This involves a carefully examination of the device's intended purpose, intended target groups with clear indications and contra-indications, and a detailed description of the intended clinical benefits to patients. We will also define relevant and specified clinical outcome parameters and establish methods for examining both qualitative and quantitative aspects of clinical safety, with a clear reference to the determination of residual risks and potential side-effects. Furthermore, we will provide an indicative list and specification of parameters, based on the state of the art in medicine, to assess the acceptability of the benefit-risk ratio for various indications and the device's intended purpose.

(b) Identification of Clinical Data: We will conduct a systematic and comprehensive scientific literature review to identify available clinical data pertinent to our device and its intended purpose.

(c) Appraisal of Clinical Data: All relevant clinical data will be carefully appraised to evaluate their suitability for establishing the safety and performance of the device under evaluation.

(d) Generation of New Clinical Data: If necessary, we will design and execute properly structured clinical investigations in strict accordance with our clinical development plan. This will allow us to generate any new or additional clinical data required to address outstanding issues or gaps in the existing evidence.

(e) Analysis of Clinical Data: We shall comprehensively analyze all relevant clinical data, using rigorous methods, to draw well-substantiated conclusions regarding the safety, clinical performance, and clinical benefits of our device.

By addressing these important elements in our clinical evaluation plan, we aim to provide a robust and comprehensive assessment of the safety, performance and clinical benefit of the medical device in accordance with MDR Annex XIV Part A(1) of Regulation (EU) 2017/745/EEC.

3. Scope of the clinical evaluation

In accordance with the Medical Device Regulation (EU) 2017/745/EEC Medical Device Directive 93/42/EEC, as amended by Directive 2007/47/EC [1] and national medical device legislation in Europe, any medical device is requested to be evaluated by the legal medical device manufacturer regarding its clinical performance and safety. This includes an evaluation of biocompatibility in accordance with EN ISO 10993-1 [2] and a clinical evaluation in accordance with MDR chapter VI and Annex XIV Part A(1)MEDDEV 2.7.1 Rev4 [3], which is intended to critically evaluate the clinical benefits of the medical device in comparison to its potential risks. Therefore, any clinical evaluation is part of the compulsory risk management process according to EN ISO 14971 [4], and critical findings must further be considered in the current risk management process of the medical device manufacturer responsible for the evaluated device.

On this background, this clinical evaluation was performed in order to comply with the current European medical device legislation, in particular with MDR chapter VI and Annex XIV Part A(1) MEDDEV 2.7.1 Rev 4 [3].

4. Device description

FREEWAY™ Paclitaxel Eluting PTA Balloon Catheter.

The product is legally manufactured by:

Eurocor Tech GmbH, In den Dauen 6a, 53117 Bonn, Germany

Drug-eluting PTA balloon catheters in general are classified as Class III medical devices under the consolidated Medical Device Directive 93/42/EEC Annex IX, Rule 6, bullet point 1 (correction of defect of the circulatory system), and according to Rule 13 (drug-eluting properties). The intended use of the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter is to improve luminal diameter and to reduce restenosis in the treatment of stenotic and restenotic lesions of peripheral arteries in patients with peripheral arterial disease (PAD).

The FREEWAY™ Paclitaxel eluting PTA Balloon Catheter was CE-marked in 2007.

FREEWAY™ is a double-lumen catheter with two markers, proximal and distal, to aid the balloon positioning under fluoroscopy. The coating of the balloon consists of a drug-eluting shellac-Paclitaxel composite (mixture 1:1), whereas the mass proportion of Paclitaxel (Ph. Eur. 5.0) is 3.0 µg/mm^2.

Shellac (Ph. Eur. 4.8) is a natural resin produced from the glandular secretion of an Indian scale insect, which infects branches of numerous trees from the East Indies. The natural non-toxic resin shellac gains importance due to toxicity discussions in case of chemical resins. Major application of shellac is among others tablet and other pharmaceutical coatings (controlled drug

release, microcapsules, and glaze). Shellac is an approved food additive (E904) and has been toxicologically tested accordingly. The coating layer in case of the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter is applied to release an effectual proportion of Paclitaxel to the vessel wall of the artery at the dilated stenosis. The drug substance Paclitaxel is known to reduce the risk of restenosis by inhibition of smooth muscle cell proliferation. During the insertion of the balloon catheter and tracking to the lesion, the folded balloon protects the loaded drug substance from early wash-off effect. The anti-proliferative drug substance Paclitaxel will be immediately released at the lesion site after 120 secs. Bioavailability of Paclitaxel is guaranteed because the drug substance is an integral part of the coating and not covered.

The FREEWAY™ Paclitaxel eluting PTA Balloon Catheter is available in different sizes (balloon length and balloon diameter) to accommodate with any kind of lesion length and vessel diameter. For FREEWAY™ 014, the available balloon lengths are 40 mm, 80 mm, 120 mm and 150 mm and the available balloon diameters are 2.00 mm, 2.50 mm, 3.0 mm, 3.50 mm and 4.00 mm. For FREEWAY™ 035, the available balloon lengths are 20 mm, 40 mm, 60 mm, 80 mm, 100 mm, 120 mm, 150 mm, 190 mm and 230 mm and the available balloon diameters are 4.00 mm, 5.00 mm, 6.0 mm, 7.00 mm and 8.00 mm.

In 2016 the high-pressure balloon sizes of the FREEWAY™035 for the treatment of arteriovenous shunt lesions in hemodialysis patients became available on the market. This version is characterized by a higher nominal pressure of 12 bar and a higher rated burst pressure of 20 bar. The FREEWAY™ Shunt balloon catheter is available in the lengths 20, 40 and 60 mm and the diameters 4.0 - 8.0 mm.

4.1 Product sales volumes

a) FREEWAY 014

The following table contains the sold quantities of the product FREEWAY™ 014 Paclitaxel eluting PTA Balloon Catheter:

	2021/2022 QTY	2022/2023 QTY	2023/2024
FREEWAY™ 014	2180	1570	2071

Total Quantity Sold: 5821

b) FREEWAY 035

The following table contains the sold quantities of the product FREEWAY™ 035 Paclitaxel eluting PTA Balloon Catheter:

	2021/2022 QTY	2022/2023 QTY	2023/2024
FREEWAY™ 035	3299	2296	4221

Total Quantity Sold: 9816

5. Clinical background and state of the art

5.1 Clinical background

Peripheral arterial disease (PAD) is a narrowing or occlusion of peripheral arteries others than those of the coronary or cerebral arterial system. PAD most commonly occurs in the arteries of the upper and lower legs, but also other arteries can be involved. The characteristic symptom of PAD is leg pain when walking and soothing with rest, called intermittent claudication. In more severe stages with complications skin ulcers and tissue loss can occur that require amputation of the affected limb. Attendant symptoms are coronary artery disease and stroke; however 50% of patients suffering PAD are without symptoms. Main risk factors for PAD are smoking, diabetes, hypertonia and hyperlipidemia. The narrowing of the arteries occurs due to a plaque buildup on the inside of the arteries, known as atherosclerosis and can proceed to a complete occlusion of the vessel.

To re-open stenotic or occlusive femoropopliteal mid and long lesions primary stenting is the recommended therapy [18]. Several studies examined the safety and efficacy of different treatment methods and compared stenting to PTA [19-23] or drug-eluting balloons (DEB) with standard balloon angioplasty [11, 24-27]. Performing PTA with drug-eluting balloons can inhibit the intimal hyperplasia after vessel dilatation and help to prevent restenosis of the target lesion. All above mentioned DEB studies show a beneficial effect of delivering Paclitaxel to the vessel wall.

Some of these studies allowed no or only provisional stenting or left it to the decision of the physician [11, 16, 24, 26-27]. The single center study of Liistro et al. [10] performed systematic stenting not before but after previous DEB or standard PTA dilatation. Their study showed a positive rate for binary restenosis and TLR after 12 months for the DEB arm. The PACUBA Trial [7] enrolled and randomized 74 patients with in-stent restenosis (ISR) in the femoropopliteal arteries to either DEB or standard PTA balloon treatment. The authors found a significant higher patency rate for the patients who underwent DEB angioplasty. The Freeway Stent Study [8] tested the safety and efficacy of post-dilatation with a FREEWAY™ versus an uncoated balloon in occlusive or stenotic femoropopliteal arteries of patients that needed primary nitinol stenting. Patients in the FREEWAY group had significant higher patency rates at 6 and 12 months and a better improvement in Rutherford categories. Besides the two randomized trials [7, 8], the FREEWAY™ DEB was examined in AV shunt registries [9, 32, 33] where it showed positive results in the treatment of failing dialysis access in hemodialysis patients.

5.2 Data from Literature - Search and Review

This clinical evaluation was performed in compliance with MEDDEV 2.7.1, appropriately considering the product classification according to the Medical Device Directive 93/42/EEC as a Class III device.

Therefore, common procedures for systematic literature research were applied, and available documents from the Technical Documentation of FREEWAY™ Paclitaxel eluting PTA Balloon Catheter as well as medical device vigilance data were analyzed.

Through this procedure, answers to the following questions regarding the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter were searched for (summary of answers to the following questions under point 5):

a. Is the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter suitable for the treatment of peripheral lesions and does it represent current medical practice and "state of the art" technologies?

b. Is the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter at least equivalent or has its advantages over conventional POBA angioplasty regarding the treatment of peripheral lesions?

c. Is the drug substance Paclitaxel, as released from the delivery balloon, effective to reduce the rate of restenosis?

d. Which undesirable effects and potential risks have been reported for drug-eluting balloons in general and are to be expected for the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter in particular?

e. Are these undesirable effects and potential risks acceptable considering their nature and frequency and comparing them to the benefits of the product?

f. Is a post market clinical follow-up investigation pursuant to MEDDEV 2.12.-2 [5], respectively pursuant to EN ISO 14155-1 and -2 necessary to further investigate potential risks and benefits of the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter?

Evaluation of Significance of Selected References

According to MEDDEV 2.7.1 all selected literature was evaluated to make clear the significance that is attached to the selected literature. For this, both the authors, the reputation of the journals and the scientific quality of the reported data were considered.

Regarding the scientific literature, most of the identified journals contained peer-reviewed articles, which are understood to provide reliable scientific information. Furthermore, the authors were checked in www.pubmed.com. For the most first respectively last authors listed in each publication it was obvious, that these authors had published several articles in the area of interventional radiology or angiology respectively regarding drug-eluting balloon catheter. Therefore, the scientific literature referred to in this report is evaluated by the Expert to contain scientifically sound information prepared by designated and experienced authors.

Sources for Systematic Literature Research

For this clinical evaluation the following scientific sources were considered:

- Technical Documentation of the manufacturer for the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter.
- Eurocor Tech study reports and publications with the device under evaluation, FREEWAY™: pre-clinical data [6, 30], PACUBA Trial [7], Freeway Stent Study [8], Italian AV Registry [9], Turkish AV Registry [33]
- Scientific literature as identified by PubMed regarding drug-eluting balloons.

Literature Review Protocol

For the selection of publications and study data of predicate devices, the medical literature database PubMed was searched for different search terms and keywords to cover a range of pertinent publications in the field of interest. The search results were evaluated according to their relevance and methodological quality. Literature that did not match these criteria was rejected and not consulted for review. One search focus was on studies of randomized trials that used drug-eluting balloons in the femoropopliteal arteries. The following tables give the search terms.

Search term "SFA" AND "drug-eluting balloon" AND "randomized trial" for data on predicate devices. **Hits: 14**	
List of selected literature:	
1	[10] Liistro, F, et al. "Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery)." JACC: Cardiovascular Interventions 6.12 (2013): 1295-1302.
2	[11] Tepe, G, et al. "Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and/or popliteal peripheral artery disease: 12-month results from the IN. PACT SFA randomized trial." Circulation (2014): CIRCULATIONAHA-114.

3	[12] Laird, JR, et al. "Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN. PACT SFA." *Journal of the American College of Cardiology* 66.21 (2015): 2329-2338.
4	[15] Fanelli, F, et al. "The" DEBELLUM"--lower limb multilevel treatment with drug eluting balloon--randomized trial: 1-year results." *The Journal of cardiovascular surgery* 55.2 (2014): 207-216.
5	[38] Antonopoulos, C N., et al. "A network meta-analysis of randomized controlled trials comparing treatment modalities for de novo superficial femoral artery occlusive lesions." Journal of vascular surgery 65.1 (2017): 234-245.
6	[37] de Boer, S W., et al. "Short-term Results of the RAPID Randomized Trial of the Legflow Paclitaxel-Eluting Balloon With Supera Stenting vs Supera Stenting Alone for the Treatment of Intermediate and Long Superficial Femoral Artery Lesions." Journal of Endovascular Therapy 24.6 (2017): 783-792.
7	[36] Schneider, P A., et al. "Mortality Not Correlated With Paclitaxel Exposure: An Independent Patient-Level Meta-Analysis of a Drug-Coated Balloon." Journal of the American College of Cardiology 73.20 (2019): 2550-2563.
8	[39] van den Berg, J C. "Drug-eluting balloons for treatment of SFA and popliteal disease–A review of current status." European journal of radiology 91 (2017): 106-115.
9	[40] Stabile, E, et al. "Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis." Journal of the American College of Cardiology 60.18 (2012): 1739-1742.
10	[41] Duda, S H., et al. "Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial." Journal of Endovascular Therapy 13.6 (2006): 701-710.
	List of rejected Literature
11	Teichgräber, U, et al. "The effectiveness of the paclitaxel-coated Luminor® balloon catheter versus an uncoated balloon catheter in superficial femoral and popliteal arteries in preventing vessel restenosis or reocclusion: study protocol for a randomized controlled trial." Trials 17.1 (2016): 528.
12	Gandini, R, et al. "Treatment of chronic SFA in-stent occlusion with combined laser atherectomy and drug-eluting balloon angioplasty in patients with critical limb ischemia: a single-center, prospective, randomized study." Journal of Endovascular Therapy 20.6 (2013): 805-814.
13	Lammer, J, et al. "Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery lesions: the randomized VIASTAR trial (Viabahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease)." Journal of the American College of Cardiology 62.15 (2013): 1320-1327.
14	Sridharan, N D., et al. "Cost-effectiveness analysis of drug-coated therapies in the superficial femoral artery." Journal of vascular surgery 67.1 (2018): 343-352.

Search term "drug-coated balloon" AND "in-stent restenosis" AND "superficial femoral artery" AND "randomized trial", Hits: 3	
List of selected literature:	
1	[13] Krankenberg, H, et al. "Drug-coated balloon versus standard balloon for superficial femoral artery in-stent restenosis: the randomized Femoral Artery In-Stent Restenosis (FAIR) trial." Circulation (2015): CIRCULATIONAHA-115.

2	[42] Jia, X, et al. "Acotec drug-coated balloon catheter: randomized, multicenter, controlled clinical study in femoropopliteal arteries: evidence from the AcoArt I trial." JACC: Cardiovascular Interventions 9.18 (2016): 1941-1949.
3	[43] Ansel, G M., et al. "Drug-Coated Balloon Treatment of Femoropopliteal Lesions Typically Excluded From Clinical Trials: 12-Month Findings From the IN. PACT Global Study." Journal of Endovascular Therapy 25.6 (2018): 673-682.

Search term "BTK" AND "drug-eluting balloon" AND "randomized trial", Hits: 9	
List of selected literature:	
1	[44] Jens, S. et al. "Randomized trials for endovascular treatment of infrainguinal arterial disease: systematic review and meta-analysis (part 1: above the knee)." European Journal of Vascular and Endovascular Surgery 47.5 (2014): 524-535.
2	[14] Liistro, F, et al. "Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia." Circulation (2013): CIRCULATIONAHA-113.
3	[15] Fanelli, F, et al. "The" DEBELLUM"--lower limb multilevel treatment with drug eluting balloon--randomized trial: 1-year results." The Journal of cardiovascular surgery 55.2 (2014): 207-216.
4	[16] Fanelli, F, et al. "Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial." Journal of Endovascular Therapy 19.5 (2012): 571-580.
	List of rejected literature
5	Haddad, S E, et al. "One Year Primary Patency of Infrapopliteal Angioplasty Using Drug-Eluting Balloons: Single Center Experience at King Hussein Medical Center." Journal of clinical imaging science 7 (2017).
6	Langhoff, R A B, and E Buschmann. "Promising role of drug-coated balloons in the tibial vessels?." The Journal of cardiovascular surgery 57.5 (2016): 667-676.
7	Mosquera, NJ A. "Drug-eluting stents remain the golden standard for below-the-knee occlusive disease." The Journal of cardiovascular surgery 57.5 (2016): 677-682.
8	Fanelli, Fabrizio, and Alessandro Cannavale. "Drug coated balloons below-the-knee: just too early?" The Journal of cardiovascular surgery 57.1 (2016): 18-22.
9	Bosiers, M., et al. "Update management below knee intervention." Minerva cardioangiologica 57.1 (2009): 117-129.

Search term was set to "drug-eluting balloon" AND "dialysis" AND "randomized trial" **Hits: 8**	
List of selected literature	
1	[17] Kitrou PM, et al. Paclitaxel-coated versus plain balloon angioplasty for dysfunctional arteriovenous fistulae: one-year results of a prospective randomized controlled trial. Journal of Vascular and Interventional Radiology. 2015 26(3):348-54.
2	[45] Portugaller, Rupert H., P I. Kalmar, and H Deutschmann. "The eternal tale of dialysis access vessels and restenosis: are drug-eluting balloons the solution?." The journal of vascular access 15.6 (2014): 439-447.

3	[46] Swinnen, JJ , et al. "Multicentre, randomised, blinded, control trial of drug-eluting balloon vs Sham in recurrent native dialysis fistula stenoses." The journal of vascular access 20.3 (2019): 260-269.
4	[47] Irani, F G, et al. "Hemodialysis arteriovenous fistula and graft stenoses: randomized trial comparing drug-eluting balloon angioplasty with conventional angioplasty." Radiology 289.1 (2018): 238-247.
5	[48] Kitrou, P M., et al. "Drug-eluting versus plain balloon angioplasty for the treatment of failing dialysis access: final results and cost-effectiveness analysis from a prospective randomized controlled trial (NCT01174472)." European journal of radiology 84.3 (2015): 418-423.
	List of rejected literature
6	Veroux, Pierfrancesco, et al. "Primary balloon angioplasty of small (≤ 2 mm) cephalic veins improves primary patency of arteriovenous fistulae and decreases reintervention rates." Journal of vascular surgery 57.1 (2013): 131-136.
7	Sakakibara, Takashi, et al. "Sirolimus-eluting stent vs. everolimus-eluting stent for coronary intervention in patients on chronic hemodialysis." Circulation Journal (2011): 1111221481-1111221481.
8	El-Menyar, Ayman A., Jassim Al Suwaidi, and David R. Holmes Jr. "Use of drug-eluting stents in patients with coronary artery disease and renal insufficiency." Mayo Clinic Proceedings. Vol. 85. No. 2. Elsevier, 2010.

5.3 Data from Literature Preclinical and Clinical data

PACCOCATH®-related studies in pigs [28]

Effectiveness of another Paclitaxel eluting balloon (coating was a mix of Paclitaxel and the contrast medium Iopromide = Paccocath technology; predicate device) was tested in an iliofemoral in-stent restenosis (ISR) model using the familial hypercholesterolemic swine (FHS). Twenty-four animals underwent balloon overstretch and implantation of a self-expanding stent in the iliofemoral segment. Resulting In-stent restenosis (ISR) lesion were treated after 21 days with either a 1µg/mm² (n=8) or a 3µg/mm² (n=8) Paclitaxel eluting balloon catheter (Mixture of Paclitaxel and the contrast media iopromide) or an identical uncoated PTA balloon catheter (n=8). 28 days after treatment, percent diameter stenosis was analyzed by quantitative vascular analysis. Degree of stenosis was higher in the control group (31.2 ± 13.7%) compared with 1 µg/mm² (19.3 ± 14.0%, 38% reduction) and 3 µg/mm² (8.6 ± 10.7%, 72% reduction) in the drug-eluting balloon groups. Intravascular ultrasound analysis showed reductions in neointimal volume stenosis of 36% (1 µg/mm² dose, $p = 0.04$) and 55% (3 µg/mm² dose, $p < 0.01$). Histological analysis showed highest degree of percent area stenosis in the control group (65 ± 14.3%). Reductions in percent area stenosis was 13.2% ($p = 0.5$) and 26% ($p = 0.04$) in the 1 µg/mm² and 3 µg/mm² dose groups, respectively [28]. The authors conclude that the FHS model of iliofemoral ISR showed a dose-dependent effect on the inhibition of neointimal proliferation by DEB treatment. Further the authors argue that this study demonstrated the biological efficacy of a drug-eluting balloon treatment in the peripheral vascular system, comparable to the findings in human clinical trials. [28]

Clinical studies using the IN.PACT™ Admiral [10-14, 24]

IN.PACT SFA Trial [11, 12]

The trial assesses the safety and efficacy of IN.PACT Admiral vs. standard PTA for the treatment of SFA and proximal popliteal arterial disease due to claudication and rest pain. The IN.PACT SFA trial was a randomized controlled dual phase trial conducted in Europe and the US. 331 Patients with symptomatic (Rutherford 2 to 4) femoropopliteal lesions were randomization in a 2:1 ratio to either a treatment with a DEB or standard PTA. DEB was used in 220 subjects with 221 lesions and standard PTA was used in 111 subjects with 113 lesions. Restenosis was either assessed by Duplex Ultrasound Core Lab or by Angiographic Core Lab which were blinded. The endpoints were primary patency and freedom from CD-TLR at 12 and 24 months. The primary safety endpoint was freedom from device-and procedure-related death through 30 days, and freedom from target limb major amputation and clinically-driven target vessel revascularization (TVR) through 12 months. At 12 months patients treated with the DEB had higher primary patency compared to standard PTA treatment (82.2% vs. 52.4%; P <0.001). The rate of clinically-driven target lesion revascularization was 2.4% in the DEB arm compared with 20.6% in the standard PTA arm (P <0.001). Vessel thrombosis in was low in both arms (1.4% after DEB and 3.7% after PTA (P =0.10)). No device or procedure-related deaths and no major amputations occurred [11]. At 24 months, patients treated with DEB had a significant higher primary patency compared to patients who had a standard PTA (78.9% vs. 50.1%; p < 0.001). The rates of CD-TLR were 9.1% and 28.3% (p < 0.001) for the DEB and PTA groups, respectively. The overall mortality rate was 8.1% in the DEB versus 0.9% in the standard PTA group (p = 0.008). No device- or procedure-related deaths and no major amputations occurred in either group through the 24-month follow-up. The rate of vessel thrombosis was low (1.5% DCB vs. 3.8% PTA; p = 0.243), with no new events reported between 1 and 2 years [12].

The authors conclude that the DEB treatment had superior treatment effects after 12 and 24 months with a significant higher primary patency, a lower rate of clinically driven TLR and a similar functional status improvement with fewer repeat interventions [11, 12].

FAIR Trial [13]

The randomized controlled trial conducted by Krankenberg et al. [13] focused on patients with in-stent restenosis in the SFA and chronic limb ischemia. Their trial recruited 109 patients in five german centers with duplex ultrasound follow-up at 6 and 12 months. The rate of patients with total occluded lesions was 28.6%, 25.2% of the lesions were moderately or heavily calcified. The primary study endpoint was recurrent ISR assessed by ultrasound. At 6 months the rate of recurrent ISR was much lower in the DEB arm (15.4%) compared to patients treated with a standard PTA balloon (44.7%). At 6 months, freedom from target lesion revascularization (TLR) was 96.4 % (DEB) vs. 81.0% (standard PTA) (P = 0.0117)). After 12 months the beneficial effect of reduced need for re-intervention was even more visible with 90.8% (DEB) vs. 52.6% (standard PTA) (P < 0.0001) freedom from target lesion revascularization. Two patients in the DEB and 3 patients in the POBA arm died without relation to the procedure. No amputations were necessary [13] The authors conclude that a treatment of SFA ISR with DEB is associated with less recurrent restenosis and a better clinical outcome with at the same time no apparent difference in safety.

PACIFIER Trial [24]

The randomized controlled PACIFIER trial enrolled 85 patients with symptomatic femoro-popliteal atherosclerotic disease in 3 centers in Germany. Patients were randomized to angioplasty with either a Paclitaxel coated IN.PACT Pacific or an uncoated Pacific balloon. The primary end point was late lumen loss at 6 months (assessed by blinded angiographic corelab). Secondary endpoints were binary restenosis, change in Rutherford class at 6 months and target lesion revascularization plus major adverse clinical events at 6 and 12 months [24]. Quantitative angiography at six month showed significant lower late lumen loss (−0.01mm (95% CI,−0.29; 0.26) versus 0.65mm [0.37; 0.93], P=0.001) and a lower rate of binary restenosis (8.6% DEB vs. 32.4% PTA; P=0.01). In the DEB group significant fewer major adverse events and a significant lower TLR rate occurred at 12 months compared to the uncoated PTA group (MAE 7.1% vs. 34.9%; P<0.01; TLR 7.1% vs. 27.9%; P=0.02). The authors conclude that the use of the Paclitaxel coated balloon leads to a significant reduction of late lumen loss and restenosis at 6 months and a significant reduction in TLR rate after 12 months.

DEBATE SFA Trial [10]

The randomized controlled DEBATE SFA trial [10] enrolled 104 patients and compared DEB with standard balloon angioplasty followed by systematic implantation of self-expanding nitinol stents (BMS) in the SFA. The primary endpoint was binary restenosis at 12 months. Secondary endpoints comprised freedom from target lesion revascularization and major amputation. After 12 months 17.0 % of the lesions in the DEB and 47.3 % (p=0.008) in the standard group had >50% diameter restenosis (by angiography) or a peak systolic velocity ratio ≥ 2.5 (by DUS). Freedom from TLR at 12 months was higher in the DEB group but did not reach statistical significance (p=0.07). No major amputations were reported. The authors conclude that a DEB treatment prior to BMS implantation reduces restenosis and the need for target lesion revascularization at 12 month follow-up [10].

Clinical studies using the IN.PACT® Amphirion Predicate Device in the lower leg [14-16]

DEBATE BTK Trial [14]

The Study by Liistro et al. [14] focused on the efficacy of a DEB compared to standard PTA treatment in below the knee angioplasty interventions. The randomized open-label, single center study enrolled 132 patients with diabetes mellitus, critical limb ischemia (Rutherford class 4 or higher) with stenotic or occluded below-the-knee vessel lesions >40 mm. Primary endpoint was in-segment binary restenosis at one year by angiographic or ultrasonographic follow-up. Secondary endpoints included major amputations and target vessel occlusion. Mean length of the treated segments was similar in both groups (129±83 mm DEB; 131±79 PTA (P=0.7)). Binary restenosis occurred in 27% of the patients in the DEB arm compared to 74% in the standard PTA arm (P<0.001). Revascularization of the target lesion was performed in 18% of the DEB patients compared to 43% of the patients in the PTA arm (P<0.001). Target vessel occlusion occurred in 17% of the DEB group and 55% of the PTA group (P<0.001). The authors conclude that a DEB treatment of below-the-knee lesions in diabetic patients with critical limb ischemia significantly reduce the rate of restenosis, the TLR-rate and the rate of target vessel occlusion (Liistro et al. 2013).

DEBELLUM Trial [15, 16]

The trial by Fanelli et al. [15,16] enrolled 50 patients with 122 lesions in the SFA (75.4 %) and BTK (26.4 %) arteries and randomized them to a treatment with either balloon angioplasty by DEB or standard balloon. Primary stenting was allowed in the SFA only. Forty percent of the patients presented multilevel lesions, the mean lesion length was 7.5 ± 3.5 cm. The primary endpoint was late lumen loss at 6 months. Secondary endpoints comprised rate of target lesion revascularization (TLR), amputation and thrombosis. At 12 months late lumen loss (LLL) was 0.64±0.9 mm in DEB group and 1.81±0.1 mm in the standard PTA group (P=0.01). LLL in the femoropopliteal region was 0.61±0.8 mm for DEB vs. 1.84±0.3 mm for standard PTA (P=0.02). LLL in the BTK arteries was 0.66±0.9 mm for DEB vs. 1.69±0.5 mm for standard PTA (P=0.03). The overall TLR was 12.2% for DEB and 35.3% for PTA (P<0.05). Amputation and thrombosis rate was lower in the DEB group (each with 4%) compared to PTA (12% and 8%), (P=0.36 and P≥0.05). Rate of major adverse events was lower (24% vs. 60%; P<0.05) and ABI improved more in the DEB group (0.81±0.3 vs. 0.68±0.13; P=0.02). The authors describe better outcomes for restenosis, TLR rate and clinical improvement for the DEB patients. They conclude that the initially found results after 6 months were again confirmed after 12 months.

Clinical studies using the IN.PACT™ Admiral for treatment of failing dialysis access

DEB Dialysis Access [17]

The study of Kitrou et al. [17] investigated the treatment of failing dialysis access by drug-eluting balloon (DEB) versus plain balloon angioplasty (PTA). 40 Patients with venous stenosis causing a failing dialysis access were randomized to treatment by either DEB or standard PTA. The study included patients with arteriovenous fistulas and synthetic arteriovenous grafts. Endpoints were technical success and primary patency at 1 year. Follow-up was performed by angiography every two months. At 1 year primary patency was significantly higher in the DEB group (35%) compared to the standard PTA group (5%) ($p < 0.001$). Median primary patency was 0.64 years for patients treated with DEB compared to 0.36 years for standard PTA treatment ($p = 0.0007$). The authors conclude that DEB angioplasty in patients with failing dialysis access significantly improves patency rates compared to standard PTA treatment. They underline that the treatment principle of "leaving nothing behind" marks DEBs as a promising technology in dialysis access management.

Clinical studies using the PACCOCATH® (now: SeQuent® Please) device

Thunder Trial [25]

The Thunder trial was a prospective, controlled, randomized, blinded, multicenter study comparing the Paclitaxel coated balloon catheter Paccocath (now: SeQuent® Please), coated with the same dosage of 3 µg Paclitaxel/mm² as the FREEWAY™ balloon catheter, with a conventional uncoated balloon catheter or local administration of Paclitaxel together with contrast medium (47). 154 patients were enrolled in this study (54 pts with POBA, 52 pts with POBA and Paclitaxel-contrast medium mixture, 48 pts with DEB Paccocath®). After 6-month follow-up the primary endpoint of the study, the late lumen loss, was measured. Secondary study endpoints

were the rate of thrombotic complications, TLR and death. The mean late lumen loss was 1.7 mm in the uncoated group, 2.2 mm in the uncoated group with local Paclitaxel-contrast medium application and 0.4 mm in the Paclitaxel-coated group. 37% of the patients in the uncoated group had a restenosis compared to 29% of the patients in the uncoated group with local Paclitaxel-contrast medium administration and 4% of the patients in the Paclitaxel-coated group. The authors conclude that the use of Paclitaxel-coated angioplasty balloons during percutaneous treatment of femoropopliteal disease is associated with significant reductions in late lumen loss and target lesion revascularization. No significant benefit is seen with the use of Paclitaxel-containing contrast medium [25].

CONSEQUENT Trial [29]

The Consequent trial was a randomized trial that enrolled 153 patients in 8 centers with *de novo* or restenotic lesions in the femoral artery and the proximal two segments of the popliteal artery. Patients were randomized to either treatment with a DEB or standard PTA. Primary endpoint was late lumen loss at 6 months (QA, corelab). Secondary endpoints included rate of binary restenosis > 50% at 6 months (QA, corelab), Clinically driven TLR rate, Ankle Brachial Index, Walking Distance and Rutherford stages at 6, 12 and 24 months. The study device was the SeQuent® Please OTW catheter with 3µg Paclitaxel/mm² and resveratrol as drug carrier and matrix builder. This excipient changed in the SeQuent® Please balloon compared to the older version that used iopromid as carrier for Paclitaxel. After 6 months late lumen loss was significantly lower in the DEB group (0.35mm vs. 0.72mm, p=0.006) and TLR rate was lower in the DEB group at 12 months (17.8 % vs. 37.7 %, p=0.008). The walking distance for DEB patients at 12 months was longer compared to patients that received standard treatment (156 vs. 94m, p=0.012). The authors conclude that a treatment with the SeQuent® Please DEB has beneficial effects for the patients as the need for re-intervention is reduced and the walking distance after 12 months significantly increased [29].

6. Device under evaluation

6.1. Type of evaluation

The clinical evaluation is based on clinical investigations made with the device under evaluation. Comprehensive data from two randomized controlled trials and registries with the FREEWAY™ catheter allow the appraisal of the device safety and efficacy. Moreover, clinical data for two comparable devices (predicate device) from literature were used to substantiate the safety and efficacy appraising for peripheral drug-eluting balloons similar to the device under evaluation.

6.2. Predicate devices

6.2.1 Identification and evaluation of predicate devices

As requested by MEDDEV 2.7.1., the experts reported about pre-clinical and clinical data generated by the manufacturer with the device under evaluation and also selected predicate devices, which are similar to the medical device under evaluation. For this, the technical, biological and clinical properties, the intended purpose, as well as type and duration of body contact of the selected predicate devices were considered.

Any clinical reports or human use history of the selected predicate devices were systematically searched and evaluated regarding the claimed clinical effectiveness and safety of the medical devices in question.

The SeQuent® Please (B.Braun) and the IN.PACT™ (Medtronic) drug-eluting balloons for percutaneous transluminal angioplasty (PTA) were selected as predicate devices to the FREEWAY™ drug-eluting balloon catheter. To date, there are several DEB on the market and the SeQuent® Please and the IN.PACT™ are drug-eluting balloons with a comparably good clinical documentation. With respect to the clinical characteristics the drug-eluting balloon under consideration is used for the same purpose (improving luminal diameter), at the same site in the body (peripheral arteries) and in a similar population (people who are in need of PTA) as the predicate devices SeQuent® Please and IN.PACT™. The IN.PACT™ technology comes on the three different balloon platforms Admiral, Pacific and Amphirion, differing in guide wire compatibility (0.035", 0.018" and 0.014" respectively) and balloon diameter (Ø 4-7 mm, Ø 4-7 mm and Ø 2-4 mm respectively).

Regarding the biological characteristics, the SeQuent® Please and the IN.PACT™ are used in the same human tissues (peripheral artery tissue) and body fluid (blood) as the FREEWAY™ drug-eluting balloon. In addition, the predicate devices SeQuent® Please and IN.PACT™ are covered with the same drug substance Paclitaxel and similar dosage (of 3.0 µg/mm² SeQuent® Please) and (3.5 µg/mm² IN.PACT™) as the device under consideration. Nevertheless, the coating differs between the devices. The SeQuent® Please OTW peripheral DEB is coated with a mix of Paclitaxel and resveratrol (the former SeQuent® Please was based on the Paccocath® technology with iopromide), whereas IN.PACT™ is based on the Freepac™ hydrophilic drug coating formulation using urea as "spacer" for separating Paclitaxel molecules. In contrast, the coating of the device under consideration is a mix of Paclitaxel and shellac (so called "BIOSHELL balloon coating technology"). Shellac is a natural resin which is free of risk for the patient. A test regarding the in vitro cytocompatibility of shellac by utilization of primary human cells showed that shellac did not impair viability of endothelial cells (EC) and smooth muscle cells (SMC), did not induce proliferation of SMC, and did not change the inflammatory status of EC. It was concluded that shellac is suitable for coating of drug-eluting intravascular devices [30].

Drug carriers such as iopromid, resveratrol, urea and shellac are applied with the intention to release an effectual portion of the drug substance Paclitaxel to the local wall of the artery at the dilated stenosis.

The technical characteristics of the device under evaluation and the predicate devices demonstrate equivalence in the properties, the principles of operation and the deployment method.

It can be concluded that substantial comparability of the predicate devices SeQuent® Please and IN.PACT™ was demonstrated in nearly all characteristics. Nevertheless, a difference regarding one excipient was identified. Whereas the FREEWAY™ drug-eluting balloon (device under consideration) is using shellac, SeQuent® Please utilizes resveratrol (in the former version the contrast medium iopromide) and IN.PACT™ the "spacer" molecule urea as coating. All other parameters of the balloon remain identical. The coatings are applied to release an effectual proportion of Paclitaxel to the vessel wall of the artery at the dilated stenosis (to reduce restenosis).

6.3 Data generated by the manufacturer / Data with the device under evaluation

6.3.1. Pre-clinical data

Study Shellac Coating [30]

In Vitro Evaluation of Cytocompatibility of Shellac as Coating for Intravascular Devices

The study of Peters et al. [30] examined the cytocompatibility of shellac as an excipient and coating on intravascular devices.

Methods: Tested was a shellac extraction in cell culture medium of human dermal microvascular endothelial cells (hDMEC) and human smooth muscle cells (hSMC). It was examined whether exposure of cells with extraction products and direct contact influence: the i) cytocompatibility/metabolic cell activity, ii) pro-inflammatory activation (IL-8 release) and iii) the cellular phenotype (cell shape, intercellular contact).

Conclusions: shellac has cytocompatibility and did show no signs of cytotoxicity by direct and indirect contact to endothelial and smooth muscle cells shellac does not induce pro-inflammatory activation in human endothelial cells [30].

FREEWAY™ Pre-clinical Trial [6]

Purpose: The aim of the present study was to investigate the pharmacokinetics (tissue Paclitaxel concentration and, implicitly, the eluting dynamics) and safety and efficacy of the Paclitaxel eluting PTA Balloon Catheter in a porcine artery overstretch injury model. A pre-clinical trial studying the effects of FREEWAY™ Paclitaxel eluting PTA Balloon Catheter use in porcine peripheral arteries was carried out at the Medical University of Vienna in 2014 [6].

Methods: Peripheral percutaneous balloon intervention. Fifty-four (54) domestic pigs (weight 30-40 kg) were pre-treated with 300 mg clopidogrel and 250 mg aspirin. After overnight fasting, the pigs were anaesthetized for peripheral intervention. The balloons were then inflated with 6–12 atm pressure to achieve a 1.3:1 balloon/ artery ratio, producing overstretch injury. Balloon inflation was controlled by angiography, and the inflated balloon size was related to the vessel size displayed by the baseline angiography. The duration of balloon inflation was 60 or 120 s, depending on the experimental setup. The animals were allowed to recover after the procedure. Upon completing the predetermined follow-up time, the animals were humanely euthanized with saturated potassium chloride.

Blood samples were taken at 5, 10, 20, and 60 min after the interventional procedure. At 1 h and 1, 3, and 9 days of follow-up, the Paclitaxel concentration in femoral and iliac arterial tissue was measured using high-performance liquid chromatography. All balloon remnants were stored for measurements of Paclitaxel on the surface.

All histopathological, histomorphometric, and immunohistochemically analyses were performed in accordance with published guidelines by experienced investigators who were blinded to the treatment (Supplementary Materials and Methods). The remodeling index was calculated as the

external elastic lamina (EEL) area of the lesion with the highest grade of stenosis divided by the EEL area of the reference segment (mean value of the proximal and distal reference EEL area).

Results: The follow-up period was 32±2 days. For the safety study, an overstretch injury was incited and histopathological and histomorphometric analyses were conducted on the vessels under study.

A summary list of results of the study is given below [6]:

a) The common iliac artery was longer and wider than the femoral arteries, representing a size similar to the human femoral arteries and better fit of human relevant DCB size. However, the iliac arteries are elastic type with dominating collagen and elastin fiber in the tunica media, with relatively few smooth muscle fibers, while the femoral arteries are muscular-type arteries with outweighed content of smooth muscle cells.

b) Overstretch balloon dilation resulted in severe vessel injury in each case con-firmed by angiography, OCT and histology. OCT images presented dissection, parietal and intraluminal floating thrombi, without acute closure of the arteries. However, no major complication, such as acute vessel closure, vessel rupture, or bleeding, or death was observed; thus, the balloon use was safe in each case.

c) Longer inflation time (2 min) was definitively more effective as regards tissue retention of the drug, as compared with the 1 min dilation in both arteries. Therefore, the efficacy studies were performed with the use of 2 min balloon inflation time, also more commonly used in human peripheral interventions.

d) FREEWAY™ DEB inflation resulted in high PTX tissue concentration both in the femoral (460±214 ng/mg) and iliac arteries (655±187 ng/mg) 1h post balloon use by 2min balloon inflation time. The drug persisted in the arterial wall up to 9 days post drug delivery.

e) The proximal and distal reference segment drug concentrations were 36.9±17.8 and 17.0±6.3 ng/mg at 1h FUP using 2 min balloon inflation time of the femoral arteries, respectively.

f) As expected, measured plasma concentration of Paclitaxel decreased with time after DCB use.

g) The total amount of remnant Paclitaxel on the balloon surface was 53.2±9.8% and 30.9±4.3% using 1 and 2 min dilation of the femoral arteries, respectively.

h) Quantitative peripheral angiography revealed significant decrease in %diameter stenosis of femoral arteries, with a trend towards less stenosis of the iliac arteries after Freeway dilation.

i) At 32±2 days FUP, OCT imaging revealed a significantly lower %area stenosis of the Freeway-group both in femoral and iliac arteries, proving the efficacy of the DCB use in peripheral arteries.

j) OCT displayed suspected vessel constriction if plain balloon dilation was used. Quantitative OCT images resulted in a remodeling index of >1 in Freeway and <1 in plain balloon dilated femoral arteries, suggesting adaptive and constrictive remodeling of the vessels, respectively. No meaningful arterial remodeling could be shown in the elastic type iliac arteries.

k) Histopathological analyses showed similar inflammation and injury scores be-tween the groups.

l) Endothelialization was complete in both device groups in femoral arteries; in the iliac arteries complete endothelialization was seen in plain balloon group, and 95±5% with the Freeway balloon. No calcification of the vessels was seen.

m) Histomorphometry showed significantly larger lumen area, smaller neointimal area and lower %area stenosis in the Freeway device group compared with the plain balloon in both arteries.

n) Paclitaxel exposure of the arterial wall inhibited fibrin deposition in the tunica intima and media in the femoral arteries, and in the intima in iliac arteries.

Conclusion: Use of Paclitaxel DEB FREEWAY™ in peripheral (femoral and iliac) arteries is safe and efficacious.

6.3.2. Clinical trials using the device under evaluation

Freeway Stent Study [8]

The Freeway Stent Study is a trial that investigated the inhibition of restenosis by stenting plus post-dilatation by FREEWAY™ Paclitaxel eluting PTA Balloon Catheter versus stenting and post-dilatation by standard PTA balloon in the treatment of occluded or stenotic superficial femoral or popliteal arteries. It is a randomized, prospective, multicenter, open study of 204 patients in 13 sites in Germany and Austria. There are two arms: a) stenting and post-dilatation by uncoated balloon catheters b) stenting and post-dilatation with Paclitaxel coated balloon catheters. The primary endpoint was the rate of clinically driven target lesion revascularization at 6 months. The secondary endpoints included primary patency at 6 and 12 months, TLR rate at 12 months, shift in Rutherford classification, and change in ankle-brachial index (ABI) from baseline to 6 and 12 months, device success and procedural success. Follow-up at 6 and 12 months after intervention included clinical examination and duplex ultrasonography.

Study protocol: The study protocol was approved by the local ethic committees and carried out in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients were intended to give written informed consent.

Methods: The Freeway Stent Study used a 1:1 block randomization to guarantee a consistent and even randomization of patients in both study arms independent of patient enrollment numbers in the study centers. CDUS and angiographic data were analyzed by a blinded corelab to guarantee an independent assessment of patient vessel data. The number of patients was chosen to

Patient data: Patient´s baseline and follow-up angiography and ultrasound data were blinded and analyzed by an independent corelab. Primary patency was determined by corelab as PVR < 2.4 in duplex ultrasound sonography or restenosis <50% of target vessel diameter by angiographic data.

Results: The rate of clinical driven TLR at six months showed a strong trend for the FREEWAY™ (4.1%) compared to the PTA group (9.0%) (p=0.234). At 12 months follow-up the difference in TLR rate between the two arms was close to significance with 7.9 % in the FREEWAY™ versus 17.7 % in the PTA arm (p=0.064). Primary patency was significantly higher in the FREEWAY™ arm at 6 months (90.3 % vs. 69.8 % p=0.001) and at 12 months (77.4 % vs. 61.0 % p=0.027) compared to the standard balloon arm. Likewise significant was the better clinical improvement in one or more Rutherford classifications from baseline to six months (94.9 % vs. 84.3% p=0.027) and twelve months (95.5 % vs. 79.9 % p=0.003) for the patients treated with the FREEWAY™ DEB.

The overall safety was very high with only 1 % of major adverse events (MAE) in both arms at six months and 2.2 % for the DEB and 3.8 % for the PTA group at twelve months. No study related amputations occurred during the whole time of follow up. During the twelve months period one patient in every group suffered a thrombosis at target lesion and two patients in the PTA group and one in the DEB group died due to reasons not related to the study.

Conclusion: The study protocol, the methods, execution, reporting and analysis were in accordance with state-of-the-art criteria for randomized controlled trials. The reported significant better results in primary patency and clinical improvement at 6 and 12 months show an advantageous effect for a treatment with the study device.

Subgroup analysis of occluded vs. stenotic lesions in the Freeway Stent Study

Results of the subgroup analysis reflect the overall results and show for both subgroups a better outcome in patency rate (Occluded 79.6 % vs. 60.8 %; Stenotic 80.0 % vs. 60.0 %), TLR rate (Occluded 9.3 % vs. 16.7 %; Stenotic 5.7 % vs. 20.0 %) and a significant improvement in Rutherford categories (Occluded 98.1 % vs. 81.5 %; Stenotic 91.4 % vs. 80.0 %) for patients treated with the FREEWAY DEB compared to patients treated with standard balloon postdilatation. The patients in the subgroup with occluded lesions seem to profit even more from a DEB treatment in terms of patency and Rutherford improvement compared to the stenotic lesion subgroup.

Presentation: "Outcome of DCB and PTA post stenting in occluded versus stenotic lesions – subgroup analysis of the randomized Freeway Stent Study" Müller-Huelsbeck, LINC 2019 Leipzig, Germany.

Subgroup analysis of males and diabetics in the Freeway Stent Study

Results of the subgroup analysis show significant better results for patency (82.1 % vs. 58.9%), significant lower TLR rate (4.1 % vs. 16.9 %) and significant better improvement in Rutherford status (97.2 % vs. 78.0 %) for males treated with FREEEWAY DEB compared to patients treated with standard balloon postdilatation at 12 months, respectively. No significant differences between the study arms in females could be found (proportion of females in the study and the subgroups is low, females in the PTA arm perform slightly better in patency and TLR rate).

Results of the diabetic subgroup analysis show that both, diabetic and non-diabetic patients benefit from a postdilatation with FREEWAY DEB. This results in a better patency rate for DEB in diabetic patients (87.5 % vs. 61.9 %) and non-diabetic patients (73.7 % vs. 63.0 %) and a lower TLR rate in diabetic (12.0 % vs. 17.4 %) and non-diabetic (6.3 % vs. 17.9%) patients in the FREEWAY™ arm at 12 months compared to the PTA arm, respectively. The Rutherford clinical status showed significant better improvement for diabetic patients in the DEB arm compared to diabetics in the PTA arm (100 % vs. 78.3 %). Also non-diabetic patients had better improvement in the DEB arm compared to the PTA arm (93.7 % vs. 80.4 %).

Presentation: "Benefits of DEB post stenting in diabetic patients and males: subgroup analysis of the randomized Freeway Stent Study" Müller-Huelsbeck, CIRSE 2019 Barcelona, Spain.

Subgroup analysis of the used stent types in the Freeway Stent Study

Results of the subgroup analysis of used stent types show that all stent brands were evenly used in both study arms. Baseline demographics and lesion characteristics show no significant differences in used stent brands between the study groups.DEB treatment was found to be favorable in almost all the stent subgroups in terms of Patency and clinical improvement of Rutherford clinical status. Poster Presentation: "Effect of stent type on hemodynamic and clinical outcome in the randomized Freeway Stent Study" Müller-Huelsbeck, CIRSE Summit 2020

Long-term follow up and mortality rate of patients of the randomized Freeway Stent Study [64]

The Freeway Long-term study was designed as a reopen of the completed Freeway Stent Study. The study collected mortality and clinical outcome data for at least 5 years after enrollment to evaluate long-term patient safety and treatment efficacy.

Methods: Previous patients were recontacted by phone or during a routine hospital visit, and medical records were reviewed. Vital and clinical status information was collected.

Results: No increased late mortality was observed at 5 years, with an all-cause mortality rate of 12.0% in the FREEWAY drug-eluting balloon group versus 15.0% in the non-paclitaxel PTA group. No accumulation of any cause of death was observed in either group, nor was there any correlation with the dose of paclitaxel used. Freedom from clinically driven target lesion revascularization at 5 years was significantly higher in the FREEWAY drug eluting balloon group (85.3%) compared to standard PTA group (72.7%) Log-rank p = 0.032.

Conclusion: The safety results presented support the recent conclusions that the use of paclitaxel technology does not lead to an increase in mortality. At the same time, the efficacy results clearly demonstrate that the potential benefits of drug-eluting balloon treatment are maintained over a 5-year period.

PACUBA Trial [7]

The PACUBA trial investigates the hypothesis that Paclitaxel eluting balloon angioplasty compared to plain balloon angioplasty will result in significantly longer one-year patency rate in in-stent restenosis in the superficial femoral or popliteal arteries. It is a prospective, randomized, single-blind study performed in one center including 74 patients with symptomatic peripheral artery disease (PAD). The patients are randomized to either the investigation group treated with a FREEWAY™ 035 Paclitaxel eluting DEB (n=35), or to the control group with standard PTA (n=39). The primary endpoint was primary patency at 6 month follow-up, defined as <50% diameter stenosis as demonstrated by duplex ultrasound and Angiography in the absence of clinically driven TLR during follow-up. The secondary endpoints include technical, clinical and procedural success, MAE rate, clinically driven TLR at 6- and 12-months post index procedure, thrombotic occlusion of the target lesion and binary restenosis rate at 6 and 12 month follow-up.

Study Protocol: The study protocol was approved by the local ethic committee and carried out in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients were intended to give written informed consent.

Results: Patients with ISR in the femoropopliteal arteries that were treated with the FREEWAY™ DEB had significant higher patency rates at 6 and 12 months after intervention compared to patients treated with standard PTA balloon.

Patency was 58% versus 31% (p=0.016) at 6 months and 40.7% versus 13.4% (p=0.01) at 12 months in the DEB versus PTA group. Freedom from clinical driven TLR was 88% versus 83% (p = 0.11) at 6 months and 49.0% versus 22.1% (p=0.11) in the DEB versus PTA group. Changes in Rutherford by ≥1 was in 68.8% versus 54.5% (p=0.87) in the DEB versus PTA group at 12-months. The odds ratio for PTA over DEB for experiencing an event was estimated 2.8 (95% CI 1.2-6.6).

Conclusion: The study protocol, the methods, execution, reporting and analysis were in accordance with state-of-the-art criteria for randomized controlled trials. In the indication of in-stent restenosis in the femoropopliteal artery the use of FREEWAY™ DEB lead to significant better primary patency rates at 6 and 12 months compared to standard PTA. However, clinical results such as ABI and TLR rate did not reach statistical significance.

FREEWAY China Study [65]

This study aimed to evaluate the efficacy and safety performance of FREEWAY paclitaxel-coated balloons vs. uncoated balloons in Chinese femoropopliteal artery lesions.

Methods: In this prospective multi-center randomized controlled FREEWAY-CHINA study, 311 patients with symptomatic lower limb ischemia (Rutherford category 2–5) and femoropopliteal lesions of 14 Chinese centers were randomly assigned in a 1:1 ratio to endovascular treatment with either FREEWAY paclitaxel-coated balloons or uncoated balloons (control). The primary endpoint was 6-month clinically-driven target lesion revascularization (CD-TLR) rate. Secondary endpoints included the device and technical success rate, the ankle-brachial indexes (ABIs), Rutherford category change, the 6-month primary and secondary patency rates, severe adverse effects, and the 12-month CD-TLR rate.

Results: The two groups were comparable in terms of their demographic and lesion characteristics. Patients' mean age was 70 years, and 70% were men. The mean lesion length was 71 mm. The 6-month CD-TLR rate was 2.6% in the FREEWAY group and 11.7% in the control group (P = 0.001). The 12-month CD-TLR rate was 2.7% in the FREEWAY group and 13.2% in the control group (P = 0.0005). Other endpoints, including patency rates, major adverse events, and ABI or Rutherford change, did not differ between the two groups.

Conclusion: The FREEWAY balloon resulted in an effective decrease in CD-TLR rates and had similar safety results compared to the uncoated balloon in Chinese femoropopliteal artery patients at the 12-month follow-up appointment.

FREERIDE Study [31]

The Freeride study investigates the inhibition of restenosis by the Paclitaxel eluting PTA Balloon Catheter FREEWAY™ versus PTA alone in the treatment of de-novo occluded, stenotic or re-occluded, restenotic superficial femoral or popliteal arteries. The procedure included successful pre-dilatation by POBA. After a satisfactory angiographic result was achieved (with stenting only in case of bail-out-stenting) patients were randomized via randomization envelopes. Patients in each of the stratification arm were randomized in a 1:1 fashion. Patients were randomized to a treatment with either FREEWAY™ Paclitaxel eluting balloon or uncoated PTA balloon. Stenting was allowed only in case of bail-out. In this case any CE marked nitinol stent which is available in the center could be used.

The primary endpoint is the rate of clinically driven target lesion revascularization at 6 months. Secondary endpoints include among others technical success defined as the rate of successfully performed index procedures after wire passage and clinical success defined as technical success without the occurrence of serious adverse events during procedure. Further secondary endpoints are late lumen loss during the follow-up at 6 months determined by angiography and ankle-brachial index improvement of ≥ 0.1 (ABI before procedure compared with ABI at discharge and at 6, 12 and 24 months) and change in WIQ (Walking Impairment Question-naire) from pre-intervention to 6, 12 (and 24) months follow-up, the rate of minor and major complications at 6 and 12 (and 24) months and a change in Rutherford classification grades of chronic limb ischemia from pre-intervention to 6, 12 (and 24) months follow-up. At 6 months, the number

of serious adverse events (MAE) was significantly lower in the Freeway arm compared to POBA (5.4% vs. 28%; p=0.01)

Freeway Shunt Registry Italy [9]

This investigator-initiated study was conducted by Troisi et al. [9] between July 2013 and December 2016. 27 hemodialysis patients with recurrent stenosis of arteriovenous fistula underwent endovascular treatment with a Freeway balloon. All patients were previously treated at the target lesion with a standard balloon angioplasty (BA). The intervals in months between standard BA and procedure with DCB (time BA-DCB) and between procedure with DCB and new restenosis (time DCB-restenosis) were evaluated and compared with T-test. 2-year estimated outcomes in terms of survival, primary patency, primary assisted patency, secondary patency, and freedom from target lesion restenosis were assessed with Kaplan-Meier curves.

Technical success was obtained in 96.3% of the cases. During the follow-up (mean duration 13.6 months, range 1-33) 13 patients (48.1%) developed a new restenosis with an estimated 2-year freedom from target lesion restenosis of 30.2%. Mean time BA-DCB was 4.8 months, and the mean time DCB-restenosis was 7.6 months with a statistically significant difference at T-test (P<0.001). Estimated 2-year rates of primary patency, primary assisted patency, and secondary patency were 31.8%, 76.4%, and 90.5%, respectively.

In the study of Troisi et al. [9] the Freeway Paclitaxel-releasing balloons showed high safety and efficacy in the treatment of recurrent stenosis in hemodialysis patients. At follow-up about half of patients had no new target lesion restenosis and the time to a new restenotic lesion was significant longer compared to recurrence of stenotic lesions after standard BA.

Freeway Shunt Registry Berlin [32]

In this smaller prospective registry study of Duda et al. [32] 22 Patients underwent DEB dilatation with mandatory pre-dilatation. The enrollment was between November 2013 and October 2014 with a planned follow up after 3 months. Patients access type were AV-Fistula (Cimino) in 30.3 %, basilic AV-Fistula in 6.1 %, cephalic AV-Fistula in 8.2 %, and AV-Graft in 45.5 % of patients. The target lesion location was arterial in 6.1 %, venous in 90.9 % and in the anastomosis in 3.0 % of patients. Time to follow-up was 120 ± 49 days. At follow-up Flow [ml/min] comparison was examined with doppler ultrasound sonography (DUS). Mean flow at discharge was 806 ± 307ml/min and 703.68 ± 255 at follow-up. Revascularization rate during follow-up was low with only 11% (2 of 18 patients).

Freeway Shunt Registry I Turkey [33]

This investigator initiated retrospective study was conducted by Çildağ et al. [33] between January 2013 and 2015. 52 patients with significant stenosis in the arteriovenous fistula (AVF) were treated with either DEB or standard PTA. There was no significant difference between both groups regarding patient age, patient gender and type of fistula (p > 0.05). The AVF was radiocephalic in 78.8 % of patients and brachiocephalic in 21.2 % of the patients. Primary patency of

target lesion was examined at 6 and 12 months by Doppler ultrasound sonography. At 12 months primary patency rates were significantly higher for the patients treated with the DEB compared to standard PTA ($p < 0.05$). At 6 months there was no significant difference in primary patency between both groups ($p = 0.449$). The authors conclude that DEB proved to be an effective treatment for patients with stenosis in hemodialysis AVF.

Freeway Shunt Registry II Turkey [51]

This retrospective study by Yildiz et al. included 96 patients with ESRD who underwent endovascular treatment with Paclitaxel eluting balloon (PEB) angioplasty (n = 32) and standard balloon angioplasty (BA) (n = 64) for a dysfunctional native arteriovenous fistula (AVF). Primary patency rate at 6 months was significantly higher in PEB than in BA group (96.9 vs. 20.3%, p= 0.001), while the two groups had similar primary patency rates at 9 months (66.8 vs. 50.0%) and 12 months (6.3% for each). No significant difference was noted between PEB and BA groups in terms of the rate (21.9% and. 31.3%), time (median 220 vs. 152.5 days) and reasons (reocclusion in 18.8 vs. 28.1%) for dysfunction recurrence as well as the number of recurrent treatments. In conclusion, their findings emphasize favorable safety and efficacy of PEB and BA in the management of dysfunctional hemodialysis AVFs with similar rates of post-PTA recurrence of AVF dysfunction. Nonetheless, there was a nonsignificant tendency for lower rate and a delay for recurrent dysfunction in patients treated with PEB and a significant association younger AVF age with an increased risk of post-PTA recurrence of AVF dysfunction.

6.3.3. Complaints of device under evaluation FREEWAY™

No patients were harmed because of individual product defects cited below.

Complaints in the year 2021/2022

Name	FREEWAY™ 014
LOT	00187H21
Country	Brazil
Complaint	It was reported that the balloon protector has not moved back and it was not possible to advance with the balloon"

Explanation	The manufacturing records show no potential manufacturing defects. Analysis of the complaint show no established device problem. Based on a thorough review of the reported complaint, the most probable cause for this complaint was considered an unintended user error.

Complaints in the year 2022/2023

Name	FREEWAY™ 035
LOT	03049H22
Country	Portugal
Complaint	The device could not be withdrawn from the 5F sheet
Explanation	Due to the testing as described above it is highly improbable that the problems during withdrawal of the balloon were caused by manufacturing or design-related deviations. Probable causes of the problem are incorrect application of the procedural steps.

Complaints in the year 2023/2024

Name	FREEWAY™ 014
LOT	10276H22
Country	Mexico
Complaint	"The device doesn't navigate through the guide."
Explanation	Probable causes of the problem are incorrect application of the procedural steps. The balloon protective cover was not removed from the balloon as intended before use. Rather, it was moved proximally onto the catheter shaft. This probably compressed the balloon so that it was no longer possible to insert it into the 5F sheath without any problems.

Name	FREEWAY™ 035
LOT	03519H23
Country	Portugal
Complaint	The device could not be withdrawn from the 5F sheet
Explanation	Due to the testing as described above it is highly improbable that the problems during withdrawal of the balloon were caused by manufacturing or design-related deviations. Probable causes of the problem are incorrect application of the procedural steps.

6.3.4 Field safety corrective actions

Since introduction to the market 1 field safety corrective actions (FSCA) occurred.

2020

Name	FREEWAY™ 014 and 035
LOT	Not applicable
Country	Switzerland, Germany, Czech Republic, Spain, Lithuania, Latvia
Description	In December 2018, Katsanos et al published a meta-analysis on the "Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg". The meta-analysis authors describe an increased risk of death at 2 and 5 years following the application of paclitaxel-coated balloons and stents in the femoropopliteal artery in the studies analyzed. The reason for the FSCA is to inform the related Healthcare Professionals with a Field Safety Notice (FSN) that updates will be made to the IFUs for FREEWAY 035 and FREEWAY 014 Paclitaxel-eluting PTA balloon in context with the publication of Katsanos and colleagues. This FSCA is only a precautionary measure for the usage of Paclitaxel coated DEB and DES to treat peripheral arteries. The indications and contra-indications of the concerned devices remain unchanged. No product batch/lot is being recalled in relation to this field safety notice. Corrective Action 1: Submission of a FSCA including a FSN to the respective competent authority. Corrective Action 2: The respective distributors of Eurocor Tech GmbH were informed immediately about the FSCA and FSN upon the submission to the respective competent authority. Corrective Action 3: The respective distributor has informed the affected customer hospitals in the respective country about the FSCA and FSN. Corrective Action 4: Annex One of the FSN was submitted to the notified body for approval to update the IFU for FREEWAY 035 and 014 accordingly. The notified body approved the update of the IFU for FREEWAY 035 and 014 on 08.02.2021. The respective updates have been implemented. Preventive Actions: none
Status	This FSCA is closed.

6.4 Summary and appraisal of clinical and pre-clinical data

6.4.1 Appraisal plan

According to MEDDEV 2.7.1, all selected literature was evaluated to make clear the significance that is attached to it. In the appraisal of data generated by the manufacturer and data from literature, the evaluators applied criteria to determine the methodological quality, and its relevance for the clinical evaluation. The evaluators performed a thorough and objective identification and appraisal of data and weighted the positive and negative content of each document.

Methodological quality of data from clinical trials was assessed by the study design and protocol, the extent of studied subjects, the compliance with the rules and norms to be applied and the method of data analysis and evaluation. Furthermore, the appraisal comprised the scientific appropriateness of data, the current medical practice, "state of the art" technologies and conclusions made by the authors. In the case of genuine clinical studies, the study design, its quality assurance measures (compliance with legal and normative requirements), the selection of primary and secondary study variables, number of patients, inclusion and exclusion criteria, as well as clinical outcome (effectiveness) and adverse incidents (safety) were assessed.

The appraisal of data generated by the manufacturer focuses on the relevance and scientific validity of that data to describe the efficacy and safety and justifies the intended clinical use. Data of undesirable effects from PMCF as well as from PMS are evaluated according to their benefit-risk criteria.

Clinical data generated by the manufacturer

The device under evaluation was examined in a pre-clinical study (4.2.2.), and for several indications in the peripheral arteries randomized trials and registries were conducted (4.2.3). It is evident from the above-mentioned publications and the data generated by the manufacturer that Paclitaxel eluting balloons, including the device under evaluation, are effective and safe in the treatment of *de novo* and in-stent lesions. Paclitaxel eluting balloons are suitable to improve luminal diameter and to reduce restenosis and the need for repeated revascularization. The rate of long-term MAE is lower with the use of bare metal stents, nevertheless incidence of bleeding and vascular complications was demonstrated to be significantly higher in hospital after stent implantation than after balloon angioplasty. Furthermore, the use of Paclitaxel eluting balloons allows a re-intervention at any time. The placement of stent in stent is not a recommended treatment in the peripheral arteries.

Paclitaxel is an approved drug substance which reduces the rate of in-stent restenosis. The available data show that FREEWAY™ demonstrated its safety and effectiveness in the treatment of peripheral lesions. The DIOR® PTCA balloon catheter is counterpart of the FREEWAY™ for coronary lesions. The DIOR® PTCA balloon catheter has the same coating and the same Paclitaxel dose load (3 µg/mm^2) as the FREEWAY™ balloon. The DIOR® balloon has also been tested previously in clinical trials. The evidence from clinical studies is strongly in favor of the drug-eluting balloons over uncoated balloons.

6.5 Safety, risk, performance and essential requirement analysis of the device under evaluation

6.5.1. Requirement on safety

The safety characteristics and the intended purpose of the FREEWAY™ are described in detail in the user instructions. A risk analysis was performed considering product design and manufacturing process. The risks were adequately addressed in the risk management documentation and user instruction, all hazards and relevant clinical information were appropriately identified. The label includes warnings and information for proper storage and safe and effective application.

6.5.2. Requirement on acceptable benefit/risk profile

A risk analysis according to EN ISO 14971: 2019 was performed considering product design and manufacturing process. In summary, considering all scientific data and findings it is concluded that the potential undesirable clinical effects and risks of the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter seems well controlled and acceptable, when weighed against their benefits in interventional procedures. Therefore, a positive risk versus benefits ratio can be stated for the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter if the product is applied in accordance with its intended use as outlined in the manufacturer's instructions for use. Therefore, a continued marketing of the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter is supported.

6.5.3. Requirement on performance

The device specifications were confirmed by the corresponding test and verifications with international standards. The procedure of labelling and packaging is predetermined. The technical documentation of FREEWAY™ includes an expert's consultation report that describes the favorable effect of the Paclitaxel eluting delivery balloon in an animal model. The short-term drug elution of the drug-coated balloon minimized smooth muscle cell proliferation and migration. It is stated that the short-term and well-timed drug release corresponds well with the wound healing process after PTA, the most important effect of stopping smooth muscle cells in stage I and II of the wound healing process is achieved. Therefore, duration of antiplatelet therapy and the risks involved with this therapy is reduced. In addition, as there will be no long-term Paclitaxel associated vessel burden in the healing stage of re-endothelialization, the healing process is not blocked and not delayed. Thus, the risk of delayed thrombosis associated with delayed arterial healing will be eliminated in case of a DEB.

6.5.4. Requirement on acceptability of side-effects

Side effects and remaining risks are adequately addressed in the user instructions. A risk analysis was performed revealing that the benefits of the product outweigh the remaining risks. Results of the study data generated by the manufacturer and described in literature clearly indicate favorable performance of the Paclitaxel eluting balloons outweighing remaining risks. It is concluded that the FREEWAY™ PTA balloon catheter is safe in use and potential medical risks are similar to those of standard PTA treatments.

6.5.5. FDA evaluation of the meta-analysis on paclitaxel device late mortality signal

In 2018, a meta-analysis published by Katsanos et al [34] reported a potential signal for an increased late mortality in PAD patients between 2 and 5 years after intervention in association with the use of paclitaxel-eluting balloons and stents. The finding of this association raised concern and scientific debate about study design, the continued use of paclitaxel devices, and the strengths, limitations, and data quality of studies such as the 2018 meta-analysis [35, 36]. The FDA (US regulatory authority) responded with advisory letters to health care providers and an expert panel meeting. Further reanalysis of the underlying patient data from the originally included randomized trials by FDA and VIVA physicians [53, 57] replicated the signal, but with a lowered hazard ratio and without the finding of paclitaxel dose dependence. In the following time and as a reason of authority call, several large real-world data analyses [58-60] as well as large new randomized data analyses [54,61] were conducted and could not find a mortality signal for paclitaxel-eluting devices at mid-term and long-term follow-up.

After analyzing several of the new large real-world data and randomized trials mentioned above and others, the FDA issued an updated letter to health care providers on July 11, 2023, [62] concluding that the totality of the data now available does not support an excess risk of mortality with paclitaxel-coated devices. In the same way, the authors of a CIRSE expert opinion paper [63] conclude that "a robust body of evidence now exists to refute the existence of a long-term mortality signal associated with PCDs" and further support that the favorable results seen with the use of these devices in terms of primary patency and TLR rate should ensure the routine use of these devices in the femoropopliteal area.

Furthermore, Eurocor Tech GmbH conducted a long-term follow up from the patients of the Freeway Stent Study to evaluate mortality. For this reason, the patients of the Freeway Stent Study were re-contacted to analyze mortality up to 5 years after inclusion in the study. Study findings at 5 years showed no increased mortality (FREEWAY DEB group 12.0% vs. 15.0% non-paclitaxel PTA group; risk ratio (RR), 0.81; 95% CI, 0.35-1.90 calculated by proportion method) [64]

7. Conclusion risks / benefits evaluation

All in all, the Technical Documentation of Eurocor Tech GmbH for the FREEWAY™ PTA balloon catheter contains appropriate evidence regarding the clinical performance and safety of the device.

Answers to the questions raised under point 5.2:

a) The FREEWAY™ Paclitaxel eluting PTA Balloon Catheter is suitable for the treatment of peripheral lesions. Peripheral intervention with a drug-eluting balloon represents a state-of-the-art technology in interventional procedures in the treatment of stenotic and restenotic lesions in peripheral arteries. It has been approved in two randomized controlled trials (PACUBA Trial [7], Freeway Stent Study [8]) that patency in stented SFA lesions (*de novo* and ISR) is significant higher after 12 months with a FREEWAY™ DEB treatment compared to a standard treatment with an uncoated PTA balloon. The application of the drug substance Paclitaxel is also a state-of-the-art procedure in interventional procedures.

b) Randomized Trials conducted with FREEWAY DEB found significantly better improvements in hemodynamics at 12 months [7,8] and significantly reduced need for target lesion revascularization at 12 months [65] and at 5 years [64] compared to standard PTA treatment.

c) Study results generated by the manufacturer as well as several studies in literature clearly show that the drug substance Paclitaxel is effective to reduce the rate of restenosis.

d) Undesirable effects and potential risks that have been reported for Paclitaxel eluting balloons in general is restenosis. Other complications that are associated with the Paclitaxel eluting balloon angioplasty is in hospital mortality after percutaneous intervention, perforation at the site of the lesion, arteriovenous fistula, dissection of the artery, rhythm disturbances and allergic reactions to contrast media. A Meta-analysis [34] reported a higher late mortality rate (3-5 years after intervention) for PAD patients treated with paclitaxel devices compared to non-paclitaxel devices. For FREEWAY™ paclitaxel coated PTA balloon catheter, a long-term data study [64] found no elevated mortality risk up to 5 years and longer for patients in the FREEWAY™ DEB group compared to patients in the standard PTA group. This is in line with several large real-world data analyses [58-60] as well as large new randomized data analyses [54,61] were conducted and could not find a mortality signal for paclitaxel-eluting devices at mid-term and long-term follow-up. In this issue FDA issued an updated letter to health care providers on July 11, 2023, [62] concluding that the totality of the data now available does not support an excess risk of mortality with paclitaxel-coated devices.

e) The undesirable effects and potential risks are acceptable considering their nature and frequency and comparing them to the benefits of the FREEWAY™ Paclitaxel eluting PTA Balloon Catheter.

f) Results of the study data generated by the manufacturer and described in literature indicate favorable performance of the Paclitaxel eluting balloon. It is concluded that the FREEWAY™ PTA balloon catheter is safe in use and a potential severe medical risk was not observed to date. Further post marked clinical follow-up investigations are recommended for collecting long term data.

8. Date of next clinical evaluation

The clinical evaluation is updated annually. The next update will be in November 2025.

9. Dates and signatures

The expert declares that to the best of his knowledge, sufficient effort was made to identify and evaluate relevant literature which allowed answering the initial questions conclusively. Based upon the selected information it was possible to critically evaluate the clinical performance, risks and benefits of the devices in question. Potentially negative contributions were not excluded from the evaluation.

Signature of Author / Expert

This clinical evaluation report was prepared in accordance with MEDDEV 2.7.1 [1]. The undersigned declares that he is suitably qualified for this clinical (see CV in Chapter **8** of this report).

29.10.2024 Dr. Stefanie Stahnke
Date

29.10.2024 Dr. Johannes Dambach
Date

10. Qualification of the responsible experts

11. References

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