Head-to-head comparison of 2 paclitaxel-coated balloons for femoropopliteal lesions

Head-to-Head Comparison of Two Paclitaxel-Coated Balloons for Femoropopliteal Lesions

1-year results from the BIOPACT RCT

Authors: MD Koen R. Deloose[a], MD Wouter Lansink[b], Prof. MD Marianne Brodmann[c], Prof. MD Martin Werner[d], MD Koen Keirse[e], Prof. MD Yann Gouëffic[f], MD Jürgen Verbist[g], MD Lieven Maene[h], Prof. MD Jeroen M. H. Hendriks[i], MD Jerome Brunet[j], Prof. MD Eric Ducasse[k], MD Kara Levent[l], MD Antoine Sauguet[m], MSc Femke Vandael[o], MSc Sofie Vercauteren[o], MD Joren Callaert[a].

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Affiliations:

[a]Department of Vascular Surgery, AZ Sint Blasius, Dendermonde, **Belgium**

[b]Department of Thoracic and Vascular Surgery, Ziekenhuis Oost-Limburg, Genk, **Belgium**

[c]Department of Angiology, Medical University of Graz, Graz, **Austria**

[d]Department of Angiology, Hanusch Krankenhaus, Vienna, **Austria**

[e]Department of Vascular Surgery, Regionaal Ziekenhuis Heilig Hart, Tienen, **Belgium**

[f]Vascular and endovascular surgical center, Groupe Hospitalier Paris Saint Joseph, Paris, **France**

[g]Department of Thoracic and Vascular Surgery, Imeldaziekenhuis, Bonheiden, **Belgium**

[h]Department of Vascular and Thoracic Surgery, Onze-Lieve-Vrouwziekenhuis Aalst, Aalst, **Belgium**

[i]Department of Thoracic and Vascular Surgery, University Hospital Antwerpen, Edegem, **Belgium**

[j]Cardiovascular Department, Clinique Rhône Durance, Avignon, **France**

[k]Department of Vascular Surgery, Hospital Center University Bordeaux, Bordeaux, **France**

[l]Stadtspital Triemli, Institute of Radiology and Nuclear Medicine, Zürich, **Switzerland**

[m]Clinique-Pasteur, Toulouse Cedex, **France**

[o]iD3 Medical, Sint-Agatha-Berchem, **Belgium**

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Correspondence – Address for correspondence

Koen R. Deloose, MD

Department of Vascular Surgery, AZ Sint Blasius, Kroonveldlaan 50, 9200 Dendermonde, Belgium

E-mail: koen.deloose@telenet.be

Telephone: +32 496 87 70 65

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In the head-to-head BIOPACT RCT, the Passeo-18 Lux and the IN.PACT Admiral DCBs demonstrate comparable results with excellent effectiveness and safety through 12 months for femoropopliteal interventions. #ACCVascular #DCB #cvPAD

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ABSTRACT

Background There is a scarcity of published head-to-head comparisons between different paclitaxel-coated angioplasty balloons. More prospective safety data to support the healthcare economic reimbursement processes is needed.

Objectives The study aim is to report the safety and efficacy of the Passeo-18 Lux drug-coated balloon (DCB) for the treatment of symptomatic peripheral artery disease due to stenosis, restenosis or occlusion of the femoral and/or popliteal arteries.

Methods 302 patients were randomized 1:1 and assigned to the Passeo-18 Lux DCB (study device) group or to the IN.PACT Admiral DCB (control device) group for testing of noninferiority. The primary efficacy endpoint was freedom from clinically-driven target lesion revascularization (CD-TLR) at 12 months. The primary safety endpoint was a composite of freedom from device-/procedure-related death through 30 days post-index procedure, - major target limb amputation and clinically-driven target vessel revascularization (CD-TVR) at 12 months.

Results At 12 months, 130 patients out of 134 in the IN.PACT Admiral group had freedom from CD-TLR (97.0%) compared to 137 out of 141 patients in the Passeo-18 Lux group (97.2%). The primary safety endpoint showed 96.3% in the control group versus 95.7% in the study device group. The null hypothesis of inferiority on both efficacy and safety was

rejected. The Kaplan-Meier estimate of primary patency at 1 year was 88.7% in the control arm versus 91.5% in the study device arm.

Conclusions The Passeo-18 Lux and the IN.PACT Admiral DCBs demonstrate comparable results with excellent effectiveness and safety through 12 months for femoropopliteal interventions.

KEYWORDS

Passeo-18 Lux; IN.PACT Admiral; RCT; Drug-coated balloon

ABBREVIATIONS

ABI = ankle-brachial index

(CD)-TLR = (clinically-driven) target lesion revascularization

(CD)-TVR = (clinically-driven) target vessel revascularization

DCB = drug-coated balloon

NPSO = negative primary safety outcome

PAD = peripheral arterial disease

PTA = percutaneous transluminal angioplasty

PSVR = peak systolic velocity ratio

RCC = Rutherford clinical category

RVD = reference vessel diameter

WIQ = walking impairment questionnaire

INTRODUCTION

Drug-eluting stents (DESs) and drug-coated balloons (DCBs) that expose the vessel to the antiproliferative agent paclitaxel have been used more and more by numerous interventionists in the last decade. Paclitaxel inhibits smooth muscle cell proliferation and neointimal hyperplasia in arterial tissue, resulting in lesser restenosis after treatment. Both the safety and effectiveness of many DCBs for treatment of peripheral artery disease (PAD) are extensively studied (1-16). In 2018, the long-term safety of paclitaxel was debated in a meta-analysis from Katsanos et al., where a higher mortality rate was found at 2 and 5 years after the use of paclitaxel-coated devices for femoropopliteal interventions (17). An association between paclitaxel dose and mortality risk was described. However, more recent clearance of the FDA (18) based on analyses of the risk of late mortality contradict these findings (19-23), and a variety of different paclitaxel DCBs are again widely used to treat PAD.

Nonetheless, head-to-head comparison studies using different DCBs to treat PAD are scarce (24-26). Different commercially available DCBs not only have a different nominal dose of paclitaxel, ranging from 2.0 to 3.5 μg of paclitaxel per mm^2 balloon surface , but also differ in paclitaxel formulations used and coating technology. The impact of the dosing of paclitaxel was studied in the randomized COMPARE trial, of which the 2-year results recently became available (27).

The BIOPACT RCT analyses the safety and efficacy of two commercially available DCBs with a similar paclitaxel dose, but different delivery matrix, in patients with symptomatic femoropopliteal lesions. The Passeo®-18 Lux® DCB (study device; Biotronik AG, Buelach, Switzerland) is compared with the IN.PACT Admiral™ DCB (control group; Medtronic Vascular, Santa Clara, CA, USA). The Passeo-18 Lux DCB is homogeneously coated with 3 µg microcrystalline paclitaxel, incorporated in a delivery matrix of hydrophobic butyryl tri-n-hexyl citrate (BTHC) per mm² balloon surface. The study device has shown superiority compared with the Passeo-18 PTA balloon in the randomized BIOLUX P-I trial (9). The safety and efficacy were also confirmed in the real-world BIOLUX P-III registry (28). The IN.PACT Admiral DCB has 3.5 µg of paclitaxel per mm², homogeneously incorporated into a hydrophilic urea formulation (FreePAC). The latter was also successfully compared to the regular Admiral PTA balloon in the IN.PACT SFA trial (4).

The quadruple aim of this randomized study is to do a head-to-head comparison of the two described DCBs, avoid class effects in analysis of DCBs, provide more safety data in the paclitaxel discussion and finally, add more efficacy data for the tested DCBs to guide authorities and healthcare providers during reimbursement processes.

Clinical Perspectives

There is a scarcity of published head-to-head comparisons between different paclitaxel-coated angioplasty balloons, as well as prospective safety data to support the healthcare economic

reimbursement processes. This study adds (a third) head to head comparison of DCB to the scientific society with a lot of safety and efficacy data on two different DCB platforms. The authors hope that in the future, more endovascular tools will be prospectively compared head-to-head in order to simplify this confusing landscape.

METHODS

Study design

The extended description of the methodology of this study can be found in the paper of Deloose et al., 2022 (29). This physician-initiated prospective, multicentre, randomized controlled BIOPACT study assigned 302 patients in a 1:1 ratio to treatment with the Passeo-18 Lux DCB (study device) or the IN.PACT Admiral DCB (control group) for testing of non-inferiority. Approval was obtained by all relevant ethical committees.

Key inclusion criteria were Rutherford clinical category (RCC) 2-4 disease, either a single or tandem stenotic lesion ≤ 180 mm with ≥ 70% stenosis, or an occluded lesion ≤ 120 mm, that was located between the ostium of the SFA and the end of the proximal popliteal artery (P1). Key exclusion criteria were acute limb ischemia, an intervention involving the target vessel within the previous 90 days, any lower extremity percutaneous treatment in the ipsilateral limb using a paclitaxel-eluting stent or DCB within the previous 90 days, and PTA of the target lesion using a DCB within the previous 180 days. A detailed list of all inclusion

and exclusion criteria can be found in the Supplemental Appendix. All patients provided written informed consent prior to their target lesion treatment. The study protocol and informed consent were approved by the ethics committee at each site. The trial registration number at clinicaltrials.gov is ID NCT03884257. Adverse events are being recorded from signing of the informed consent, until the 60-month follow-up or until study end, whichever comes first.

Prior to the index procedure, information regarding demographics, ABI and RCC, medication, physical examination, Walking Impairment Questionnaire (WIQ), medical history, and laboratory testing as per Standard of Care , was collected. The WIQ score is the result of the analysis of PAD-specific problems, comorbidities, walking distance, walking speed and capability to climb stairs. Only questionnaires with the total WIQ score available were taken into account.

Procedure

It was mandatory to pre-dilate the target lesion for at least 90 seconds with an uncoated PTA balloon. Following successful predilatation and after confirmation of the angiographic inclusion and exclusion criteria, each patient was randomized 1:1 to treatment with either the Passeo-18 Lux or IN.PACT Admiral DCBs by using an electronic data collection program. Both devices were used according to the instructions for use (IFU) with a DCB diameter that matched the reference vessel diameter (RVD) distal to the target lesion on a 1.1:1 ratio, a DCB

length that extends past the target lesion 5 mm proximally and distally, and an overlap of at least 10 mm if multiple DCBs were used. Balloon inflation was at or beyond nominal pressure during at least 180 seconds. A patient was considered enrolled when the study device or control device was introduced into their vasculature. Additional treatment of the target lesion was to be avoided as much as possible. If a flow-limiting dissection or > 30% residual stenosis were present, a second prolonged balloon inflation (>180 seconds) was to be attempted before bailout stenting per standard of care with an SFA-indicated bare nitinol stent that was as short as possible to treat the dissection or residual stenosis. Acute procedural success was defined as restoration of the target lesion with ≤30% residual stenosis in the final angiogram. Closure of the access site was per standard of care. Medication and procedural details were recorded. Angiographic examinations were sent to an independent core lab for review. Before discharge, information regarding ABI, RCC, medication and physical examination was collected. Unless clinically contraindicated, lifelong aspirin (or coumarins/ Direct-acting oral anticoagulant) and at least one month of clopidogrel were to be prescribed.

Follow-up assessments

Clinical follow-up consists of a 1-, 6-, 12-, 24-, 36-, 48-, and 60-month follow-up visit. During the first year of follow-up, the following data were collected: RCC, ABI, duplex ultrasonography and medication assessment. Information from the WIQ was gathered. The same data will be collected during the 24-month follow-up. The 36-, 48-, and 60-month follow-

up consist of RCC classification and medication registration. Information regarding adverse events is collected until 60-month follow-up.

Endpoint definitions

The primary efficacy endpoint was freedom from clinically driven target lesion revascularization (CD-TLR) at 12 months, defined as any re-intervention at the target lesion due to symptoms, drop of ABI > 20% or > 0.15 compared to post-procedural ABI. The primary safety endpoint was a composite of freedom from device- / procedure-related death through 30 days post-index procedure, freedom from major target limb amputation, and clinically-driven target vessel revascularization (CD-TVR) through 12 months post-index procedure.

The key secondary endpoints were acute device success (defined as successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below rated burst pressure) and acute procedural success, primary patency (defined as a composite of freedom from CD-TLR and binary restenosis (restenosis defined as duplex ultrasonography PSVR ≥ 2.4 or ≥ 50% stenosis as assessed by an independent core lab)), , major adverse events (defined as a composite of all cause death, CD-TVR, major target limb amputation, or thrombosis at the target lesion), sustained clinical improvement (defined as freedom from major target limb amputation, -TVR, -worsening of RCC compared to baseline and -decrease in target

limb ABI or TBI ≥ 0.15 compared to baseline), as well as the change of walking impairment questionnaire score, change in target limb RCC and change in target limb resting ABI from baseline to 6 and 12 months. The complete list of secondary endpoints can be found at clinicaltrials.gov, ID NCT03884257.

An independent clinical events committee (CEC) blinded to the treatment arm, which comprises physicians with expertise in vascular surgery and/or vascular intervention, was responsible of evaluating and adjudicating specified clinical endpoints; TLR, TVR, death, major target limb amputation and thrombosis, and determining their device- and procedure-relatedness. Twelve-month follow-up duplex ultrasound images were assessed by an independent Core lab.

Statistical analysis

Outcomes were analyzed using the intention-to-treat principle. Categorical data were expressed as frequency counts and percentages, and continuous data as mean ± SD. Student's t-tests or comparison of proportions were used to compare both treatment groups. Software used was R v4.2.0, MedCAlc® v20.210, and Microsoft Excel® (Microsoft 365®). The primary efficacy and safety analysis sets were exported to verify the results of the hypothesis tests for primary efficacy and safety in SAS version 9.4. The primary efficacy endpoint, primary safety endpoint, and secondary endpoints related to overall survival and primary patency were assessed by StatGent (Ghent University - Department of Applied Mathematics, Computer

Science and Statistics), using R, with time-to-event analyses through 395 days (365 days + 30-day window). Patients without events at 395 days of follow-up or later were censored at 395 days. Non-inferiority regarding CD-TLR and safety were assessed using a Farrington-Manning test on the risk difference between both treatment groups with a 10% non-inferiority margin at the (one-sided) 5% significance level.

RESULTS

In total, 302 patients were randomized 1:1 and enrolled between April 2019 and September 2021. Study subjects were included in 14 European centers in Belgium (59.3%), Austria (27.5%), France (12.9%) and Switzerland (0.3%). For one patient that was randomized in the IN.PACT Admiral group, no further information was available. Therefore this article is based on the study results of 301 instead of 302 patients.

The IN.PACT Admiral treatment arm (control group) included 149 patients, and the Passeo-18 Lux (study device) accounted for 152 patients.

Baseline characteristics and preoperative assessments

Of all 301 enrolled patients, 68.8% were male and 31.2% were female. The mean age at the time of enrolment was 67 years old in the IN.PACT Admiral treatment group and 69 years old in the Passeo-18 Lux group. The most prominent risk factors in both treatment groups were hypertension and hypercholesterolemia. A more detailed overview of the medical history and

risk factors can be found in Table 1. There was no statistically significant difference between the baseline characteristics in both groups, with the exception of current nicotine use, which was higher in the control group. Baseline ABI was measured in 285 patients, with a mean of 0.68 in the IN.PACT Admiral study arm and 0.67 in the Passeo-18 Lux study arm. Most patients presented with Rutherford category 3 (69.1% and 66.9% in the IN.PACT Admiral and Passeo-18 Lux group, respectively). For 245 patients, a total WIQ score at baseline was available. There were no statistically significant differences in the preoperative assessments between both groups.

Lesion and operative characteristics

An inflow lesion was treated in 26 patients, resulting in < 30% residual stenosis in all cases. One of the patients in the Passeo-18 Lux group had a target lesion from the first to the third segment of the popliteal artery, resulting in a protocol deviation. The mean target lesion length and reference vessel diameter was 65.6 mm and 5.4 mm in the IN.PACT Admiral arm, and 74.0 mm and 5.3 mm in the Passeo-18 Lux arm, respectively. Moderate to severe calcification was the most frequent lesion characteristic. A more detailed overview of the study lesions can be found in Table 2.

All lesions were predilated with an uncoated PTA balloon, as per study protocol. Successful predilatation, with residual stenosis ≤ 50% and the absence of a flow-limiting dissection grade D, E and F, was achieved in all 301 cases. There were 149 patients treated with a total of 189 IN.PACT Admiral DCBs, whereas 152 patients were treated with a total of 164 Passeo-18 Lux DCBs. Bailout stenting occurred in 17 (11.4%) and 20 (13.2%) patients, respectively. Forty-three patients were treated with a post-dilatation balloon. Angiographic imaging showed good outflow for all subjects. Access site closure was achieved by a closure device in most cases (86.6% in the IN.PACT Admiral and 82.2% in the Passeo-18 Lux group).

Follow-up

The patient flow from inclusion through 12-month follow-up can be seen in Figure 1.

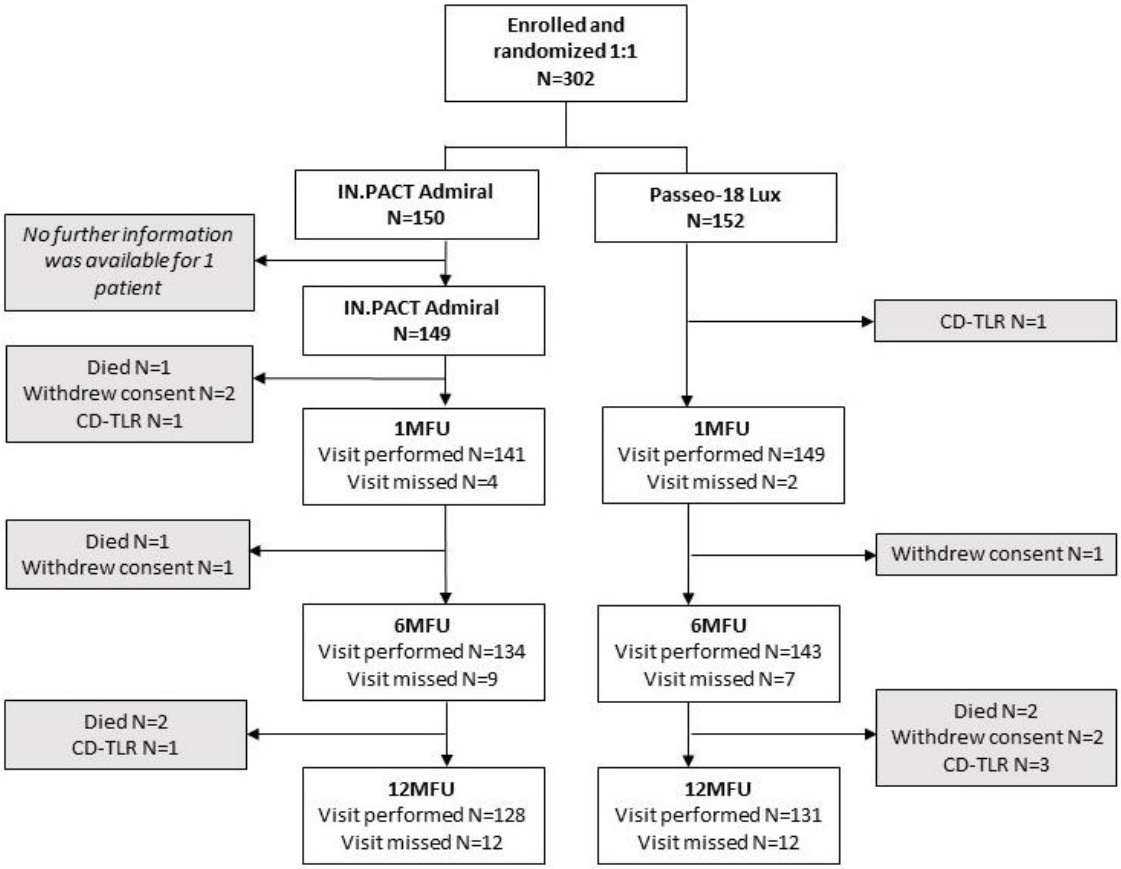


Figure 1. Patient flow from enrolment until 12 months

Patients were randomized 1:1 in either the IN.PACT Admiral (control device) group or the Passeo-18 Lux (investigational device) group. No further information was available for 1 patient in the former treatment arm, resulting in 149 patients and 152 study patients respectively.

N=number of patients. CD-TLR=clinically-driven target lesion revascularization.

One-month follow-up data were available for 290 patients (96.3%). The access site of all patients was examined, and two patients in the control group showed a hematoma at the puncture site. Six-month follow-up data were available for 277 patients (92.0%) and 12-month follow-up data were available for 259 patients (86.0%). In total, after 1-year follow-up, six patients had died, six withdrew consent, six patients underwent target lesion revascularization, and another 24 patients did not perform the 12-month follow-up.

Primary efficacy endpoint

Patients that were excluded from the analysis were patients who died (four in the control group and one in the study device group), withdrew consent (three and one, respectively), or had no evaluation (eight patients in the control and nine in the study device group). In the IN.PACT Admiral group, 130 out of 134 patients had freedom of CD-TLR (97.0%), compared to 137 out of 141 patients in the Passeo-18 Lux group (97.2%). The null hypothesis of inferiority was rejected with a p-value of 2.36×10^{-4}.

Figure 2 depicts 1- the cumulative incidence of CD-TLR in the first year of follow-up. In the IN.PACT Admiral group (control device), this number was 97.7% (95% CI: 93.9% - 99.4%) and in the Passeo-18 Lux group (investigational device) this number was 97.3% (95% CI: 93.6% - 99.1%). Death before CD-TLR is considered to be a competing risk.

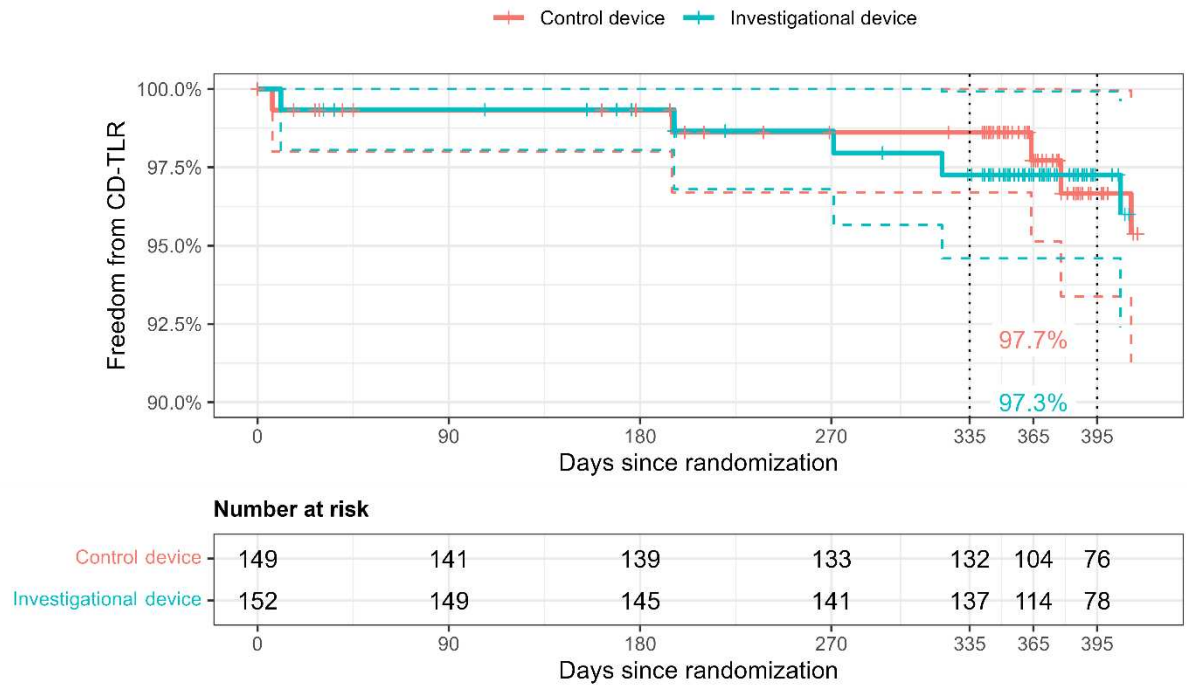


Figure 2. 1- the cumulative incidence of CD-TLR at 12 months

1- the cumulative incidence of CD-TLR at 12 months was 97.7 % (95% CI: 93.9% - 99.4%) in the IN.PACT Admiral group and 97.3% (95% CI: 93.6% - 99.1%) in the Passeo-18 Lux group. Death before CD-TLR is considered to be a competing risk.

Primary safety endpoint

The same patients who were excluded for the efficacy endpoint were also excluded for the primary safety analysis. In the control group, 96.3% of the patients and 95.7% of the patients in the study device group did not experience one of the adverse events from the composite safety endpoint. Only one patient in the IN.PACT arm committed suicide before the 1-month follow-up. The death was adjudicated by an independent CEC as not related to the control device. There were no major amputations. There were five CD-TVRs in the control group and six in the study device group. Non-inferiority was assessed using a Farrington-Manning test on the risk difference between both treatment groups with a 10% non-inferiority margin at the (one-sided) 5% significance level. The null hypothesis of inferiority was rejected with a p-value of 8.42 x 10-4.

Figure 3 presents 1 - the cumulative incidence of NPSO (Negative Primary Safety Outcome) in the first year of follow-up. This freedom from NPSO number was 97.0% (95% CI: 93% - 99.0%) in the control group, and 95.9% (95% CI: 91.8% - 98.3%) in the Passeo-18 Lux group. Death before NPSO is considered a competing risk.

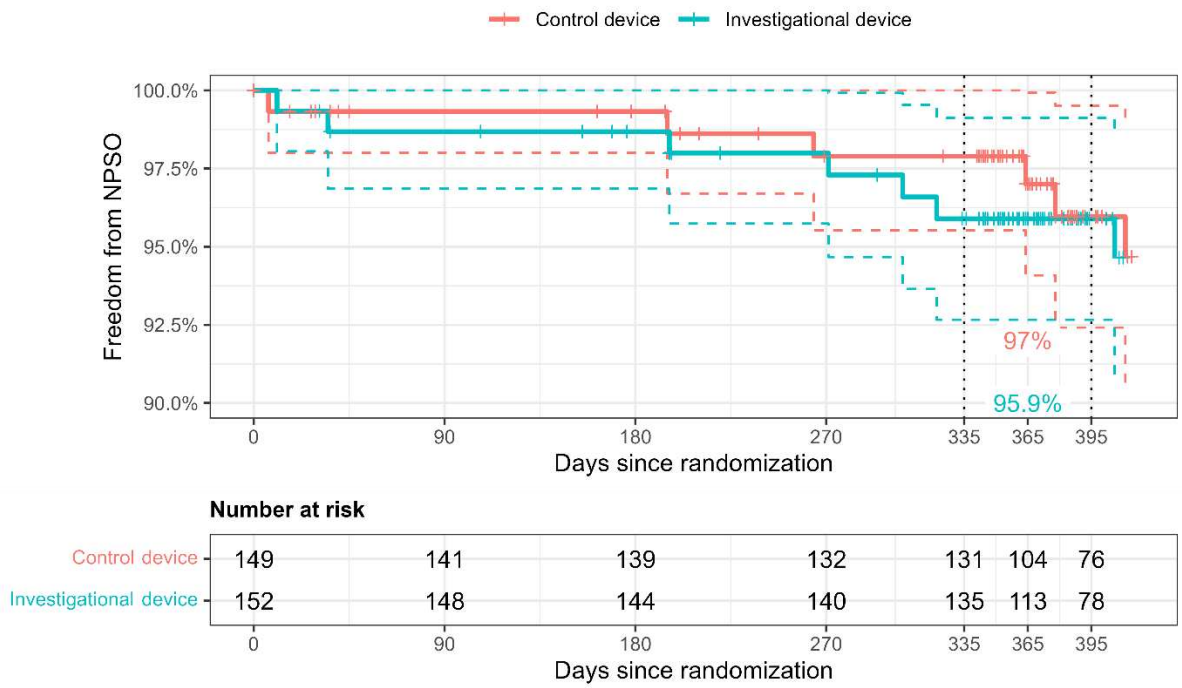


Figure 3. 1- the cumulative incidence of negative primary safety outcome at 12 months

1- the cumulative incidence of negative primary safety outcome at 12 months was 97.0% (95% CI: 93.0%-99%) in the IN.PACT Admiral group and 95.9% (95% CI: 91.8% - 98.3%) in the Passeo-18 Lux group. Death before NPSO is considered to be a competing risk.

Secondary endpoints

Primary patency

Patients that were excluded from the analysis are patients who died (four in the control group and one in the study device group), withdrew consent (three and one, respectively), or had no (duplex) evaluation in window (32 and 31, respectively). In the IN.PACT Admiral group, 98 out of 110 patients had no loss of primary patency (89.1%), compared to 105 out of 119 patients in the Passe-18 Lux group (88.2%). The null hypothesis of equality of proportions was not rejected with a p-value of 1.

Figure 4 shows the Kaplan-Meier estimate of freedom from loss of primary patency in the first year of follow-up. In the IN.PACT Admiral group (control device), this number was 88.7% (95% CI: 83.2% - 94.5%) and in the Passeo-18 Lux group (investigational device) this number was 91.5% (95% CI: 86.9% - 96.5%).

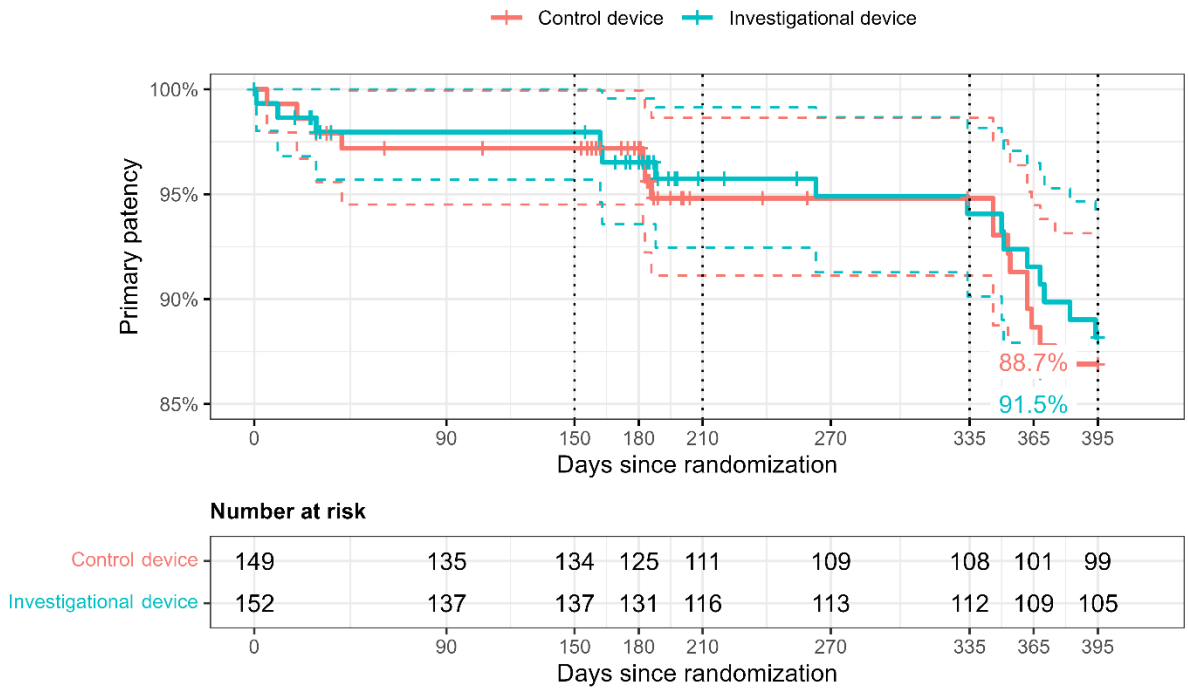
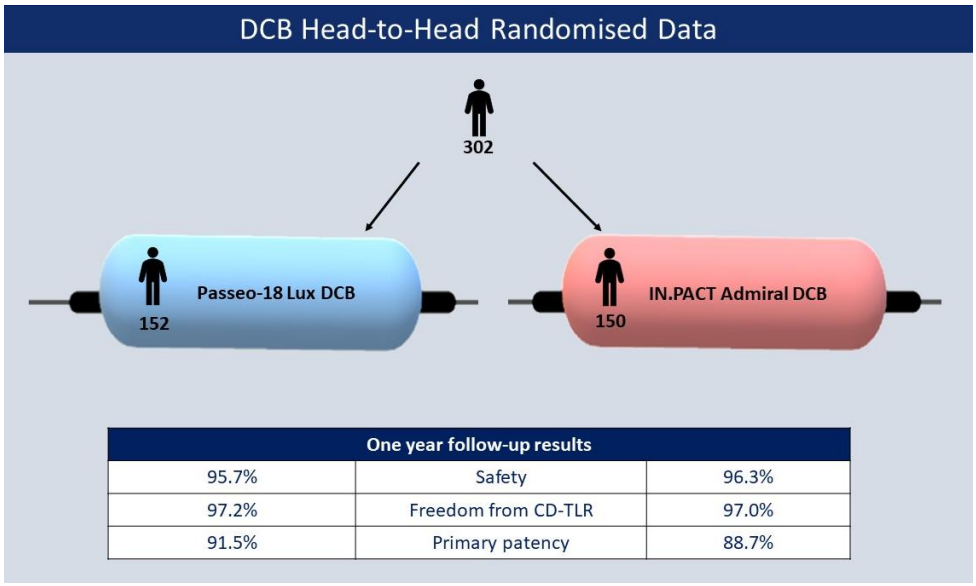


Figure 4. Primary patency at 12 months

Primary patency at 12 months was 88.7% (95% CI: 83.2% - 94.5%) in the IN.PACT Admiral group and 91.5% (95% CI: 86.9% - 96.5%). in the Passeo-18 Lux group. Patency was assessed by evaluation of duplex ultrasound images by an independent Corelab.

The results of the primary safety and -efficacy endpoint, as well as the primary patency are summarized in the figure below.



DCB Head-to-Head Randomised Data (central illustration)

Overview of the 1 year safety-, efficacy- and patency data of both treatment arms in the BIOPACT RCT.

Major adverse events

Six patients died during the first year of follow-up (four in the control group and two in the investigational group), resulting in survival rates of 97.2% and 98.5% in the IN.PACT Admiral and Passeo-18 Lux group respectively. None of these deaths were related to the device nor the procedure. Eleven patients underwent a CD-TVR (five and six, respectively), and one patient from the Passeo-18 Lux group had a thrombosis at the target lesion. No major target limb amputations occurred.

Adverse events

In total, there were 53 adverse events reported between the procedure and the end of the 1-month follow-up window, and 141 by the end of the 6-month follow-up window. There was no significant difference between the number of adverse events in both groups ($p=0.4556$ at 1-month follow-up and $p=0.2890$ at 6-month follow-up). There was a statistically significant difference in the total number of adverse events reported from inclusion until the end of the 12-month follow-up (102 adverse events in the IN.PACT Admiral group and 132 in the Passeo-18 Lux group, $p<0.0007$). This difference was not determined by a difference in death nor TLR nor device-or procedure related adverse events.

Sustained clinical improvement

The overall mean change in WIQ score at 6 months compared to baseline was +38.8 for the IN.PACT Admiral group and +33.3 for the Passeo-18 Lux group. At 12 months, this was +34.2 and +35.8, respectively. The mean change in target limb RCC at 6 months compared to baseline was -2.6 for both treatment groups. At 12 months, this was -2.5 for the IN.PACT Admiral group and -2.4 in the Passeo-18 Lux group. The mean change in target limb resting ABI compared to baseline was +0.25 for the IN.PACT Admiral group and +0.26 for the Passeo-18 Lux group after 6 months, and +0.14 and +0.18 after 12 months. More information can be found in Table 3 and in Figures 5, 6 and 7

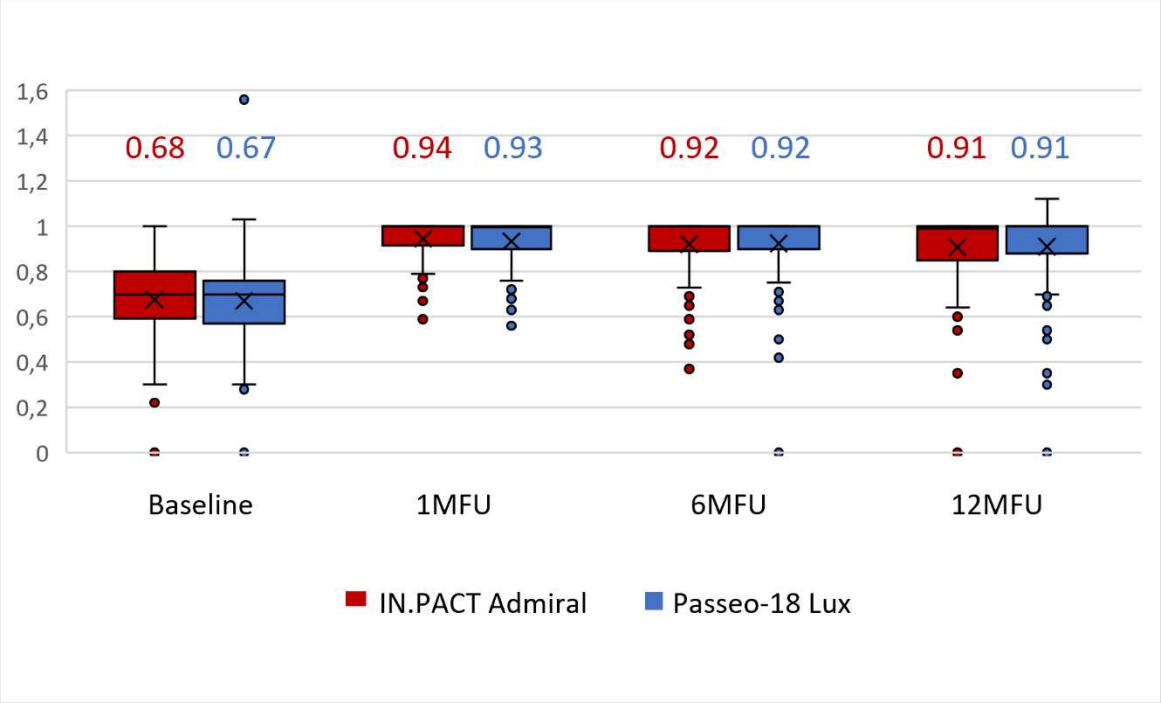


Figure 5. Evolution of mean ankle-brachial index

The evolution of the mean ankle-brachial index from baseline to the subsequent follow-up visits was comparable between both treatment arms. The mean change in target limb resting ABI compared to baseline was +0.25 for the IN.PACT Admiral group and +0.26 for the Passeo-18 Lux group after 6 months, and +0.14 and +0.18 respectively after 12 months.

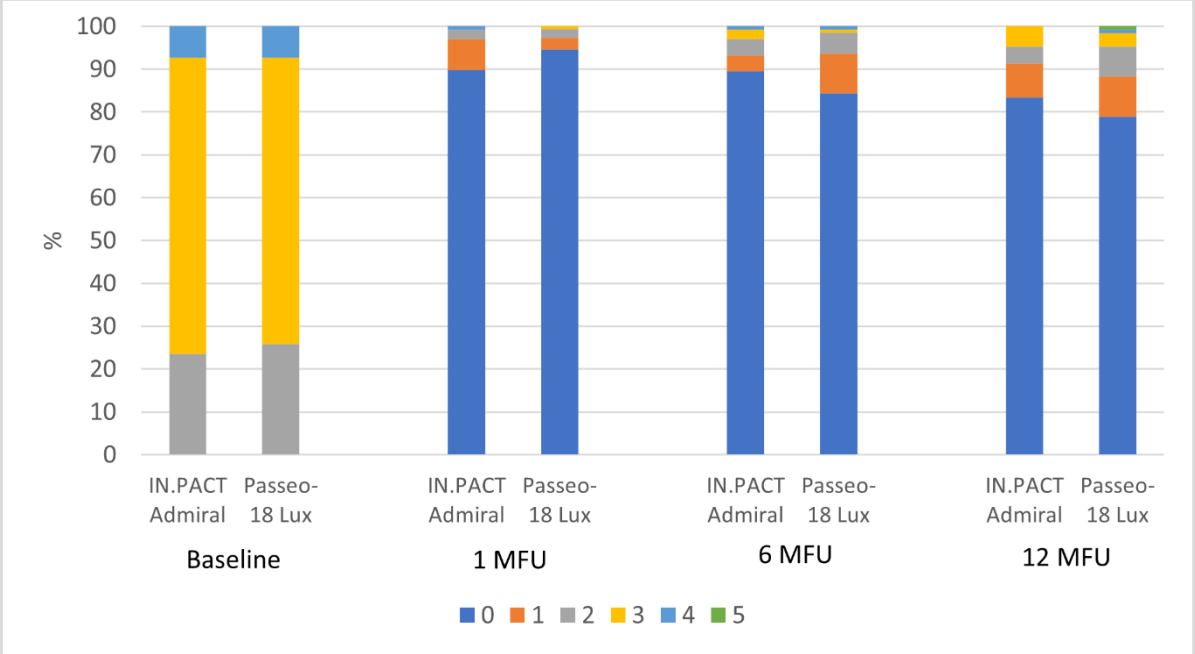


Figure 6. Evolution of Rutherford clinical classification

The evolution of the Rutherford clinical classification *from baseline to the subsequent follow-up visits was comparable between both treatment arms. The mean change in target limb RCC at 6 months compared to baseline was -2.6 for both treatment groups. At 12 months, this was -2.5 for the IN.PACT Admiral group and -2.4 in the Passeo-18 Lux group*.

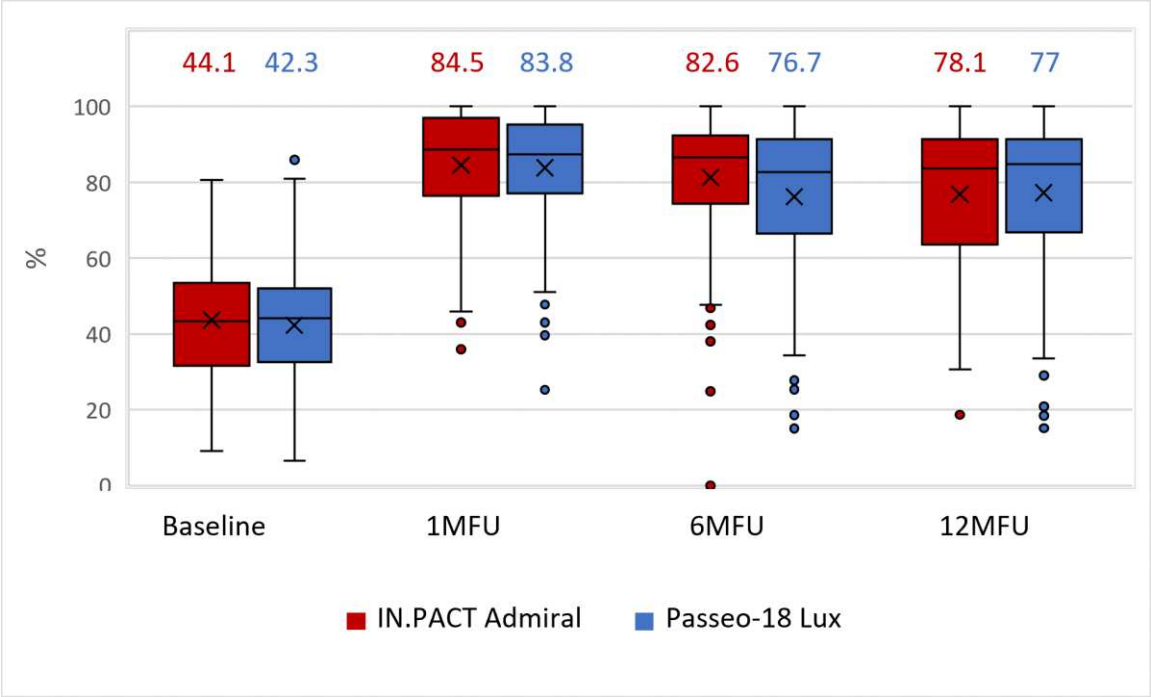


Figure 7. Evolution of mean Walking Impairment Questionnaire score

The evolution of the mean WIQ score from baseline to the subsequent follow-up visits was comparable in both treatment arms. The overall mean change in WIQ score at 6 months compared to baseline was +38.8 for the IN.PACT Admiral group and +33.3 for the Passeo-18 Lux group. At 12 months, this was +34.2 and +35.8, respectively. Only WIQ questionnaires where the total score was available were taken into account.

DISCUSSION

Numerous randomized controlled trials have demonstrated the superior efficacy and equal safety of DCBs over PTA alone for femoropopliteal interventions (1-16). DCBs address several complex and contradictory demands. They must ensure a balance between drug retention during the transfer to the lesion and an effective drug transit into the vessel wall to optimize the drug uptake. This transfer needs to be realized in a rather short time window, and the therapeutic drug dose has to remain in the tissue for several weeks. This balance can only be achieved through a combination of the correct drug, the optimal drug dosing, the right excipient, the best way of coating/manufacturing, pharmacokinetics, and the ideal balloon type and material (30). All these factors play a crucial role in the outcome of every DCB.

In addition, differences in trial designs, endpoint definitions, patient-, lesion- and procedural characteristics stress the need for uniformly designed head-to-head randomized effectiveness and safety research.

Last but not least, DCBs for femoropopliteal interventions have been challenged by a meta-analysis identifying a late mortality signal beyond 2 years in patients who were treated with paclitaxel-coated devices compared to uncoated control devices (17). Subsequent research and more recent analyses disproved this finding (19-23).

With the BIOPACT RCT, the investigators wanted to add scientific input to all aspects of this field and to advance the level of evidence to a broad group of stakeholders, including physicians, regulators, healthcare-payers, and most importantly, patients who want to know

they are getting the safest and most effective therapies to improve their quality of life. This study provides controlled, randomized data, eliminating class effects between two different types of DCB and will deliver more prospective safety data up to 5 years concerning the so called “high-dose” paclitaxel DCBs (between 3 and 3.5µg/mm² paclitaxel nominal dose). The IN.PACT Admiral DCB was selected as the comparator in this trial because it was the first reimbursed paclitaxel-coated balloon in Belgium, the most widely used balloon and the one with the most high quality data available at the time the study was designed.

The comparison of the two evaluated DCBs is especially interesting, as they each have a distinctly different coating formulation, knowing that the excipient profoundly impacts paclitaxel drug loss, including particulate embolization during delivery. The majority of the previous published DCB trials were performed with a lipophilic antiproliferative drug (paclitaxel) and hydrophilic excipients (1-8, 10-16), whereas the excipient of the study device,

Passeo-18 Lux, is BTHC. BTHC was selected for its capability to adhere to the balloon, low amount of particles generated, stability and hydrophobic characteristics (Figure 8).

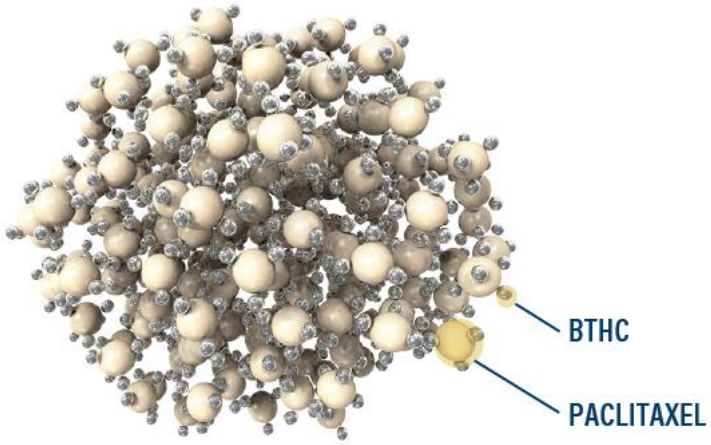


Figure 8. Paclitaxel and BTHC microcrystalline structure

BTHC was selected for its capability to adhere to the balloon, low amount of particles generated, stability and hydrophobic characteristic.

This hydrophobic characteristic helps prevent the drug from washing off prematurely during the transit to the target lesion, thus maximizing the drug availability at the target (Data on file at Biotronik AG). The combination of BTHC and paclitaxel ensures an efficient performance of the drug at the target lesion over time. A preclinical porcine study demonstrated a prolonged presence of paclitaxel in the target vessel tissue up to 28 days following treatment (Data on file at Biotronik). Systemic blood levels decreased to low levels after 7 days and reached levels

below quantification at day 28. There were no signs of adverse events related to the Passeo-18 Lux DCB.

The study device has been compared with the Passeo-18 PTA balloon in the randomized BIOLUX P-I clinical trial (9) and the BIOLUX P-III real-world all-comer registry (28). In the femoropopliteal subgroup of the BIOLUX P-III registry, the freedom from clinically driven target lesion revascularization (CD-TLR) was 93.6%, with freedom from major adverse events being 90.5% at 12 months.

Two very similar groups without different baseline patient characteristics and preoperative assessments were included in the randomized study. A mean target lesion length of 65.6 mm in the control group versus 74.0 mm in the study group (p= 0.3027) was treated. Predilatation was mandatory according to the study protocol (100% of the enrollments). The authors are of the opinion that lesion preparation is very important as, beside the mechanical advantage of creating lumen gain, it reduces damage to the drug coating of the DCB during balloon transport through the lesion and thus decreases the amount of drug loss (31-33). Extensive vessel preparation may also increase balloon-wall apposition and ensure uniform local drug distribution (34). Finally, moderate plaque /vessel wall damage can facilitate antiproliferative drug delivery, as well as tissue retention (35). The balloon diameter used was 5.4 mm in both control and study groups and bailout stent ratios were 11.4% and 13.2%, respectively. Although between 71.1% and 79.6% of the treated lesions respectively in control and study groups were categorized as moderately/severely calcified, according to the PACCS

scoring system, a procedural success rate of 100% was reached in the entire population, defined as angiographically < 30% residual stenosis in two different projections,.

At 12 months, in the IN.PACT Admiral group, 130 patients out of 134 had freedom from CD-TLR (97.0%) compared to 137 out of 141 patients in the Passeo-18 Lux group (97.2%). The null hypothesis of inferiority was rejected with a p-value of 2.36×10^{-4} thus demonstrating the non-inferiority of Passeo-18 Lux compared to IN.PACT Admiral with regards to efficacy. The Kaplan-Meier estimate of primary patency at 1 year shows 88.7% in the IN.PACT Admiral group versus 91.5% in the Passeo-18 Lux arm. The primary safety endpoint, defined as a composite of freedom from device- and procedure-related death through 30 days post-index procedure, freedom from major target limb amputation and CD-TVR through 12 months, showed 96.3% in the control group versus 95.7% in the study device group. The null hypothesis of inferiority regarding safety was rejected with a p-value of 8.42×10^{-4}, showing non inferior safety of the Passeo-18 Lux compared to IN.PACT Admiral.

In the IN.PACT Admiral group, 17 patients were treated with bailout stenting. None of them had a TLR or a NPSO in the first year of follow-up. In the Passeo-18 Lux group, 20 patients were treated with bailout stenting. Two of these patients underwent TLR, and one patient experienced a NPSO in the first year of follow-up.

A sustained clinical improvement up to 12 months post-procedure was noted in both groups in terms of mean ABI, RCC and WIQ score evolution without any statistically significant difference between both arms.

A total of six patients out of 301 died within the first year of follow-up. None of the deaths were related to the procedure nor the device. The "paclitaxel mortality signal" debate started after the initiation of the BIOPACT RCT study (17). A prolonged follow-up to 5 years is implemented by amendment in order to deliver more data on this topic. The observed mortality rates at 1 year in both treatment arms are among the lowest reported in femoropopliteal trials.

The BIOPACT study safety and efficacy primary endpoints were met. The Passeo-18 Lux DCB was shown to be non-inferior in its primary safety and efficacy endpoints at 12 months compared with the IN.PACT Admiral DCB. The primary patency rates and freedom from TLR rates in this trial are consistent with the earlier published results of the BIOLUX P-III and IN.PACT SFA trials at 12 months (14, 28). Regardless of the used excipients, these two "high-dose" paclitaxel DCBs have shown in identical circumstances (patient population, used technique, etc,) outstanding safety and efficacy results. The authors suspect that these results will be sustained in the ongoing 5-year follow-up for both treatment groups.

Limitations

Important to mention is that our study was solely designed to assess non-inferiority for freedom of CD-TLR and a combined safety endpoint, but not for functional outcomes.

The study was challenged by authorities' paclitaxel warnings and the COVID-19 pandemic, which created temporary enrolment and in-hospital follow-up problems. Despite these challenges, the study completed enrolment goals on time, with more than 86% of subjects completing follow-up at 12 months.

Another limitation is the fact that the operators, responsible for all procedural decisions, were not blinded in this study. Nevertheless, duplex ultrasound technicians, independent core laboratory staff and members of the clinical event committee were blinded to the received treatment.Finally, due to exclusion of dedicated lesion prepping devices like atherectomy, specialty balloons, or intravascular lithotripsy in the study protocol, our study results could be limited for generalization globally.

Conclusions

While a number of DCBs have demonstrated superiority compared to plain old balloon angioplasty (POBA) for femoropopliteal interventions, they are not equal. Excipient and coating characteristics will govern the overall performance of a DCB and impact the clinical outcomes. A hydrophobic excipient such as BTHC will prevent paclitaxel from being prematurely washed off, enabling better transfer of the drug to the lesion.

The BIOPACT RCT is a large, prospective, multicentre, randomized trial of patients with symptomatic femoropopliteal disease demonstrating that the Passeo-18 Lux DCB with the hydrophobic excipient BTHC is non inferior in terms of freedom from CD-TLR and safety compared to the IN.PACT Admiral DCB with hydrophilic excipient. The Passeo-18 Lux and the IN.PACT Admiral DCBs demonstrate comparable results with excellent effectiveness and safety through 12 months for femoropopliteal intervention. Long-term follow-up to 5 years is ongoing and will reveal if these positive results can be maintained.

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Figures

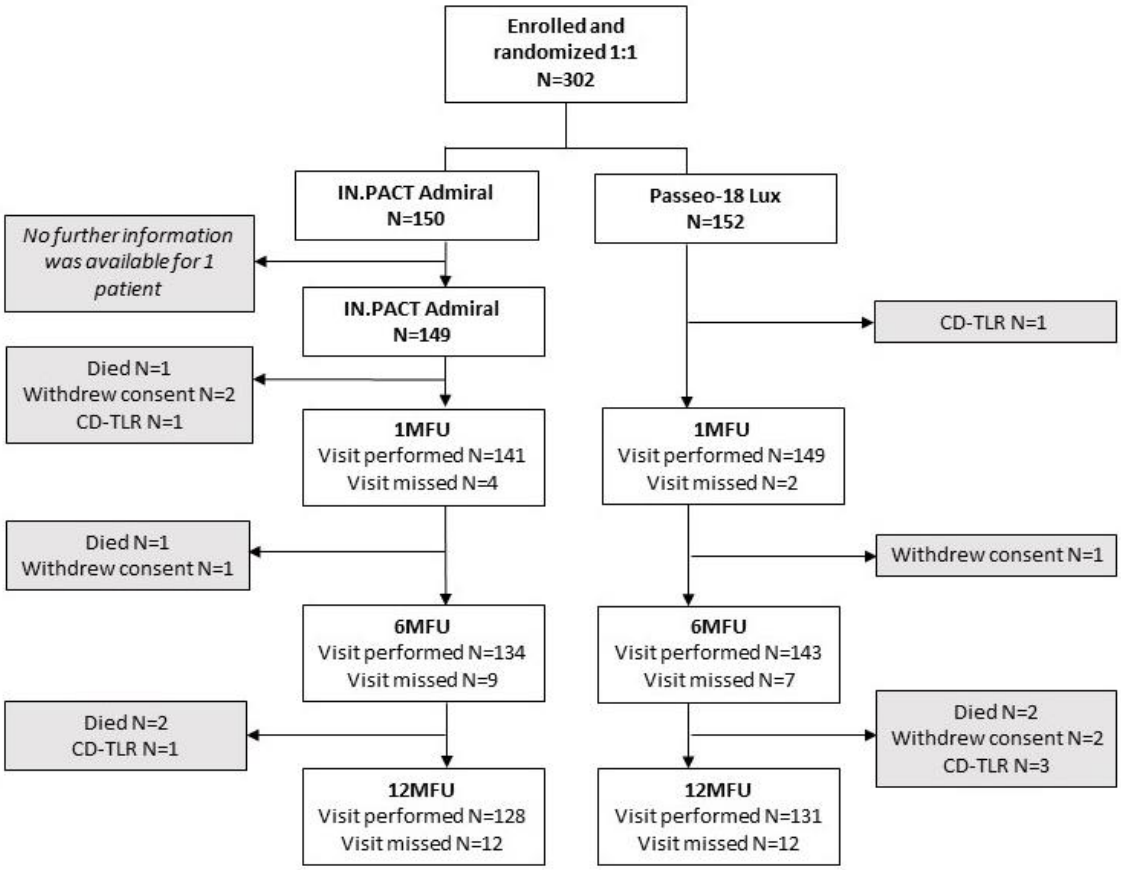


Figure 1 Patient flow from enrolment until 12 months

Patients were randomized 1:1 in either the IN.PACT Admiral (control device) group or the Passeo-18 Lux (investigational device) group. No further information was available for 1 patient in the former treatment arm, resulting in 149 patients and 152 study patients respectively.

N=number of patients. CD-TLR=clinically-driven target lesion revascularization.

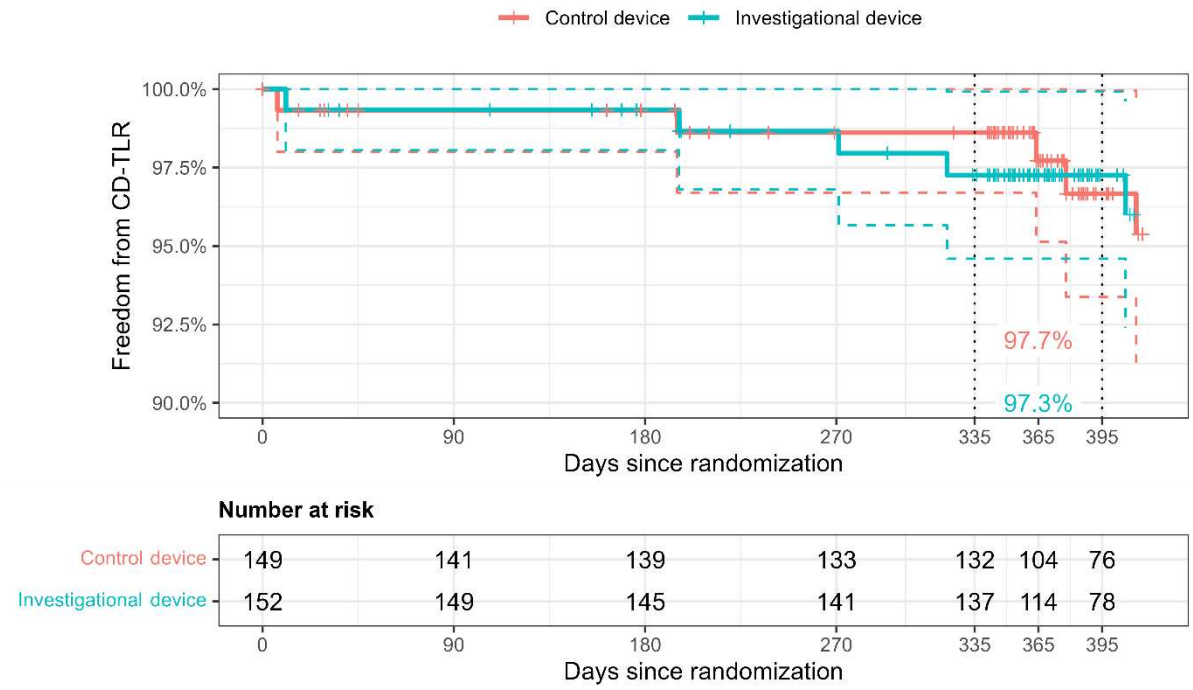


Figure 2. 1- the cumulative incidence of CD-TLR at 12 months

1- the cumulative incidence of CD-TLR at 12 months was 97.7 % (95% CI: 93.9% - 99.4%) in the IN.PACT Admiral group and 97.3% (95% CI: 93.6% - 99.1%) in the Passeo-18 Lux group. Death before CD-TLR is considered to be a competing risk.

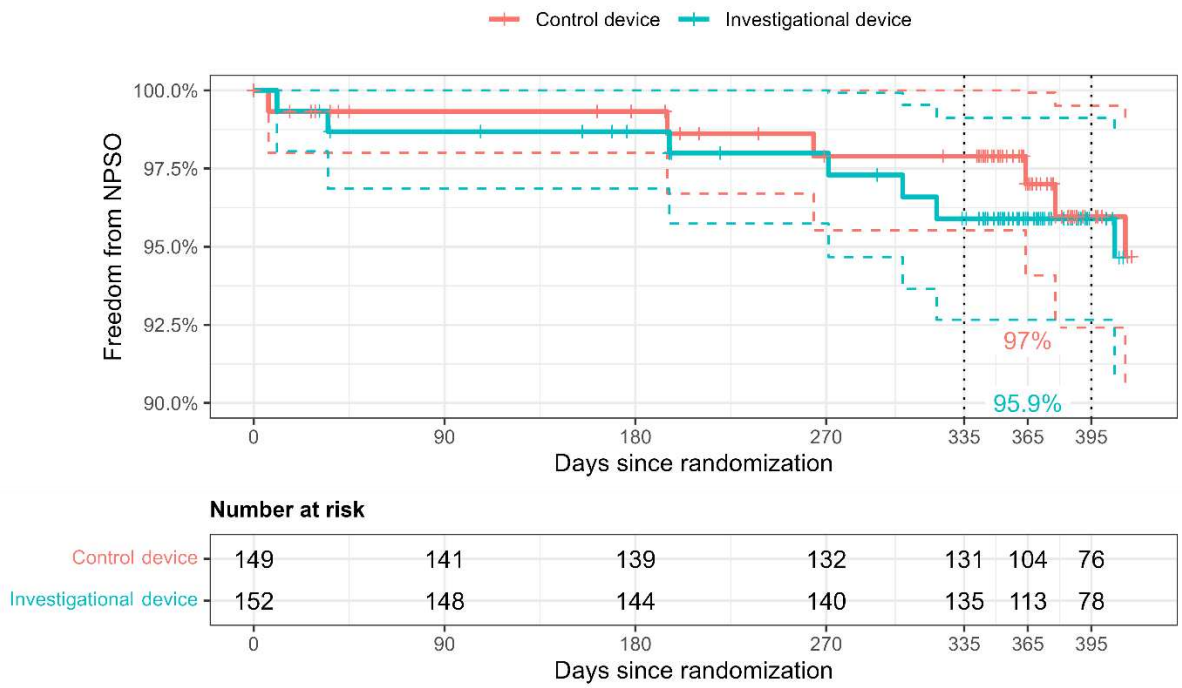


Figure 3. 1- the cumulative incidence of negative primary safety outcome at 12 months

1- the cumulative incidence of negative primary safety outcome at 12 months was 97.0% (95% CI: 93.0%-99%) in the IN.PACT Admiral group and 95.9% (95% CI: 91.8% - 98.3%) in the Passeo-18 Lux group. Death before NPSO is considered to be a competing risk.

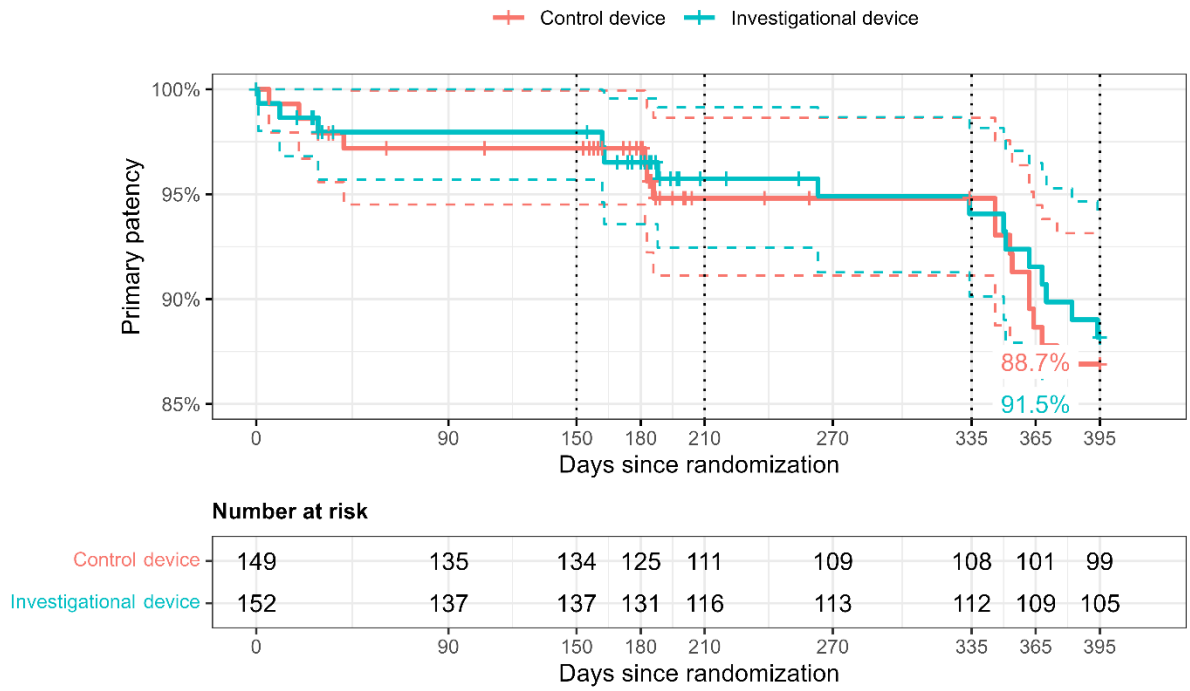
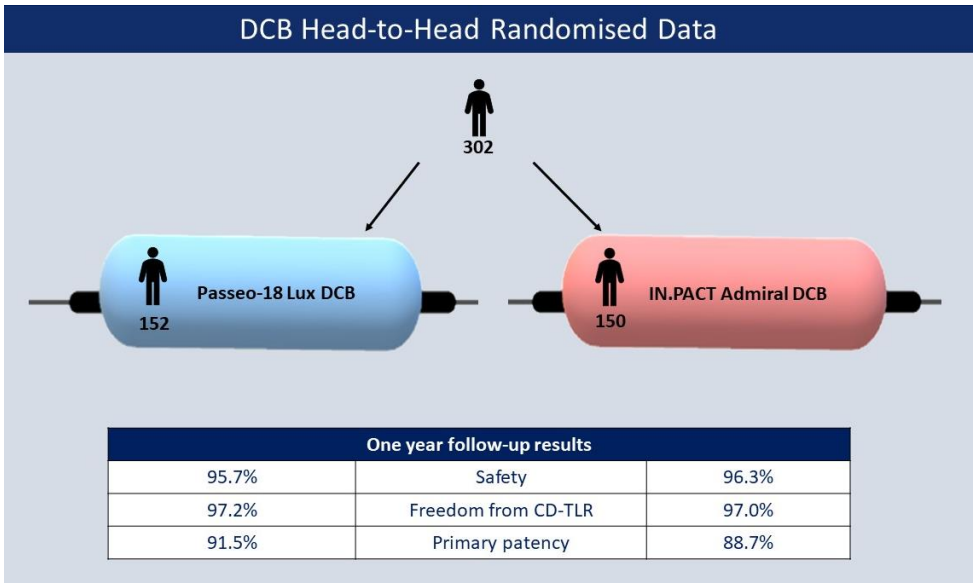


Figure 4. Primary patency at 12 months

Primary patency at 12 months was 88.7% (95% CI: 83.2% - 94.5%) in the IN.PACT Admiral group and 91.5% (95% CI: 86.9% - 96.5%). in the Passeo-18 Lux group. Patency was assessed by evaluation of duplex ultrasound images by an independent Corelab.



One year follow-up results		
95.7%	Safety	96.3%
97.2%	Freedom from CD-TLR	97.0%
91.5%	Primary patency	88.7%

DCB Head-to-Head Randomised Data (central illustration)

Overview of the 1 year safety-, efficacy- and patency data of both treatment arms in the BIOPACT RCT.

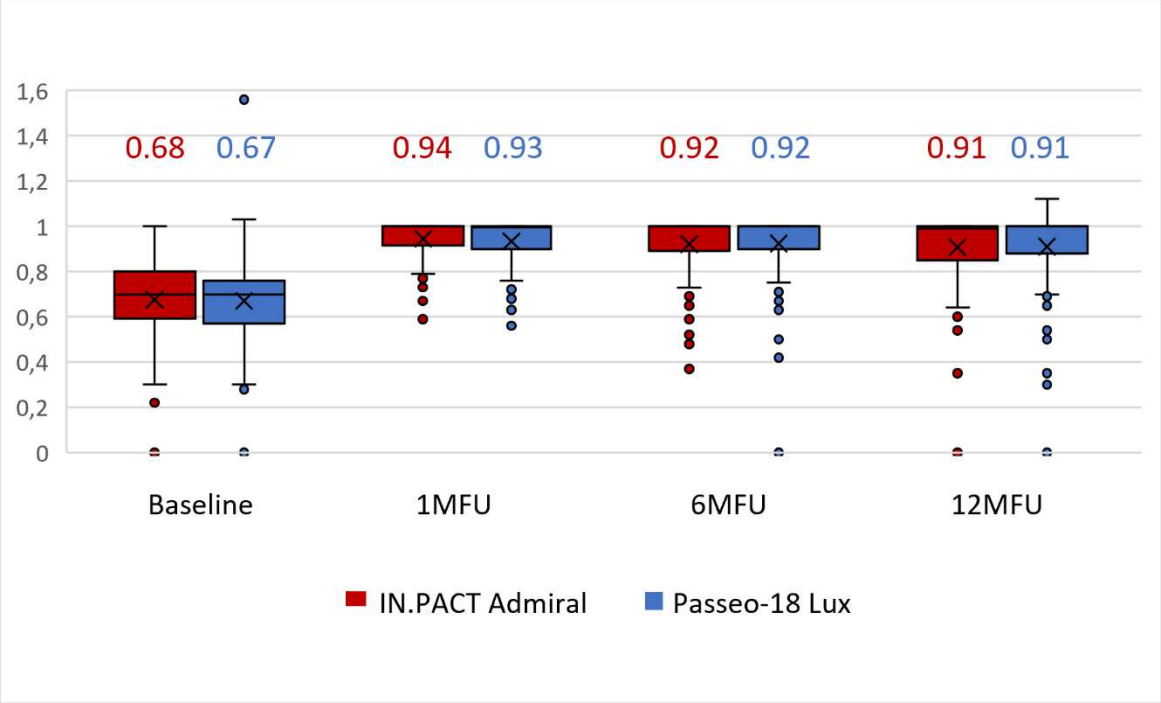


Figure 5. Evolution of mean ankle-brachial index

The evolution of the mean ankle-brachial index from baseline to the subsequent follow-up visits was comparable between both treatment arms. The mean change in target limb resting ABI compared to baseline was +0.25 for the IN.PACT Admiral group and +0.26 for the Passeo-18 Lux group after 6 months, and +0.14 and +0.18 respectively after 12 months.

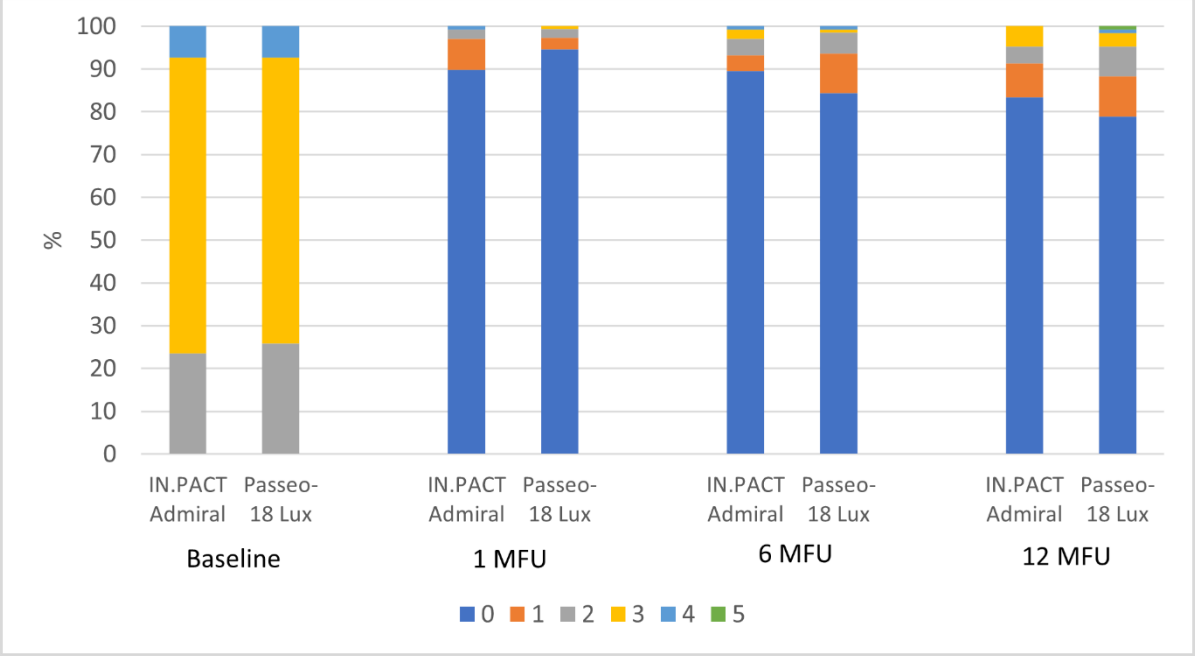


Figure 6. Evolution of Rutherford clinical classification

The evolution of the Rutherford clinical classification *from baseline to the subsequent follow-up visits was comparable between both treatment arms. The mean change in target limb RCC at 6 months compared to baseline was -2.6 for both treatment groups. At 12 months, this was -2.5 for the IN.PACT Admiral group and -2.4 in the Passeo-18 Lux group*.

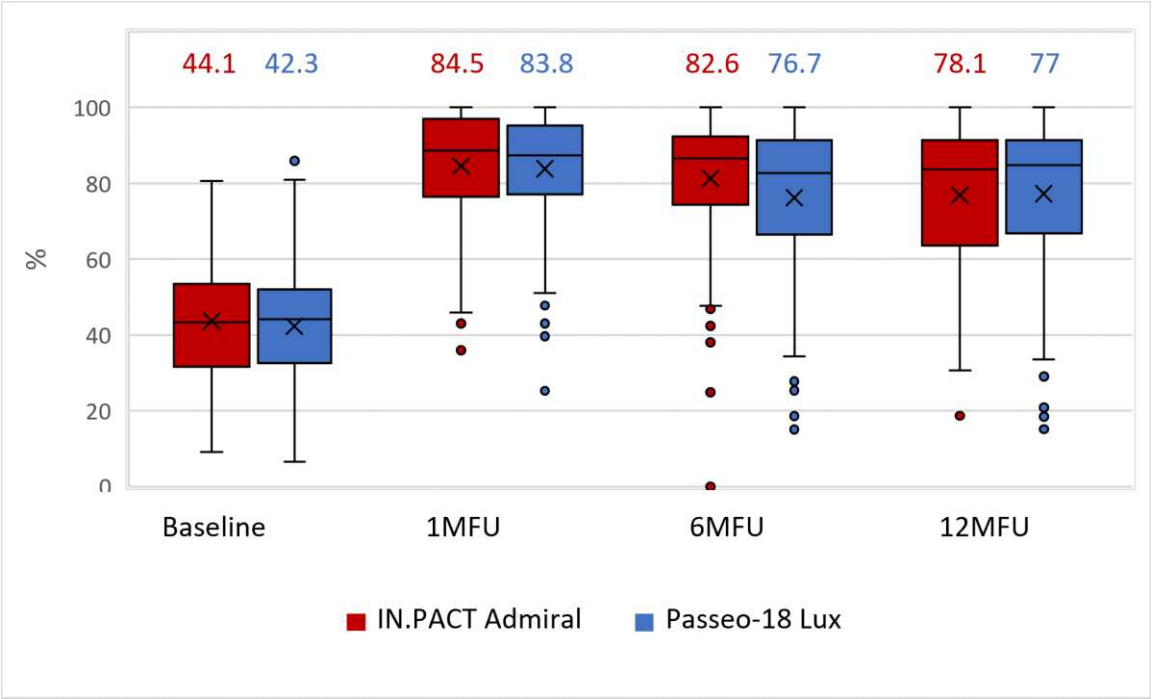


Figure 7. Evolution of mean Walking Impairment Questionnaire score

The evolution of the mean WIQ score from baseline to the subsequent follow-up visits was comparable in both treatment arms. The overall mean change in WIQ score at 6 months compared to baseline was +38.8 for the IN.PACT Admiral group and +33.3 for the Passeo-18 Lux group. At 12 months, this was +34.2 and +35.8, respectively. Only WIQ questionnaires where the total score was available were taken into account.

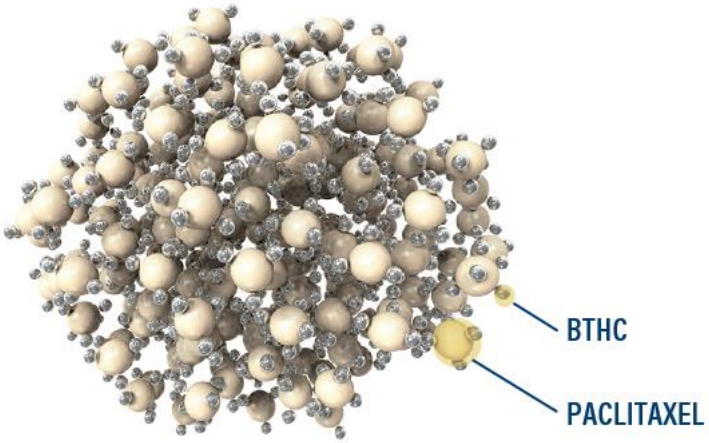


Figure 8. Paclitaxel and BTHC microcrystalline structure

BTHC was selected for its capability to adhere to the balloon, low amount of particles generated, stability and hydrophobic characteristic.

Tables

Table 1. Baseline characteristics and preoperative assessments

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Baseline characteristics	**IN.PACT Admiral (N=149)**	**Passeo-18 Lux (N=152)**	**p-value**
Gender Male Female	 108 (72.5%) 41 (27.5%)	 99 (65.1%) 53 (34.9%)	0.1695
Age	67 ± 9 (44 – 90)	69 (47 – 87 ± 8)	0.0536
Current nicotine use	74 (49.7%)	58 (38.2%)	**0.0446**
Hypertension	118 (79.2%)	109 (71.7%)	0.1323
Hypercholesterolemia	116 (77.9%)	110 (72.4%)	0.2722
Previous arterial intervention	55 (36.9%)	73 (48%)	0.0516
Previous coronary	37 (24.8%)	42 (27.6%)	0.5816
Type 2 diabetes	44 (29.5%)	39 (25.7%)	0.4530
Obesity	28 (18.8%)	24 (15.8%)	0.4916
Renal insufficiency	8 (5.4%)	16 (10.5%)	NA
Previous neurological event	14 (9.4%)	10 (6.6%)	NA
Preoperative assessments	**IN.PACT Admiral ABI (n=142), RCC (n=149), WIQ (n=119)**	**Passeo-18 Lux ABI (n=143), RCC (n=151), WIQ (n=126)**	**p-value**
ABI ± SD (min – max)	0.68 ± 0.18 (0 – 1)	0.67 ± 0.2 (0 – 1.56)	0.7983
RCC 2 3 4	 35 (23.5%) 103 (69.1%) 11 (7.4%)	 39 (25.8%) 101 (66.9%) 11 (7.3%)	0.6949
WIQ ± SD (min – max)	44.1 ± 14.3 (10.0 – 80.6)	42.3 ± 14.6 (6.5 – 85.9)	0.3501

Values are mean ± standard deviation (SD) with (min-max) or counts with the percentage between brackets. p-values were calculated using independent samples t-tests / comparison of proportions / Not Applicable (NA) if the number of observations was too small.

Table 2. Operative characteristics

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	IN.PACT Admiral	**Passeo-18 Lux (N=152)**	**p-value**
TLL ± SD (min – max) (mm)	**65.6 ± 39 (5 -180)**	**74.0 ± 49.4 (4 – 180)**	**0.3027**
RVD ± SD (min – max) (mm)	5.4 ± 0.7 (4 – 7)	5.3 ± 0.7 (4 – 7)	0.5842
DS ± SD (min – max) (%)	84.8 ± 9.4 (70 – 99)	84.1 ± 9.7 (50 – 99)	0.3107
Total occlusion	n=31 (20.8%)	n=26 (17.1%)	0.4135
Lesion location			
Proximal SFA	15 (10.1%)	16 (10.5%)	NA
Mid SFA	76 (51.0%)	71 (46.7%)	0.4309
Distal SFA	54 (36.2%)	68 (44.7%)	0.1676
Proximal popliteal artery (P1)	21 (14.1%)	16 (10.5%)	0.3343
Lesion characteristics			
Calcification[a] (moderate – severe)	106 (71.1%)	121 (79.6%)	0.0887
Ulceration	7 (4.7%)	1 (0.7%)	NA
Thrombus	4 (2.7%)	5 (3.3%)	NA
Dissection	3 (2.0%)	2 (1.3%)	NA
Predilatation	**n=149**	**n=152**	
Balloon diameter ± SD (min – max) (mm)	4.5 ± 0.7 (3 – 6)	4.5 ± 0.7 (3 – 7)	0.9792
Balloon length ± SD (min – max) (mm)	68.7 ± 34.6 (20 -200)	70.3 ± 39 (20 -200)	0.7021
DCB dilatation	**n=149**	**n=152**	
Average number of DCBs used	1.1 ± 0.3 (1 – 2)	1.2 ± 0.4 (1 – 3)	
Balloon diameter ± SD (min – max) (mm)	5.4 ± 0.7 (4 -7)	5.4 ± 0.7 (4 – 8)	0.5574
Balloon length ± SD (min – max) (mm)	91.2 ± 36.1 (40 – 150)	88.7 ± 30.3 (40 – 120)	0.6692
Bailout stenting	**n=17 (11.4%)**	**n=20 (13.2%)**	NA
Stent length ± SD (min – max) (mm)	75.2 ± 34.4 (28 – 150)	91.1 ± 43.8 (40 – 150)	NA
Postdilatation	**n=20 (13.4%)**	**n=23 (15.1%)**	0.6724
Balloon diameter ± SD (min – max) (mm)	5.4 ± 0.8 (3 – 7)	5.3 ± 0.6 (4 – 7)	0.4426
Balloon length ± SD (min – max) (mm)	80.5 ± 32.6 (20 – 150)	87.4 ± 35.2 (20 – 150)	0.5040
Acute procedural success			
≤30% residual stenosis	149 (100%)	152 (100%)	NA
Acute device success[b]	149 (100%)	152 (100%)	NA
Supportive information			
Procedure time ± SD (min – max) (min)	44.5 ± 29.1 (11-255)	44.8 ± 19 (12 – 120)	0.1081
Volume contrast ± SD (min – max) (ml)	69.8 ± 35.7 (15 – 235)	70.8 ± 31.7 (3 – 156)	0.7947

[a] according to PACCS scoring system. Values are mean ± SD or counts with the percentage between brackets. p-values were calculated using independent samples t-tests / Mann-Whitney-U test if the variances where not equal

(for Target Lesion Length (TLL), DCB length, procedure time) / comparison of proportions. A p-value was not applicable (NA) if the number of observations was too small or if two groups were identical.DS: Diameter Stenosis, RVD: Reference Vessel Diameter, SFA: Superficial Femoral Artery.

Table 3. Sustained clinical improvement

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	6 MFU		**12 MFU**	
	IN.PACT Admiral	**Passeo-18 Lux**	**IN.PACT Admiral**	**Passeo-18 Lux**
	N=123	N=122	N=114	N=119
Freedom from major amputation	123 (100.0%)	122 (100.0%)	114 (100.0%)	119 (100.0%)
Freedom from CD-TVR	121 (98.4%)	119 (97.5%)	109 (95.6%)	113 (95.0%)
Freedom from RCC increase	122 (99.2%)	121 (99.2%)	114 (100%)	117 (98.3%)
Freedom from ABI decrease ≥ 0.15	121 (98.4%)	118 (96.7%)	113 (99.1%)	113 (95.0%)
Total nr of patients with clinical improvement	118/123 (95.9%)	114/122 (93.4%)	108/114 (94.7%)	105/119 (88.2%)

There is no significant difference between the proportions of clinical improvement at 6 months (p=0,3852) and 12 months (p=0,0772) follow-up. p-values are calculated using comparison of proportions.