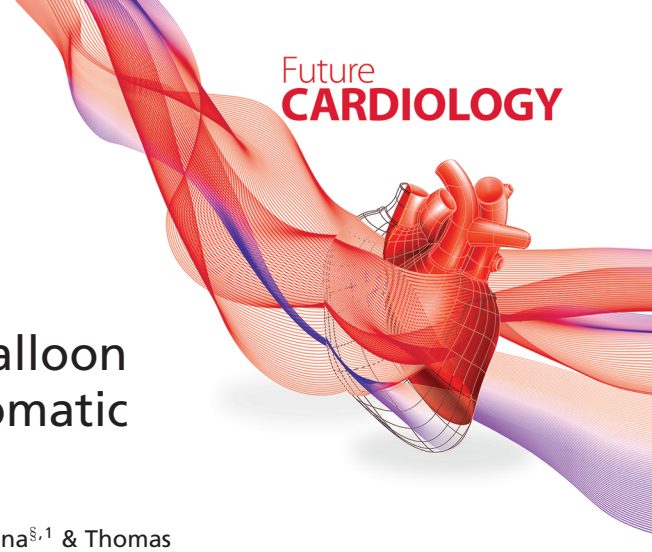
Device Evaluation



The SELUTION SLR™ drug-eluting balloon system for the treatment of symptomatic femoropopliteal lesions

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Endovascular treatment has become first line therapy for the treatment of femoropopliteal disease. Drug-coated devices play a key role in maintaining vessel patency. In the past antiproliferative coating of drug-coated balloons (DCBs) exclusively consisted of paclitaxel. Use of limus drugs was limited by a short residency time in the vessel wall. Besides the drug, the SELUTION SLR™ drug-eluting balloon system consists of a coating formulation of four excipients. The first excipient is a biodegradable polymer (poly(lactic-co-glycolic acid)) that is intermixed with the sirolimus to form micro-reservoirs and regulates drug release via matrix degradation. This review summarizes the existing pre-clinical and clinical literature on treatment of femoropopliteal artery lesions with the SELUTION SLR DCB.

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The pathological degeneration of arteries known as 'atherosclerosis' is responsible for a third of all human mortality [1,2]. It represents a tremendous current and future health burden projected to cause more than 23 million annual deaths by the year 2030 [3]. Atherosclerosis involving lower extremity arteries (peripheral arterial occlusive disease, PAOD), affects 74% of the population over 70 years old [4]. Approximately 20% of patients present with symptoms, which, if left untreated, can lead to severe disability, limb loss and/or death [5–9]. An estimated 11% of patients afflicted with PAOD present with the most severe form of the disease: critical limb ischemia (CLI) [10–12]. CLI is characterized by a baseline perfusion of the extremity being inadequate to sustain its viability. It carries a dismal prognosis; only about half of affected patients will be alive with viable limbs only 6 months after the diagnosis is made [5,13–15].

The historical revascularization strategy of patients with symptomatic PAOD includes open surgical bypass of chronically diseased arterial segments [16,17]. The results are often favorable; revascularization with autogenous vein confers 70% primary graft patency at 5 years [5,18,19]. However, while the durability of surgical bypass grafting has been thoroughly documented, so has its significant mortality and morbidity [20–23]. With the primary goal of achieving effective mechanical revascularization with reduced complications, endovascular techniques including balloon angioplasty and stent implantation were approved in the 1980s and established as viable alternative treatment strategies in 2005 [24–26]. However, their effectiveness remained limited as up to 40% of conventional endovascular procedures were be complicated by arterial restenosis within the first year [18,27–31]. Angioplasty balloons sprayed or dipped in pharmacologic compounds including the anti-proliferative drug paclitaxel, so-called 'drug-coated balloons' (DCB) have demonstrated enhanced patency compared with uncoated balloons and comparable outcomes compared with drug-eluting stents [32–37]. As a result, most recent international guidelines recommend endovascular therapy as first-line strategy for the treatment of femoropopliteal artery disease, some still reserving lesions longer than 25 cm for bypass surgery [38,39].

Future Medicine

Table 1. Differences in characteristics of the antiproliferative drugs sirolimus and paclitaxel for drug-coated balloons.

Attribute	Limus	Paclitaxel
Mode of action	Cytostatic	Cytotoxic
Margin of safety	10,000-fold	100-fold
Antirestenosis	Optimal	Good
Tissue absorption and elution	Difficult	Easy
Level of competition	Low	Very high
Physician perception	Positive	Controversial

A recent meta-analysis of paclitaxel-coated device trials has revealed that these drug-device formulations may carry an increased risk of late mortality, possibly derived from long-term, low-level exposure to the cytotoxic drug [40]. The analysis suggested that patients treated with paclitaxel-coated devices sustain significantly higher all-cause mortality than patients treated with bare devices when examined at 2 years (7.2 vs 3.8%) and at 5 years (14.7 vs 8.1%). However, the potential mechanism resulting in a possible excess mortality remains unknown. This finding led a US FDA Consensus Panel to conclude that, "*a late mortality signal associated with the use of paclitaxel-coated devices to treat femoropopliteal PAOD was present*" [41].100 This finding has led to a significant dampening of enthusiasm for their use, even if recent patient level and real world analyses could not confirm the meta-analysis finding [41–45].

Until end of 2019 commercially available DCB used the cytotoxic drug paclitaxel as the antirestenotic drug. The current immediate comparator – as used in coronary drug-eluting stents (DES) – is the cytostatic sirolimus (or its analogs) supported by solid clinical-based evidence in terms of safety and efficacy [46]. Indeed, a sirolimus-coated balloon could offer a treatment that has a more potent antiproliferative effect on the prevention of restenosis, includes anti-inflammatory protection, in addition to a wider therapeutic range and a greater safety margin compared with a paclitaxel-coated balloon (Table 1) [47]. However, due to the hydrophilic nature of sirolimus drug retention in the vessel wall and sustained drug release was a major challenge in designing an appropriate microreservoir coating technique for a balloon-based application of an antirestenotic drug. The technique of intermixing paclitaxel with an excipient – a kind of dissolvent – in order to transfer the active drug from the balloon surface into the vessel wall was much easier as compared with design a micro-reservoir based coating for a sirolimus-coated balloon. Regarding safety assessment of DCB, two main aspects should be considered: local vessel wall toxicity and microparticulate embolization from the balloon coating into the distal microvasculature (so called 'wash-off'). Local vessel wall toxicity and delayed healing has been observed in animal studies after paclitaxel-coated balloon angioplasty and is characterized by excess fibrin deposition along the vascular circumference and medial thinning with replacement of smooth muscle cells by collagen [48]. As for wash-off, the authors of the meta-analysis postulated a diffuse organ dissemination of the crystalline drug resulting in the late excess mortality. In patients with CLI, downstream paclitaxel particulate may result in a delayed wound healing and increased amputation rate [40]. Therefore, a more extensive understanding of the mechanism of action, pharmacokinetics and use of alternative antiproliferative drugs like sirolimus are key aspects in the further improvement of the DCB technology.

Introduction to the SELUTION SLR™ drug-eluting balloon system: device design & preclinical testing

The SELUTION SLR™ 018 Sirolimus-Eluting PTA Balloon Catheter (SELUTION SLR DCB), MA Med Alliance SA, Rue de Rive 5, 1260 Nyon, Switzerland is intended for use as a percutaneous transluminal angioplasty (PTA) balloon catheter to dilate *de novo* or restenotic femoropopliteal lesions, for the purpose of improving limb perfusion and decreasing the incidence of restenosis. It has an over-the-wire shaft design that uses dual stiffness, high at the proximal part and low at the distal part, in order to increase pushability while maintaining a high level of flexibility. The uncoated PTA balloon catheter that serves as device component for the SELUTION SLR is based on a standard, Conformite Europeenne (CE) approved PTA platform Available balloon dimensions are summarized in Table 2. The balloon part of the SELUTION DCB is coated with the antirestenotic drug sirolimus, that is both FDA and EMA approved.

The ancillary medicinal substance used on the SELUTION DCB is sirolimus (also known as rapamycin or RAP), the purpose of which is to inhibit neo-intimal proliferation after PTA treatment. Sirolimus was first approved by the FDA in 1999 as Rapamune, manufactured by Wyeth Pharmaceuticals Inc. and used for the prevention of organ transplant rejection, before later being incorporated into DES as a well-proven and well-tolerated antiproliferative

Table 2. Available sizes and specifications of the SELUTION drug-coated balloons.

Balloon diameter (mm)	Balloon nominal pressure (bar)	Sheath compatibility minimum size (Fr)	Balloon length (mm)						
			Balloon-rated burst pressure (bar)						
			20	40	60	80	100	120	150
2.0	6.0	5	12	12	10	10	10	10	10
3.0	6.0	5	12	12	10 10	10 10	10 10	10 10	10 10
4.0	6.0	6	12	12	10	10	10	10	10
5.0	6.0	6	12	12	10	10	10	10	10
6.0	6.0	7	12	12	10	10	10	10	10
7.0	6.0	7	12	12	10	10	10	10	10

Table 3. SELUTION SLR™ 018 PTA balloon catheter – sirolimus drug dosage chart.

Parameters		Balloon length ↔ (mm)						
		20	40	60	80	100	120	150
Balloon diameter Ø (mm)	2.0	126 µg	251 µg	377 µg	503 µg	628 µg	754 µg	942 µg
	3.0	188 µg	377 µg	565 µg	754 µg	942 µg	1131 µg	1414 µg
	4.0	251 µg	503 µg	754 µg	1005 µg	1257 µg	1508 µg	1885 µg
	5.0	314 µg	628 µg	942 µg	1257 µg	1571 µg	1885 µg	2356 µg
	6.0	377 µg	754 µg	1131 µg	1508 µg	1885 µg	2262 µg	2827 µg
	7.0	440 µg	880 µg	1319 µg	1759 µg	2199 µg	2639 µg	3299 µg
							Sirolimus dose density	
Sirolimus drug dose (µg)	=	Balloon diameter Ø (mm)	× Balloon length ↔ (mm)	×	π ≈3.1415	×	1.0 (µg/mm^2)	

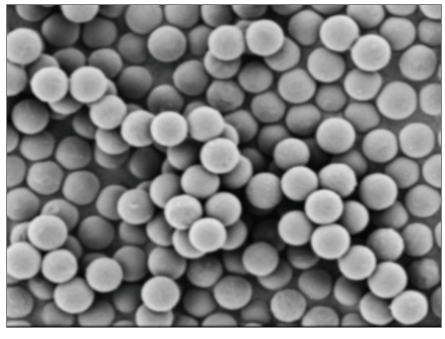

Figure 1. Scanning electron microscope image of biodegradable poly(lactic-co-glycolic acid) microspheres with encapsulated sirolimus.

drug to reduce restenosis. Numerous DES studies have demonstrated the safety and effectiveness of this drug. Similar to the applied dosages seen on coronary DES, the approximate drug loading on the SELUTION SLR is 1 µg/mm^2. Table 3 summarizes the total sirolimus dose calculated for each balloon dimension and the corresponding mathematic formula.

Besides the drug, the coating formulation of the SELUTION SLR DCB consists of four excipients that are intermixed using a specific ratio. The first excipient is a biodegradable polymer poly(lactic-co-glycolic acid) (PLGA) that is intermixed with the sirolimus to form micro-reservoirs and in this way regulates drug release via matrix degradation (Figure 1). The remaining three excipients constitute a phospholipid blend, all of which have previous human vascular use. These phospholipids aim at reducing drug coating wash off in the bloodstream during insertion, tracking and lesion crossing, optimizing drug transfer to the tissue during the short-term balloon dilatation and helping to adhere the micro-reservoirs to the surrounding tissue when the SELUTION DCB is deflated and removed.

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Pharmacodynamics, pharmacokinetics & metabolism of the drug coating components

Sirolimus

Sirolimus inhibits T- and B-lymphocyte activation and smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The Sirolimus-FKBP-12 complex binds to and inhibits activity of the mTOR. mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy and transcription. As the inhibition of mTOR stops cell cycle progression from the G1 to the S phase, sirolimus is considered to be cytostatic and therefore less toxic than drugs that act later in the cycle such as paclitaxel, which is cytotoxic.

Sirolimus is extensively metabolized by the hepatic CYP3A4 enzyme [49] and is also a substrate for the P-glycoprotein (P-gp) transmembrane efflux pump found in the intestinal epithelium, liver cells, proximal tubule of the kidney and capillary endothelial cells. The clearance of sirolimus is affected by both of these pathways and displays a large interpatient variability. The majority of the metabolites, including demethyl and hydroxydemethyl sirolimus are formed via O-demethylation and hydroxylation. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity. The metabolites account for less than 10% of the immunosuppressant activity of sirolimus. Billiary and fecal pathways serve as the primary routes of sirolimus elimination. The half-life of sirolimus in aqueous media is approximately 63 h [50].

Poly(lactic-co-glycolic acid)

The first excipient is a biodegradable polymer PLGA that is mixed with sirolimus by means of coacervation into micro-reservoirs having a 4 μm diameter. This way, a controlled and sustained drug release via matrix degradation is achieved, resulting in a long-term distribution of sirolimus into the tissue to maintain therapeutic levels. Homo and copolymers derived from lactic and glycolic acids monomers are used as excipients since 1973 in the pharmaceutical industry due to their unique properties [51]: 'biodegradability' and biocompatibility; approval in drug delivery systems for parenteral administration by the FDA and EMA; well-established methods of production for hydrophilic or hydrophobic small molecules or macromolecules in various carrier-based drug-delivery systems in humans; 'drug protection from degradation'; 'sustained release'; modification of PLGA for better interaction with biological materials; and possibility to target specific organs such as the vessel wall [52,53]. The lactide/glycolide polymer chains are eliminated by hydrolysis to the monomeric lactic acid and glycolic acid, which gets eliminated from the body by metabolism and exhaled as carbon dioxide and water.

Phospholipid blend

The remaining three excipients constitute a biodegradable phospholipid blend, all of which have previous human vascular use [54]. This phospholipid blend aims at:

- Reducing drug coating wash-off in the bloodstream during insertion, tracking and lesion crossing;
- Optimizing drug transfer to the tissue during the short-term balloon dilatation;
- Helping to adhere the microreservoirs to the surrounding tissue post SELUTION DCB treatment.

After mixing of the excipients with the microspheres with a solvent, the drug-coating formulation is sprayed onto the inflated balloon surface, yielding a coating of sirolimus-loaded microspheres adhered to the balloon surface with the phospholipid blend layer comprising the three excipients, which is designed to facilitate adhesion of the drug-coated microspheres onto the vessel wall (Figure 1).

Upon balloon expansion at the target lesion site, controlled and sustained release of drug from the SELUTION SLR 018 DCB is intended to provide therapeutic concentrations of drug within the vessel wall for up to 60 days post angioplasty. The anti-proliferative properties of sirolimus make it a useful agent to reduce the risk of restenosis for several months post-angioplasty.

Formulation & coating technique

The coating components are weighed and combined in a vial along with a processing solvent. The formulation is then mixed and sonicated and then tested for sirolimus content with a validated UV spectrophotometer method. After meeting specification for percent Sirolimus content, the formulation is loaded onto the spray coating machine.

Table 4. Overview of all device performance and safety testing conducted with the SELUTION drug-coated balloons.

Test	Description
Dimensional and functional attributes	Dimensional and functional attributes of finished sterilized SELUTION DCB have been tested to assure that the device performs as intended with adequate strength and design features to mitigate patient risks. Results demonstrated that the SELUTION DCB meets all dimensional and functional requirements for its intended use. In addition, selected dimensional and functional attributes are being conducted on a per lot basis.
Drug and coating characterization	Characterization of the drug sirolimus was conducted on finished sterilized SELUTION DCB. The characterization consisted of the following tests: – Drug identity; – Drug content; – Drug content uniformity; – Drug impurities/related substances; – Drug coating appearance; – Drug coating durability The results of the characterization demonstrate that the drug content, content uniformity, identity and appearance were acceptable and that the impurity profile has been characterized. In addition, as part of product release, each lot of SELUTION DCB will be tested for identity, content, content uniformity, impurity profile, drug coating durability and appearance.
Biological evaluation	A biological evaluation of the finished sterilized SELUTION DCB was designed to determine the effects of the device on tissues and to mitigate potential biological risks arising from the use of the device. Results demonstrated that the SELUTION DCB is biocompatible for its intended use.
Pharmacokinetic and histological animal safety studies	Preclinical *in vivo* animal studies were conducted to evaluate functional device performance and safety of the SELUTION DCB for up to 6 months. Results demonstrated the feasibility of long-term (up to 60 days) arterial tissue retention of sirolimus with therapeutic levels, safety up to 6 months after treatment with the device and functional device performance as intended.
Sterilization validation	Results obtained from the sterilization validation studies demonstrated that the sterilization process by E-beam radiation satisfies a minimum SAL of 10^{-6} and as such the sterilization process using 25–30 kGy as a routine dose was deemed validated. The sterilization cycle is being continually reaffirmed with quarterly bioburden and sterility audits.
Packaging integrity	The SELUTION DCB packaging was tested to verify packaging integrity after simulated distribution conditioning. The package integrity test results demonstrated the SELUTION DCB packaging is capable of surviving shipment without significant damage or loss of sterile barrier.
Stability and shelf life	Expiration dating was established following evaluation of the materials used in the device, the construction of the device and the packaging of the device. The SELUTION DCB will be labeled with a 6-month expiration date until longer-term stability and shelf life data will be available.

DCB: Drug-coated balloon; SAL: Sterility assurance level.

The coating formulation is applied to the bare balloon surface using a spray-coating process. A spray-coating machine utilizes an ultrasonic spray nozzle, which is able to atomize the coating formulation into fine drops and allows a uniform deposition of the coating around the balloon surface. The balloon catheter is placed inside a dedicated balloon catheter fixture that is attached to a rotating shaft. The nozzle is mounted above the surface of the balloon, which is inflated during the entire spray coating process. The shaft rotates and translates such that the balloon surface is sprayed along its entire length and circumference. During the coating process, sacrificial balloon segments are occasionally coated and weighed to ensure that the proper amount of coating is being applied to the balloon. The processing solvent is allowed to evaporate and then a protective sheath is placed over the folded balloon.

Preclinical testing

Prior to use in humans, the SELUTION DCB has been extensively and systematically evaluated to demonstrate safety and appropriateness for clinical use and that the device fully complies with the applicable standards. Testing included verification of dimensional and functional attributes, drug and coating characterization, biological evaluation, pharmacokinetic and histological animal safety studies, sterilization validation, packaging integrity, as well as stability and shelf life. An overview of all the device performance and safety testing that has been conducted with the SELUTION DCB is summarized in Table 4.

Pharmacokinetic and histological animal safety studies: preclinical *in vivo* animal studies were conducted to evaluate safety and overall device performance of the SELUTION DCB for up to 6 months. Two pharmacokinetics and histological safety studies were conducted in rabbit iliac arteries, with time points up to 28 and 180 days, respectively. An additional histological safety study at a clinically relevant vascular location (i.e., using swine internal and external femoral arteries) was conducted with time points at 28 and 90 days. The two pharmacokinetic and histological studies in rabbit iliac arteries demonstrated the feasibility of long-term (up to 60 days) arterial tissue retention of sirolimus with therapeutic levels (Figure 4), as well as safety up to 6 months after treatment with the SELUTION DCB. The SELUTION DCB was also considered safe in an additional histological study up to 90 days using swine internal and external femoral arteries, while supporting device performance as intended.

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Table 5. Main study inclusion and exclusion criteria.

Key inclusion criteria	Key exclusion criteria
• SFA and PA • Male or nonpregnant female ≥18 years of age • *De novo* or restenotic lesion(s) with composite length ≤15 cm • Target vessel reference diameter ≥3.0 and ≤7.0 mm	• Known hypersensitivity or contra-indication to aspirin, heparin or other anticoagulant/antiplatelet therapies • Prior vascular surgery of target lesion • Known inadequate distal outflow/significant inflow disease

PA: Popliteal artery; SFA: Superficial femoral artery.

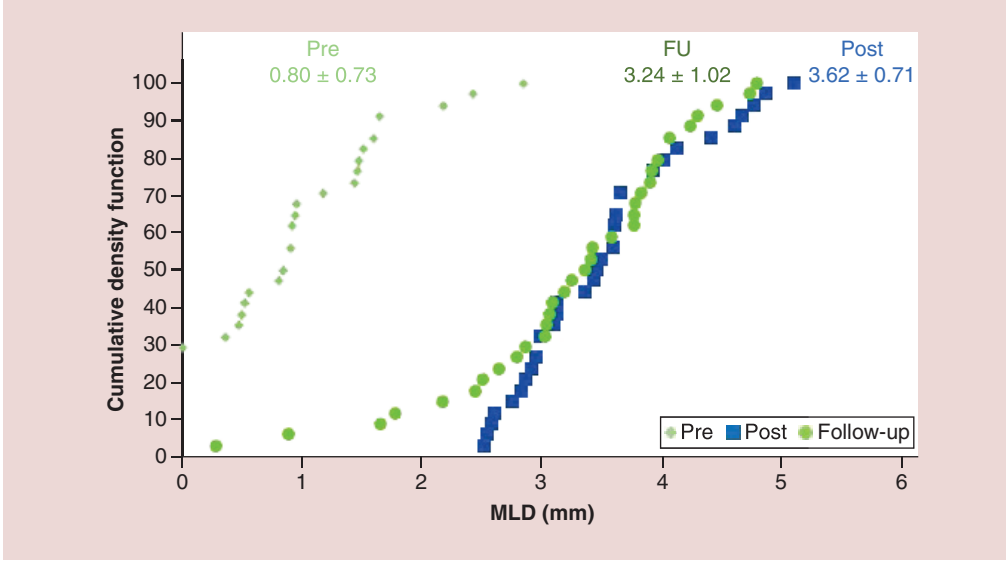


Figure 2. Minimal lumen diameter at baseline, postprocedure and after 6 months.
MLD: Minimal lumen diameter.

During organ evaluation no indication of infarction/scarring or distal emboli involving microreservoirs in any of tissues assessed (i.e., lung, left and right kidney, liver, spleen and left gastrocnemius muscle) was found.

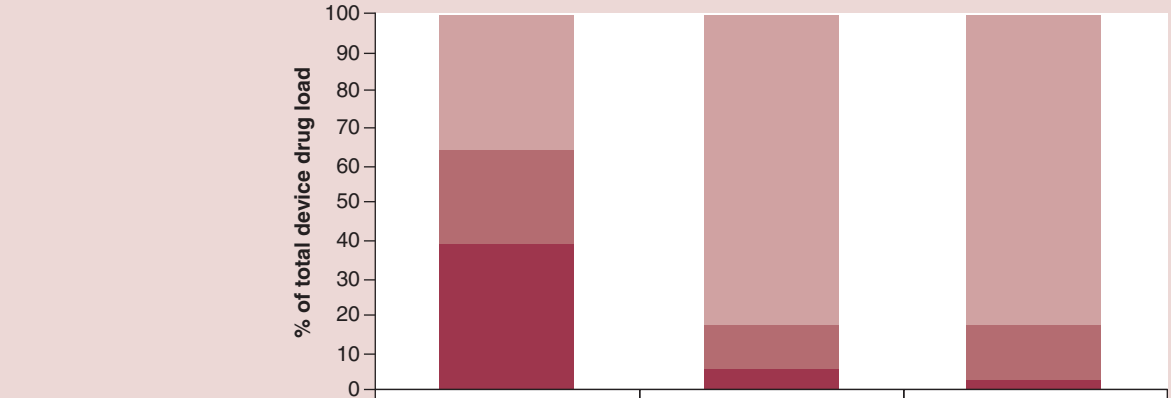
Clinical efficacy & safety: first-in-human results

Currently, the only clinical trial conducted is the first-in-human clinical trial titled: 'Prospective, Controlled, Multi-Center, Open, Single-Arm Clinical Investigation for the Treatment of Patients with Femoropopliteal Artery Lesions with a Novel Drug-coated Balloon (SELUTION DCB)'. The 6-month primary end point results had been published recently [55].

The purpose of the SELUTION first-in-human trial in femoropopliteal arteries (ClinicalTrials.gov NCT02941224) was to evaluate the safety and efficacy of the novel SELUTION DCB in the treatment of femoropopliteal lesions. Between October 2016 and May 2017, 50 subjects (mean age 69.6 ± 10.4, 29 male) with symptomatic lower limb ischemia Rutherford categories 2–4 were enrolled at four German centers.

The primary trial objective was comparison of angiographic late lumen loss (LLL) at 6 months (the primary efficacy end point) against an objective performance criterion value of 1.04 mm for uncoated balloon angioplasty. Secondary end points included device, procedural and clinical success; clinical and imaging assessments of primary patency and restenosis; functional assessments including Rutherford classification and ankle–brachial index; and major adverse events (composite of cardiovascular mortality, index limb amputation, target limb thrombosis and clinically driven target lesion revascularization [TLR]) as primary safety end point. Key study criteria are summarized in Table 5.

At 6 months, median angiographic LLL following SELUTION SLR treatment was 0.19 mm (range: -1.16–3.07 mm). Mean angiographic late lumen loss was 0.29 ± 0.84 mm (95% CI: -0.01–0.58), significantly lower than the 1.04 mm objective performance criterion value ($p < 0.0001$). The LLL was related to acute luminal gain or minimal luminal diameter, the smaller the post procedure minimal luminal diameter the higher the LLL with a cut-off value of 3 mm Figure 2). The rate of primary patency by duplex ultrasound was 88.4% and freedom from



	Med alliance SELUTION	Bard LUTONIX	Medtronic IN.PACT
Lost during procedure	36%	83%	83%
Retained on balloon	25%	12%	14%
Transferred to vessel (1 hr)	39%	5%	3%

Figure 3. Drug transfer SELUTION SLR™ drug-coated balloon compared with market leading paclitaxel-coated drug-coated balloon. In green the percentage of the total drug dose released to the vessel wall measured 1 h after balloon inflation, in yellow the percentage of the total drug retained on the balloon surface after removal from the model and in red the percentage of the total drug dose released into the circulation.
Source: MedAlliance – Bench Test Data on File, Bard-LUTONIX & Medtronic-IN.PACT – Presentation Granada at CRT 2014. Reproduced with permission from MedAlliance.

angiographic binary restenosis was 91.2%. Through 6 months, there was significant improvement over baseline in Rutherford categories ($p < 0.0001$) and in ankle–brachial index measurements ($p < 0.0001$). A single case (2%) of clinically driven TLR occurred at 5 months. There were no other major adverse events. The final 2-year data will be published during 2020, mortality and major amputation rates at study end were 0% each.

Future study program

Planned sponsor initiated studies in Europe are the randomized controlled SAVE study (SAVE trial – use of the Selution sirolimus-eluting balloon for dysfunctional AV-accEss treatment Indications). The trial will include 84 patients comparing the SELUTION SLR 018 DCB versus high-pressure balloon angioplasty. Primary end point will be primary patency of the treated lesion and of the treated circuit at 6 months post-intervention.

The planned US study program is comprising of randomized controlled trial (RCTs) with SFA and arterio-venous (AV) access indication as well as a below-the-knee study.

Planned or ongoing investigator initiated trials include the STEP Trial (20 patients with pedal artery lesions, primary efficacy outcome measure: freedom from binary occlusion at 30 days defined by duplex ultrasound and the PRESTIGE trial (Physician initiated, prospective, nonRandomized single center trial, investigating the safety and Efficacy of the Treatment with the Selution Sirolimus-coated Balloon in TASC C and D Tibial occlusive disease In patients with critical limb Ischemia from SinGaporE (NCT04071782). End points are freedom from device- or procedure-related mortality through 30 days annd freedom from TLR at 6 and 12 months post procedure. A total of 30 patients will be compared with historic control (treated same way at the center).

Regulatory affairs

As second sirolimus-coated DCB the SELUTION DCB system received CE mark in January 2020 for commercial distribution in Europe. In the USA, the Center for Devices and Radiological Health of the FDA granted designation of the SELUTION SLR DCB as a Breakthrough Device indicated for percutaneous transluminal angioplasty, after predilatation, of *de novo* or restenostic lesions up to 150 mm in length in native arteries below the knee with reference vessel diameters of 1.5–4.5 mm and for AV access treatment.

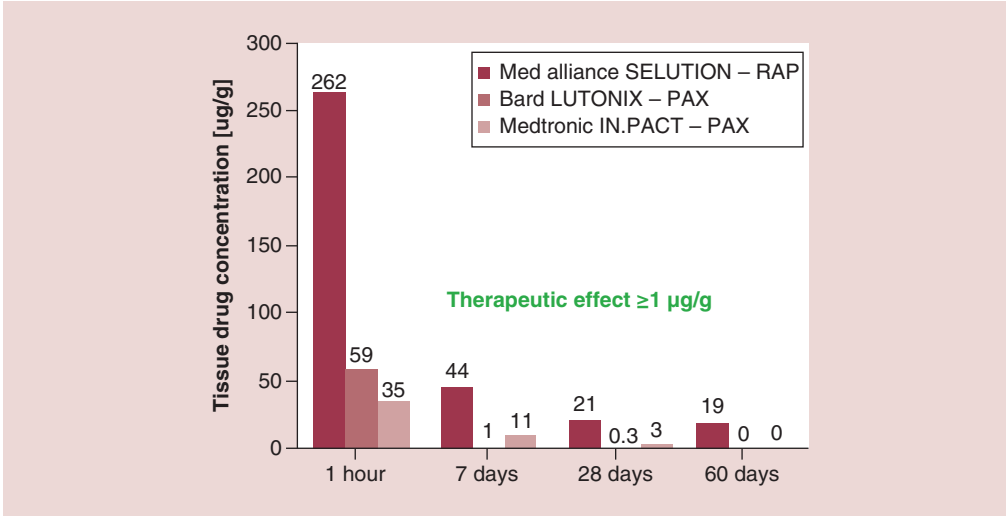


Figure 4. Arterial wall tissue drug concentration sirolimus (rapamycin) versus paclitaxel SELUTION SLR™ drug-coated balloon compared with market leading paclitaxel-coated drug-coated balloon 1 h, 7, 28 and 60 days after drug-coated balloon inflation.
Source: Med. Alliance – Pharmacokinetics Study (2014-004) – Medtronic – RJ Melder. *Catheterization and cardiovascular interventions.* Presented at: Leipzig Interventional Course 2012, Leipzig, Germany, 25–28 January 2012. Reproduced with permission from MedAlliance.

Reimbursement for DCB use in the femoropopliteal anatomy differs across countries. In Europe, some systems offer the same reimbursement for DCB as for uncoated balloons and others offer more on either a general or brand-specific basis for drug-eluting technologies.

Economic analyses have estimated cost savings associated with DCB use for various payer systems, driven by the reduced number of reinterventions versus standard balloon angioplasty and bare metal stenting [56–58]. However, these cost-saving models are exclusively based on paclitaxel-coated DCB study outcomes.

Conclusion

The SELUTION SLR DCB system was designed to address the issue of restenosis following revascularization procedures in the arteries of the upper leg. Initial clinical findings suggest a good safety profile and potential for reducing the need for reinterventions in the femoropopliteal artery. Larger scale comparative studies will more fully characterize its clinical efficacy, better define the patient population most likely to benefit from sirolimus DCB use (versus a different treatment modality) and quantify health–economic implications.

An important additional advantage of the SELUTION DCB, compared with currently available paclitaxel-coated DCB, is the relatively low drug dose, coupled with a high drug coating transfer efficiency and reduced drug coating wash-off (Figures 3 & 4). Even if some drug is washed off, sirolimus is a well-proven and well-tolerated drug that has limited deleterious effect on the function of downstream vascular and skeletal muscle, especially when compared with paclitaxel. Therefore, the combination of low drug dose, high drug coating transfer, reduced wash-off and higher tissue tolerance for sirolimus versus paclitaxel, should result in greater safety margin when using the SELUTION SLR DCB, especially when larger, longer and multiple DCB are required for treatment.

Financial & competing interests disclosure

The institution of the authors received study fees for participating at the to date only clinical trial, which is cited in the review. The authors have not directly received fees. T Zeller received honoraria from Abbott Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Philips-Spectranetics, Shockwave, BIBA Medical. He consulted for Boston Scientific Corp., CSI, Gore & Associates, Medtronic, Veryan, Intact Vascular, Shockwave, Bayer, Vesper Medical. He is holding common stock of QT Medical. E Noory received honoraria from BARD, Boston Scientific, Abbott, Medtronic. Ulrich Beschorner, Roland Macharzina and Tanja Böhme have nothing to declare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Executive summary

Overview of the market

- Peripheral arterial occlusive disease is highly prevalent worldwide and effects on the lower extremities include pain and impaired mobility.
- Endovascular treatment options for lower extremity peripheral arterial disease include balloon angioplasty and stent implantation and newer technologies incorporate antiproliferative drug coatings to prevent restenosis and avoid the need for reintervention.

SELUTION SLR™ drug-coated balloon system device design

- The SELUTION SLR™ sirolimus-coated drug-coated balloon (DCB) system (MA Med Alliance SA, Rue de Rive 5, 1260 Nyon, Switzerland) consists of a coating formulation of four excipients.
- The first excipient is a biodegradable polymer (poly(lactic-co-glycolic acid)) that is intermixed with the sirolimus to form micro-reservoirs and regulates drug release via matrix degradation over time.
- The remaining three excipients constitute a phospholipid blend.

Clinical efficacy & safety: first-in-human results

- The first-in-human single-arm study of SELUTION SLR DCB for treatment of lesions in femoropopliteal arteries resulted in a high patency rate and good safety profile.

Postmarketing surveillance & health–economic assessments

- Several studies are in the pipeline to further investigate the performance of SELUTION SLR DCB in the femoropopliteal and infra-popliteal anatomy.
- Results from ongoing studies will better define the patient population most likely to benefit from sirolimus-coated DCB use.

No writing assistance was utilized in the production of this manuscript.

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