Rationale and Design of the IN.PACT BTK Randomized Pilot Study: A Paclitaxel Drug–Coated Balloon vs Standard Percutaneous Transluminal Angioplasty for Infrapopliteal Chronic Total Occlusions

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Abstract

Objectives. This is a pilot feasibility study and the objective is to evaluate the safety and effectiveness of the investigational device, IN.PACT 014 drug-coated balloon (DCB), compared with standard percutaneous transluminal angioplasty (PTA) in the treatment of patients with chronic limb-threatening ischemia (CLTI) with chronic total occlusions (CTOs) of below-the-knee (BTK) arteries. **Methods and Design.** The IN.PACT BTK randomized study is a prospective, multicenter, randomized pilot study. Baseline angiography and duplex ultrasonography analyses were performed to confirm that participants met all anatomic and functional eligibility criteria. Successful predilation and strict intraprocedural angiographic and duplex sonographic criteria were conditions of enrollment and randomization. A total of 50 participants were enrolled and randomized 1:1 into DCB (n = 23) or control PTA (n = 27) treatment groups. The primary effectiveness endpoint is late lumen loss at 9 months post procedure. Secondary endpoints include a composite safety endpoint (freedom from device- and procedure-related mortality within 30 days, and freedom from major target-limb amputation and freedom from clinically driven target-lesion revascularization within 9 months after the procedure) and the rate of major adverse events. Participants are being followed through 5 years. All angiographic and duplex ultrasonography images are reviewed by independent core laboratories and all major adverse events are adjudicated by an independent clinical events committee. **Discussion and Conclusion.** This is a rigorously designed BTK trial in which participant selection and enrollment were a unique aspect, guided by a strict requirement for successful vessel preparation before randomization using explicit angiographic and duplex ultrasound parameters.

Chronic limb-threatening ischemia (CLTI) represents the most advanced form of peripheral artery disease (PAD) and is defined as the presence of ischemic rest pain, ischemia lesions, or gangrene. CLTI patients usually have extended degree of below-the-knee (BTK) involvement and are considered a high-risk population with high comorbidity and late mortality.[1] Treatment options include open surgical intervention and endovascular techniques. Bypass surgery is effective but associated with significant procedural and postprocedural morbidity and mortality. Endovascular interventions include percutaneous transluminal angioplasty (PTA) and

implantation of bare-metal stents, which are associated with decreased morbidity and faster recovery times compared with bypass surgery. High rates of restenosis after PTA and stenting, however, show that these modalities have limited durability of effect.[2-5] In addition, the placement of a permanent stent implant can limit options for patients who require surgical intervention in the future.

Randomized controlled trials have demonstrated the superiority of drug-eluting stents over PTA and bare-metal stents in the treatment of BTK lesions, suggesting that the use of drug-coated
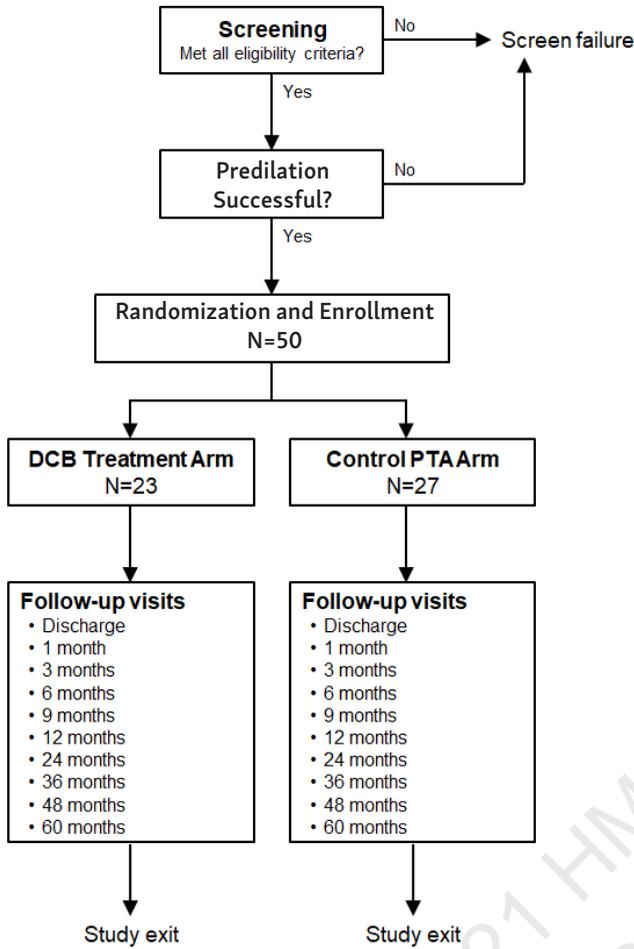
FIGURE 1. Participant flow through the IN.PACT BTK randomized study. BTK = below the knee; DCB = drug-coated balloon; PTA = percutaneous transluminal angioplasty.

FIGURE 2. Follow-up schedule for participants with ischemic wounds on the target limb. Participants with ischemic wounds on the target limb at baseline, or who develop ischemic wounds on the target limb over the course of the study, have an additional follow-up schedule for specialized wound care.

devices may contribute an added benefit by inhibiting restenosis.[6-9] Despite favorable results in trials, there are outstanding concerns regarding the use of any kind of stent, including the risk of fractures, in-stent restenosis, and thrombosis. Clinical studies of drug-coated balloons (DCBs) for BTK lesions have shown equivocal clinical and angiographic benefit compared with standard therapy, with some studies showing superior effect of DCB vs standard PTA with an uncoated balloon catheter, and other studies showing no difference in effectiveness between treatment groups.[10-16] Although chronic total occlusions (CTOs) are prevalent in BTK lesions among CLTI patients, reports evaluating safety and effectiveness of angioplasty for BTK-CTOs are very limited.

The IN.PACT 014 is an investigational catheter device (Medtronic) and is part of the IN.PACT Admiral formulation of paclitaxel DCBs. While similar in design to the IN.PACT Admiral catheter (Medtronic), which is approved for the treatment of femoropopliteal lesions, the IN.PACT 014 has a 0.014″ guidewire compatibility to accommodate 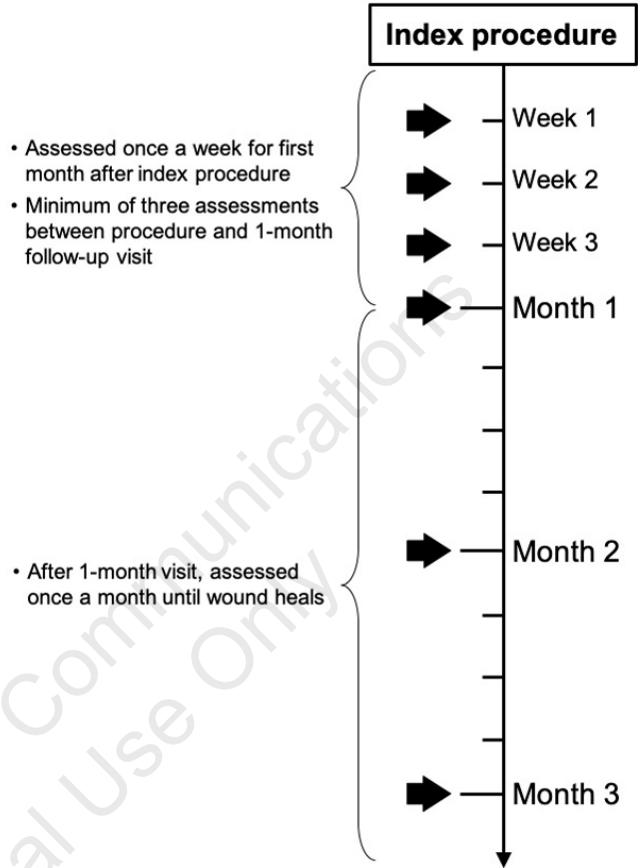narrower BTK vessels. The current study aims to assess the safety and effectiveness of the IN.PACT 014 paclitaxel DCB vs standard PTA for the treatment of patients with CTO in the infrapopliteal arteries. Herein, we describe a study design that is characterized by a series of rigorous imaging and vessel preparation requirements, intending to provide clear and consistent results on the safety and effectiveness of the IN.PACT 014 for the treatment of BTK-CTOs. Since this is a feasibility study, there is no formal hypothesis test specified.

Methods

Study design. The IN.PACT BTK study is a prospective, multicenter, randomized, pilot study to evaluate the safety and effectiveness of the IN.PACT 014 DCB vs PTA in the treatment of patients with CTOs (100% stenosis with total lesion length ≥40 mm by visual estimation) in the infrapopliteal arteries. Participant flow through the study is shown in Figure 1. A total of 50 participants were enrolled and randomized 1:1 into DCB (n = 23) or PTA (n = 27)

TABLE 1. Key inclusion and exclusion criteria for the IN.PACT BTK Randomized Study.

Inclusion Criteria

- Age ≥18 years.
- Patient has been informed of the nature of the study, agrees to participate, and has signed an EC-approved consent form.
- Female patient of childbearing potential who has a negative pregnancy test ≤7 days before the procedure and is willing to use a reliable method of birth control for the duration of study participation.
- Patient has documented chronic limb-threatening ischemia in the target limb prior to the study procedure with Rutherford clinical category 4 or 5.
- Life expectancy >1 year in the investigator's opinion.
- Reference vessel diameter 2-4 mm, confirmed by duplex ultrasound assessment.
- Total occlusions (100% stenosis) with total lesion length ≥40 mm (by visual estimate).
- The lesion must be located in the infrapopliteal arteries and above the ankle joint. Lesions may not extend above the tibioperoneal trunk (P3 segment of the popliteal artery) or below the ankle joint (arteries of the foot), nor can the treatment (investigational device or standard PTA, including predilation) extend beyond these indicated regions for >1 cm.[a]
- Presence of documented run-off to the foot (clearly visible dorsalis pedis, pedal arch, or plantar arteries by angiography). Target vessel should give direct or indirect run-off to the foot.
- Inflow free from flow-limiting lesion, confirmed by angiography. Patients with flow-limiting inflow lesions (≥50% stenosis) can be included if lesion(s) have been treated successfully before enrollment, with a maximum residual stenosis of ≤30% per visual assessment. If an inflow lesion must be treated within or above the P3 segment of the popliteal artery, there must be a minimum of 3 cm of healthy tissue between this (treated) lesion and the infrapopliteal target lesion.
- Successful predilation of the (entire) target lesion. Success being documented by angiographic visual estimate of ≤30% residual stenosis of the target lesion and by functional assessment of the distal flow by intraoperative Doppler; recording of biphasic or triphasic signal with rapid take-off distal to the target lesion.

Exclusion Criteria

- Patient unwilling or unlikely to comply with the appropriate follow-up times for the duration of the study.
- Prior stent(s) or bypass surgery within the target vessel(s) including stents[b] placed within target vessels during the index procedure prior to randomization.
- Previous drug-coated balloon angioplasty in the target vessel within 6 months prior to index procedure.
- Aneurysm in the target vessel.
- Angiographic evidence of thrombus within target limb.
- Recent myocardial infarction or stroke <30 days prior to the index procedure.
- Heart failure with ejection fraction <30%.
- Impaired renal function (glomerular filtration rate <20 mL/min) and patient on dialysis.
- Patient with vasculitis, systemic lupus erythematosus, or polymyalgia rheumatica on active treatment.
- Patient receiving systemic corticosteroid therapy.
- Known allergies or sensitivities to heparin, aspirin (acetylsalicylic acid), other anticoagulant/antiplatelet therapies that could not be substituted, and/or paclitaxel or an allergy to contrast media that cannot be adequately pretreated prior to the index procedure.
- The patient is currently enrolled in another investigational device or drug trial that is interfering with the endpoints of this study.

[a] A target lesion can extend into the P3 segment in case it involves a straight lesion extending from the target vessel. Non-significant stenosis below the ankle joint can be allowed in case this is not part of the target lesion and does not require treatment. [b] Use of stents is only allowed for bailout treatment.
EC = European Commission.

treatment groups. The study will continue follow-up through 1, 3, 6, 9, 12, 24, and 36 months post procedure. After the initial protocol approval, Medtronic and regulators worldwide want to better understand the long-term effects of paclitaxel-coated DCBs in patients with vascular disease; therefore, it was decided to extend the length of follow-up from 36 months to 60 months. Angiography will be performed 9 months after the procedure, or sooner for symptomatic patients.

There is an additional follow-up schedule for participants with ischemic wounds on the target limb at baseline or those who develop new ischemic wounds on the target limb during the study (Figure 2). Participants with wounds are assessed once a week for the first month after the index procedure, for a minimum of 3 assessments between the procedure and 1-month follow-up visit. Thereafter, participants with wounds are assessed once a month until the wound heals. Wound-care follow-up occurs at a

dedicated wound-care or foot clinic with a wound-care specialist who is part of the study team.

Participants were those with chronic CLTI who met all eligibility criteria and were candidates for percutaneous endovascular intervention. A list of inclusion and exclusion criteria is presented in Table 1. Participants were recruited from patients referred to an angiography suite or a non-invasive vascular laboratory for assessment of PAD, or patients presenting to an investigator's clinical practice with chronic symptoms of PAD in the lower extremity. Participants with a signed and dated informed consent form and who met all study eligibility criteria were eligible for enrollment. This included intraprocedural anatomical eligibility criteria, such as successful predilation of the target lesion(s). If the aforementioned criteria were fulfilled, the patient could be randomized to one of the treatment arms and, at that point, the patient was considered enrolled. The point of

enrollment was defined to occur after successful predilation of the target lesion(s) because, until then, only standard-of-care procedures were followed. After successful predilation and randomization, subjects in the PTA arm did not receive further treatment unless delayed recoil, flow-limiting dissection not previously detected, persistent >50% residual stenosis, or other untoward event required additional PTA or bail-out stent. Subjects in the treatment arm received additional angioplasty with DCB. In the event of >50% residual stenosis, perforation, occlusive complication (recoil), or a flow-limiting dissection, prolonged balloon inflation was allowed. If this prolonged balloon inflation did not provide the expected result, bail-out stenting was allowed. All other adjunctive therapies (including but not limited to laser, atherectomy, cryoplasty, cutting/scoring balloons, or brachytherapy) were not allowed. The schedule of study procedures and assessments is presented in Table 2.

Randomization was 1:1, stratified by study site, and performed after confirmation that the participant met all eligibility criteria. Randomization was processed centrally by means of a web-based system that provided the assigned treatment arm. Randomization was at the participant level, including those with multiple target lesions.

Multiple design elements were incorporated to minimize bias during the study. The use of multiple study sites ensured that a representative sample of physicians was performing the procedures. This is a pilot study with small sample size and preferably 1 interventional operator per site was identified to perform all procedures to minimize interoperator-induced bias. Since the duplex ultrasound (DUS) examination is operator dependent, all efforts were made to have 1 dedicated operator per site performing all study-required DUS examinations.

The study is being monitored by a data-monitoring committee and a blinded independent clinical-events committee that will adjudicate all major adverse events including revascularization events (Syntactx). An independent DUS core laboratory (VasCore) and angiography core laboratory (Beth Israel Deaconess Medical Center Angiographic Core Lab) will analyze all images. Members of the DUS and angiography core laboratories that analyze follow-up images are blinded to the treatment assignment. Due to the nature of the procedure, it was not possible to blind the patient, clinician performing the intervention, or study site staff.

Index procedure

Medication. Participants were administered dual-antiplatelet therapy per institutional standard of care. For the purposes of this study, the recommended duration of dual-antiplatelet therapy has been 3 months. Prolonged antiplatelet therapy can be given at the discretion of the physician and should be considered after stent placement.

Angiography. Baseline, postprocedural, and late angiography were conducted following a prespecified protocol that ensured visualization of the target lesion in a consistent and unforeshort-

ened view sequentially during the study. A radiopaque ruler was placed on the leg before the start of the procedure and used to define anatomical measurement references and assess lesion length. Selective angiography of the index limb was performed, including ipsilateral femoral, popliteal, and tibioperoneal vessels (up to and including the pedal level) to identify the anatomical characteristics of the vasculature and to visualize and define the lesion(s).

Non-target lesions. Successful treatment of an inflow lesion was defined by residual diameter stenosis of ≤30%. Inflow lesions were treated per institutional standard of care. If an inflow lesion was treated within or above the P3 segment of the popliteal artery, a minimum of 3 cm of healthy tissue was required between the inflow lesion and the infrapopliteal target lesion. Non-target lesions in the index limb, including outflow lesions, had to be treated per institutional standard of care before enrollment. Intervention for any contralateral disease that required treatment was to be performed at least 30 days after the index procedure.

Target-vessel/target-lesion predilation. All eligible participants underwent predilation of the target vessel/lesion. Operators followed a rigorous imaging protocol to characterize vascular anatomy before and after predilation. Before predilation, the operator acquired both digital subtraction standard angiography and duplex images of the target lesion to visualize the occlusion in a view that minimized the degree of vessel overlap. The operator also acquired DUS imaging according to core lab guidelines that supported reference vessel diameter (RVD) measurement.

After imaging, predilation was performed with a non-drug coated semicompliant balloon. The predilation balloon was sized at a 1:1 ratio to the RVD as determined by ultrasound, and a length that covered the entire length of the target lesion. More than one predilation balloon was allowed, and the balloon could be inflated more than once according to protocol. The inflation time of 3 minutes is recommended, but prolonged inflation is allowed at the discretion of the operator. Any CE-marked PTA balloon could be used.

Multiple lesions in 1 vessel should be treated as a single lesion, with no gaps left untreated. Multiple lesions in separate vessels can also be treated, but all lesions must meet the protocol-specified criteria and must be treated with the assigned randomized treatment including subsequent target lesions. In cases with multiple target lesions, the operator could select the first target lesion for predilation at their discretion. If a lesion had a CTO with a section of stenosis that also required treatment, the entire lesion (occluded and stenotic sections) was to be treated as a single lesion. No other vessel-preparation devices, such as cutting/scoring balloons, were allowed.

After predilation, the operator used angiography and DUS to image the target lesion, distal run-off vessels, and the entire vessel distally through the pedal arch and evaluate the flow. Successful predilation was defined as residual stenosis ≤30% per visual estimation, and intraprocedural Doppler exam showing

TABLE 2. Schedule of study procedures and assessments.

	Screening	Procedure			Post Procedure									Unscheduled
		Pre Procedure	Index Procedure	Discharge	30 Days (± 7 Days)	3 Months (± 15 Days)	6 Months (± 30 Days)	9 Months (± 60 Days)	12 Months (± 30 Days)	24 Months (± 30 Days)	36 Months (± 30 Days)	48 Months (± 30 Days)	60 Months (± 30 Days)	
Screening														
Eligibility screen	X													
Informed consent	X													
Physical exam	X			X	X	X	X	X	X	X	X			X
Medical history	X													
Demographics	X													
Enrollment		X												
Randomization		X												
Intervention														
DUS		X[c]		X[e]	X	X	X	X	X	X	X			X
Angiography		X						X						X[f]
Predilation		X												
DCB angioplasty			X[d]											
Assessments														
RCC	X				X	X	X	X	X	X	X			X
Medications	X	X	X	X	X	X	X	X	X	X	X			X
WIfI assessment	X			X	X	X	X	X	X	X	X			X
Wound care, assessment[a]	X[b]			X	X	X	X	X	X	X	X			X
EQ-5D	X			X	X	X	X	X	X	X	X			X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

[a] For as long as applicable.
[b] Includes WIfI classification at baseline visit.
[c] DUS for reference vessel diameter measurements and procedural DUS Doppler examination to determine successful predilation.
[d] Participants in the DCB group only.
[e] DUS assessment, if available, should be prior to discharge.
[f] In the case an angiography of the study limb is done during an unscheduled visit, it has to be provided to sponsor.
DCB = drug-coated balloon; DUS = duplex ultrasound; EQ-5D = EuroQol 5-dimension scale; RCC = Rutherford clinical category; WIfI = wound, ischemia, and foot infection.
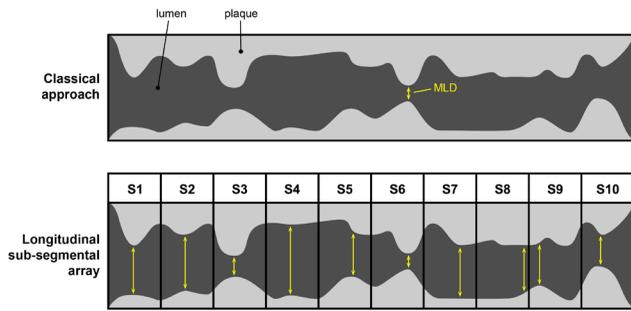
FIGURE 3. Angiographic measurements. In the classical approach to quantitative angiographic evaluation, a minimal lumen diameter (MLD) value is obtained from a single longitudinal plane and used to represent the lesion morphology along the entire proximal-to-distal extent of the target lesion. This MLD value, and other data obtained from this single plane, are used to calculate all quantitative angiographic data that comprise the angiographic profile for the target lesion at this time point. In contrast, quantitative angiography using a longitudinal subsegmental array obtains data from each individual subsegment, and either compiles these values into a data series or uses the data to generate a mean value. In this way, the subsegmental array approach takes into account morphological variation that occurs along the proximal-to-distal length of the target lesion and supports a more comprehensive and accurate angiographic characterization of the lesion.

FIGURE 4. Measuring vessel size with duplex ultrasound after predilation. Vessel size measurements are taken to assess maximum lumen diameter (Max LD) and minimum lumen diameter (MLD) proximal to the target lesion, within the lesion (in the proximal, mid, and distal lesion portions), and distal to the lesion.

a biphasic (with rapid take-off) or triphasic wave signal, with absence of a major (grade D) flow-limiting dissection (observed on 2 orthogonal views). Participants who met the above criteria for successful predilation were formally enrolled in the study and randomized into treatment groups.

Target-vessel/target-lesion treatment. For participants randomized to the PTA arm, no additional treatment was performed after successful predilation according to the study protocol. Those randomized to the treatment arm received an IN.PACT 014 DCB that was sized at a 1:1 ratio to the RVD. The coating of this investigational device includes paclitaxel as the antiproliferative

agent at a dose of 3.5 μg/mm^2 with urea as the excipient. IN.PACT 014 is available in 2 usable catheter lengths — 100 cm and 150 cm — in a range of balloon sizes from 2.0-4.0 mm in cylindrical balloon diameter and 40-120 mm in length. The guidewire lumen (central lumen) will permit the use of guidewires to facilitate advancement of the IN.PACT 014 catheter to and through the stenosis to be dilated. The catheter will be compatible with 0.014″ diameter guidewires. An inflation for 3 minutes was strongly recommended with a nominal pressure for all DCB sizes of 8 atm while the rated burst pressure (RBP) is 14 atm for all sizes. The length of the DCB was sized to ensure the balloon extended beyond the proximal and distal edges of the target lesion by 1 cm. In cases where the target lesion required treatment with multiple DCBs, a 1 cm overlap was required to maintain continuous coverage of the target lesion. To minimize the risk of embolic events, the operator was encouraged to consider using a single DCB and maximizing balloon length when treating a long lesion.

After treatment of the target lesion was complete, the operator performed angiography to image the target lesion run-off of all vessels distal to the treatment area including the dorsal pedis, pedal arch, and plantar arteries.

Adjunctive therapies. Additional prolonged balloon inflation was allowed in cases of a suboptimal result, such as >50% residual stenosis, perforation, occlusive complication, or flow-limiting dissection. Bail-out stenting was allowed if prolonged balloon inflation did not provide the expected result. All other adjunctive therapies were not allowed, including but not limited to laser, atherectomy, cryoplasty, cutting/scoring balloons, and brachytherapy.

Endpoints and assessments. The primary effectiveness endpoint is late lumen loss (LLL) at 9 months after the procedure for DCB vs standard PTA. LLL is assessed by comparing the minimal lumen diameter (MLD) within the treated segment immediately after the procedure with the MLD of the treated segment 9 months later, or sooner in the event of recurrent symptoms due to restenosis. Based on the recognized limitations of using a single MLD value to represent angiographic restenosis along the entire length of a treated segment, due to axial relocation of the MLD, additional analyses will be performed to assess the totality of vessel narrowing within the treated segment (Figure 3). For the purposes of these analyses, each treated lesion is divided into a tandem array of 10 equally spaced subsegments. For example, a 25 cm-long lesion would be subdivided into a series of ten 2.5 cm subsegments. Subsegmental measures are then taken to determine the mean and minimal diameters within each subsegment, which are matched with the baseline, postprocedural, and follow-up angiograms. These measures are used to calculate subsegmental mean and minimal acute lumen gain immediately after the procedure, mean and minimal LLL at follow-up, mean and minimal net lumen gain from baseline to follow-up, mean and minimal loss index (defined as the ratio

TABLE 3. Primary and secondary endpoints of the IN.PACT BTK Randomized Study.

Primary Effectiveness Endpoint

- Late lumen loss at 9 months after index procedure[a]

Secondary Endpoints

- Composite safety endpoint: freedom from device- and procedure-related mortality within 30 days, freedom from major target-limb amputation and freedom from CD-TLR within 9 months after index procedure.
- Major adverse event rate through 3, 6, 9, 12, 24, 36, 48, and 60 months.[b]
- Functional flow assessment at 3, 6, 9, 12, 24, and 36 months.[c]
- Death from any cause and cardiovascular-related deaths through 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Rate of major target-limb amputation through 1, 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Rate of CD-TLR through 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Rate of mechanically driven TLR through 37 days.
- Rate of TLR through 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Rate of CD-TVR through 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Rate of TVR through 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Status of wound healing at 30 days, 3, 6, 9, 12, 24, and 36 months.[d]
- Rate of thrombosis at the target lesion(s) through 30 days, 3, 6, 9, 12, 24, 36, 48, and 60 months.
- Device success.[e]
- Clinical success.[f]

[a] Late lumen loss will be assessed by means of Quantitative Vascular Angiography by an independent angiographic core lab at 9 months post-index procedure or at the time of TLR (prior to any intervention on target lesion).
[b] Major adverse events defined as a composite of all-cause mortality, major target limb amputation, and CD-TLR.
[c] Functional flow defined as the absence of target lesion occlusion (no flow) assessed by duplex ultrasound.
[d] Wound healing assessed as a categorical outcome: completely healed, improved, unchanged, worsened, amputation, or skin graft.
[e] Device success defined as successful drug delivery, balloon inflation, deflation and retrieval of the intact study device without burst below the rated burst pressure.
[f] Clinical success defined as residual stenosis ≤30% without procedural complications (death, major target limb amputation, thrombosis of target lesion, or TVR) prior to discharge.
BTK = below the knee; CD-TLR = clinically driven target lesion revascularization; CD-TVR = clinically driven target vessel revascularization; DCB = drug-coated balloon; TLR = target-lesion revascularization; TVR = target-vessel revascularization.

of LLL divided by acute gain), percent stenosis at follow-up, and presence of stenosis ≥50% at follow-up. Taken together, the sub-segmental analysis of treated lesions will provide more detailed insight into the totality of lumen renarrowing between active and control treatments (Figure 4).

Secondary endpoints include a composite safety endpoint and the rate of major adverse events at each follow-up visit. The composite safety endpoint is a composite of freedom from device- and procedure-related mortality within 30 days, and freedom from major target-limb amputation and freedom from clinically driven target-lesion revascularization (CD-TLR) within 9 months post index procedure. Major adverse events are defined as a composite of all-cause mortality, major target-limb amputation, and CD-TLR. A full list of all study endpoints is presented in Table 3.

Statistical analysis

Sample size considerations. Pilot feasibility studies do not have the statistical power of large trials, but may provide scientific signals to be validated in larger studies. The number of participants considered valuable for this type of investigation was described previously.[17] Since no formal hypothesis is specified for the IN.PACT BTK study, the sample size is justified by a precision approach, which provides acceptable precision on the primary endpoint estimate. The sample size was calculated based on previous BTK studies with reported LLL data.[10,13-15] All of the studies reported LLL data at 6 months or 12 months post index procedure. Based on these studies, the standard deviation of LLL at 9 months was estimated to be approximately 0.60 mm for the DCB and PTA groups. Assuming 15% attrition due to death and loss to follow-up, and multiple lesions per participant (approximately 1.1 on average) allowed in the study, it is estimated that there will be 21 participants with 23 evaluable LLL measurements at 9 months in each treatment group. The precision of the estimated LLL was assessed by calculating the distance from the upper limit of the 95% confidence interval to the mean. With 23 lesions in each group, the precision (half of the width of the confidence interval) of the LLL estimate was calculated to be 0.25 mm. The precision of the LLL difference between the 2 groups was calculated to be 0.35 mm.

Statistical methods. The intention-to-treat analysis cohort will include all randomized participants in the groups to which they are randomized regardless of the treatment received and will serve as the primary analysis cohort for each objective unless otherwise specified. Baseline demographics and characteristics will be summarized on a participant basis, and lesion characteristics will be summarized on a lesion basis. For baseline characteristics, continuous variables will be described as mean ± standard deviation, and comparisons between treatment groups will be performed with the Student's t-test. Dichotomous and categorical variables will be described as counts and proportions, and comparisons between treatment groups will be performed with the Fisher's exact test or Cochran-Mantel-Haenszel test. Overall missing data will not be imputed, and the level of statistical significance will be set at .05 for 2-sided test and .025 for 1-sided test. Statistical analyses will be performed using SAS, version 9.4 (SAS Institute).

Discussion

Several studies have demonstrated a significant reduction in restenosis and vessel reocclusion after DCB treatment in the femoropopliteal artery.[18-32] The same has not been consistently shown, however, after DCB treatment in BTK arteries, where

available data come from studies with different designs and various schedules for patient care and surveillance.[10-16] The IN.PACT BTK randomized study is a pilot study designed to assess the safety and effectiveness of the IN.PACT 014 DCB in BTK vessels of CLTI patients with CTOs. The study is designed to assess the effectiveness of the IN.PACT 014 by comparing LLL after treatment with the investigational product vs standard (conventional) PTA.

The IN.PACT BTK randomized study design has multiple unique elements, each of which will serve to enhance the overall rigor of the study. These include the requirement for successful predilation before enrollment in the study, and a series of strict imaging-based criteria to determine the success of predilation, a separate follow-up care schedule for participants with ischemic wounds on the target limb not only at baseline but also on those who develop an ischemic wound on the target limb during the study, and, perhaps most especially, a novel method of performing quantitative angiographic analysis that will provide measurements of the target lesion that are both more representative and more comprehensive compared with classical approaches.

In the IN.PACT BTK randomized study, the requirement for successful predilation and the explicit criteria used to define this parameter are critical to select for participants who are amenable to treatment with a DCB. A paclitaxel DCB prevents restenosis by inhibiting intimal hyperplasia and negative vessel remodeling over several months after the angioplasty procedure.[33] Based on this DCB mechanism of action, the IN.PACT BTK randomized study design is using rigorous criteria to identify and exclude causes of patency failure that occurred shortly after the procedure, were "mechanical" in nature, or otherwise not specifically associated with the use of the DCB. These strict criteria are necessary considering that this is a pilot study with a small sample size, which limits the power of a randomization design for group balance. Thus, the study limited enrollment to those patients with CTOs who have optimal results after angioplasty and adhere to a strict follow-up schedule over the first month, which has supported the rigorous surveillance of vessel patency in the immediate period after the procedure and the identification of potential early vessel recoil or reocclusion. The use of strict predilation criteria varies among DCB-BTK studies. While studies such as DEBATE-BTK and Lutonix BTK[11,12] have required predilation or stated that predilation was always performed, the IN.PACT BTK randomized study is the only study to date to apply a series of rigorous imaging-based criteria to determine the success of pre-dilation to select the best candidates for paclitaxel DCB treatment.

In contrast to most other DCB-BTK studies,[10-15,34,35] the IN.PACT BTK randomized study is being conducted at centers with a specialized wound-care program. For patients with ischemic wounds on the target limb at baseline, or those who develop new wounds throughout the study, there is an additional postprocedural wound-care schedule to facilitate optimal evaluation and treatment. Rigorous surveillance for patency and wound healing, combined with a fast-track strategy for repeat revascularization, was designed to ensure an immediate clinical response and reduce the risk of major amputation. This was an important differentiation between the present study and the IN.PACT DEEP trial,[14] which did not have a standardized protocol to guide wound management. Among other DCB-BTK studies, the only other study to include a separate follow-up schedule focused on wound care was the DEBATE-BTK study of patients with PAD and diabetes, a population known to be at increased risk of wounds and amputation.[11,36] Otherwise, to date, the IN.PACT BTK randomized study is the first study of a DCB for BTK lesions that includes a separate follow-up schedule to monitor and manage the development of ischemic wounds in a general population of patients both with and without diabetes. Apart from the wound management, there were also significant differences between the IN.PACT BTK and the IN.PACT DEEP trials in terms of interventional strategies. The investigational IN.PACT 014 DCB is markedly different than the IN.PACT Amphirion DCB that was used in the IN.PACT DEEP BTK trial,[14] including balloon material and coating methods. The coating and balloon material of the IN.PACT 014 DCB is similar to that of IN.PACT Admiral DCB, which is approved for femoro-popliteal indication. The IN.PACT 014 DCB used a fully automated coating process that applied at a nominal paclitaxel dose density of 3.5 µg/mm^2 to the balloon surface area.

Immediate angioplasty outcomes are being determined with the combined assessment of functional parameters by DUS and anatomical parameters by angiography. A series of DUS analyses are then scheduled over the first 30 days post procedure to monitor for late (>24 hours) recoil or reocclusion due to mechanical failure, which would trigger a fast-track strategy for reintervention and "mechanically driven TLR." While the study sample size is small, the rigorous evaluation of DCB effectiveness and, in particular, the calculation of LLL in longitudinal subsegments will provide a comprehensive representation of the different patency patterns that occur after DCB vs conventional angioplasty. This novel method of quantitative angiographic evaluation is a defining feature of the IN.PACT BTK randomized study and may represent a new way of evaluating lesion patency in future studies. Classical angiographic assessments are based on measurements taken at a single longitudinal plane within the entire length of a target lesion. While the ability to quantify vessel anatomy with this approach has been invaluable, there are multiple limitations. First, lesion morphology is not uniform along the length of the lesion, and a single data value taken from a single longitudinal plane cannot faithfully represent the varying degrees of stenosis that occur along the entire proximal-to-distal extent of the lesion. Second, many of the values that are calculated with classical quantitative angiography are based on measurement of the MLD, which may occur at different locations within, before, and after the target lesion. Therefore, single MLD measurements taken at varying

locations for each follow-up assessment may not represent true LLL. A novel approach has been introduced in the IN.PACT BTK randomized study, using a longitudinal subsegmental array to divide the target lesion into 10 equal subsegments and acquiring individual measurements from each subsegment. Then, individual values are reported for each subsegment and averaged to provide a comprehensive representation of the entire target lesion. In this way, the subsegmental array approach takes into consideration that lesions have varying morphology from the proximal-to-distal length of the target vessel and incorporates these variations into the final angiographic data. Another limitation of the study is that due to the nature of the procedure, it was not possible to blind the patient, clinician performing the intervention, or study site staff. However, the clinical events committee and core laboratories are blinded.

If the IN.PACT BTK randomized study demonstrates the effectiveness and safety of the IN.PACT 014 DCB in patients with CTOs in the infrapopliteal arteries, a larger study will be needed to support the clinical benefit of DCB for reducing TLR, preventing major amputation, and enhancing wound healing. One of the major challenges in designing such a study would be standardizing the wound clinical governance program that is mandatory when managing CLTI in real-world practice.

Study status. The study is in the follow-up phase. A total of 50 participants were enrolled between March 2, 2017 and February 14, 2019. The anticipated date for the final participant follow-up is early 2024. The clinical investigation plan (CIP) was revised after the start of the study and included modifications to the inclusion/exclusion criteria. Throughout the enrollment phase, inclusion and exclusion criteria were updated based on investigator feedback to allow for additional flexibility in subject enrollment matching the actual targeted patient population and to clarify certain criteria to ensure correct understanding of the eligibility criteria. There was a reduction of the sample size from 60 participants to a minimum of 50 participants, a decision that was driven by slow enrollment due to a combination of rigorous and limiting inclusion and exclusion criteria. The recommended sample size for such a pilot study is between 30 and 50 patients;[17] therefore, the amended sample size of 50 participants is still within the range. The patient follow-up period, which had initially been reduced from 36 months to 24 months (which is in line with peripheral vascular clinical study standards in BTK studies), was updated to 60 months after feedback from competent authorities. All changes to the CIP were approved by ethics committees and competent authorities, if applicable, before implementation at the sites, and have been reflected in the study entry at ClinicalTrials.gov.

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