Design and rationale of a randomized noninferiority trial to evaluate the SurVeil drug-coated balloon in subjects with stenotic lesions of the femoropopliteal artery — the TRANSCEND study

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Background Drug-coated balloons (DCBs), developed to reduce restenosis after percutaneous intervention in peripheral arterial disease (PAD), have been shown to be safe and efficacious, particularly in treating PAD affecting the femoropopliteal segment. The SurVeil DCB uses an excipient intended to optimize both the uniformity and transfer of paclitaxel to the vessel wall, allowing for efficient drug loading and lower systemic exposure than currently available DCBs, Heretofore, clinical outcomes have not previously been compared to other DCBs.

Study Design and Objectives This prospective, multicenter, international, randomized, single-blind, trial will compare 1:1 the SurVeil DCB with the IN.PACT Admiral DCB for treatment of patients with Rutherford classification 2 to 4 due to femoral and/or popliteal arterial disease. The trial will randomize 446 subjects (with reference vessel diameter 4–7 mm and total lesion length ≤180 mm). Subjects will be followed for 60 months. The primary efficacy endpoint is 1 year primary patency, defined as composite freedom from clinically-driven target-lesion revascularization (TLR) and binary restenosis (core lab-adjudicated duplex ultrasound peak systolic velocity ratio ≥2.4, or ≥50% stenosis via angiography). The primary safety endpoint is composite freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically-driven target vessel revascularization through 12 months. The primary analysis is a test of noninferiority of the SurVeil vs. IN.PACT Admiral on the primary efficacy and safety endpoints according to absolute deltas of 15.0% and 10.0%, respectively.

Conclusion The Randomized And Controlled Noninferiority Trial to Evaluate Safety and Clinical Efficacy of the SurVeil DCB in the Treatment of Subjects with Stenotic Lesions of the Femoropopliteal Artery Compared to the Medtronic IN.PACT Admiral (TRANSCEND) study will assess safety and efficacy of the SurVeil DCB relative to a commonly used DCB. (Am Heart J 2019;209:88-96.)

Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis, affecting about 8.5 million American adults.[1] In addition, lower-extremity function declines over time.[2] Overall, the manifestations of PAD are associated with a large personal, medical, social, and economic burden that drives the need to identify appropriate treatments for this disease.[3]

Historically, the primary endovascular treatment for symptomatic PAD was percutaneous transluminal angioplasty (PTA). Intermediate- and long-term patency rates after PTA in the femoropopliteal anatomy were relatively low, however, with an average primary patency rate of 33% at 1 year for short-to-medium length lesions,[4] and as many as 50% of patients demonstrating significant restenosis leading to target-lesion revascularization (TLR) within 6 months of the initial intervention.[5] Drug-eluting stent (DES) deliver local anti-proliferative medication to the target vessel site to prevent restenosis of the lesion and provide some clinical benefit over PTA or bare metal stents (BMS) in femoropopliteal lesions.[6] However,

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metallic stents face challenges beyond restenosis in PAD. PAD lesions tend to be longer and exposed to mechanical forces, which contribute to high rates of in-stent restenosis.[5,7] Furthermore, peripheral stents are prone to fracture,[8] possibly due to dynamic forces imparted on the superficial femoral and popliteal arteries.[9] The long-term presence of a stent within the vasculature can lead to concern for stent thrombosis[10-12] and may require prolonged use of dual antiplatelet therapy (DAPT).[10]

Drug-coated balloons (DCBs), developed to reduce restenosis after percutaneous intervention in peripheral vessels, have been shown to be safe and to possess superior efficacy relative to PTA in treated treating PAD, particularly in the femoropopliteal segment.[13-19] Currently, three DCBs are approved by the FDA for treatment of the femoropopliteal arterial disease, the Lutonix 035 paclitaxel-coated balloon catheter, the Medtronic IN.PACT Admiral paclitaxel-coated balloon catheter, and the Spectranetics Stellarex drug-coated angioplasty balloon catheter. At 12 months, each DCBs have achieved higher primary patency rates than with PTA.[20-22] While DCBs have many of the same risks associated with PTA, including acute vessel dissection[23] and acute recoil,[10] risks unique to DCBs include embolization from microparticulate shed from the balloon coating into the distal vasculature[24] and possible paclitaxel release into the blood stream at doses higher than those released with DES.[10,24] Prior studies have demonstrated that paclitaxel levels in the blood peak shortly after DCB inflation and diminish rapidly, never reaching toxic levels. However, a measurable amount of paclitaxel does reach the systemic vasculature.[19,25]

Successful transfer of a paclitaxel coating from a balloon to an artery surface requires a durable coating during the transfer process to avoid systemic drug exposure; but once at the lesion site, durability is not desirable, in order to successfully transfer and retain drug at the site. The rationale for the current randomized trial is to evaluate the efficacy and safety of the SurVeil DCB. The SurVeil DCB utilizes two propriety coating that seeks to improve efficiency and uniformity of paclitaxel drug transfer to the target lesion and minimize variability in the manufacturing process (i.e. paclitaxel drug form, crystal size and shape, and distribution of drug coating the balloon length) relative to currently available DCBs. The aforementioned advances in drug coating further allow for a lower drug loading on the balloon (2.0 $\mu g/mm^2$) compared to the Medtronic IN.PACT Admiral DCB (3.5 $\mu g/mm^2$) while maintaining efficacy. Within the PREVEIL Early Feasibility Study, the SurVeil DCB was associated with low peak plasma paclitaxel levels (Cmax 1.07 ng/mL) and low 6-month late lumen loss.[26] The TRANSCEND Trial is therefore designed to evaluate the SurVeil DCB for noninferiority compared with the Medtronic IN.PACT Admiral DCB, in subjects with symptomatic PAD due to a stenotic lesion of the femoral and/or popliteal arteries.

Materials and methods

Design and objective

This will be a prospective, multi-center, single-blind, randomized, controlled trial to evaluate the noninferiority of the SurVeil DCB in the treatment of subjects with stenotic or occlusive lesions of the femoropopliteal artery compared to the Food and Drug Administration (FDA)-approved/CE-marked Medtronic IN.PACT Admiral DCB. Subjects with a stenosed femoral and/or popliteal artery will be randomized in a 1:1 ratio to the SurVeil or IN.PACT Admiral DCB, respectively, and followed for 60 months (Figure 1). The study will be deemed a success if at a minimum the hypotheses of inferiority of the safety and efficacy of the SurVeil DCB are rejected. Up to 446 subjects will be randomized at approximately 60 sites within and 18 sites outside of the United States. No one site will be allowed to randomize more than 10% of the total study cohort.

Subjects

Subjects with symptomatic PAD presenting for percutaneous revascularization of stenosed or occluded femoral and/or popliteal arteries (either de novo lesions or non-stented restenotic lesions >90 days from prior PTA or > 180 days from prior DCB treatment; either one long lesion or multiple serial lesions with a reference vessel diameter [RVD] of ≥4 mm and ≤7 mm and a total lesion length ≤180 mm) will be screened according to the protocol inclusion and exclusion criteria (Table I). Subjects who sign the consent form will be enrolled. Enrolled subjects who meet all the clinical inclusion criteria and none of the clinical exclusion criteria will then be screened for angiographic criteria. Once angiography is complete and the subject has met all of the remaining study eligibility criteria, the subject may be randomized. Enrolled subjects who are not randomized will be considered screen failures and exited from the study.

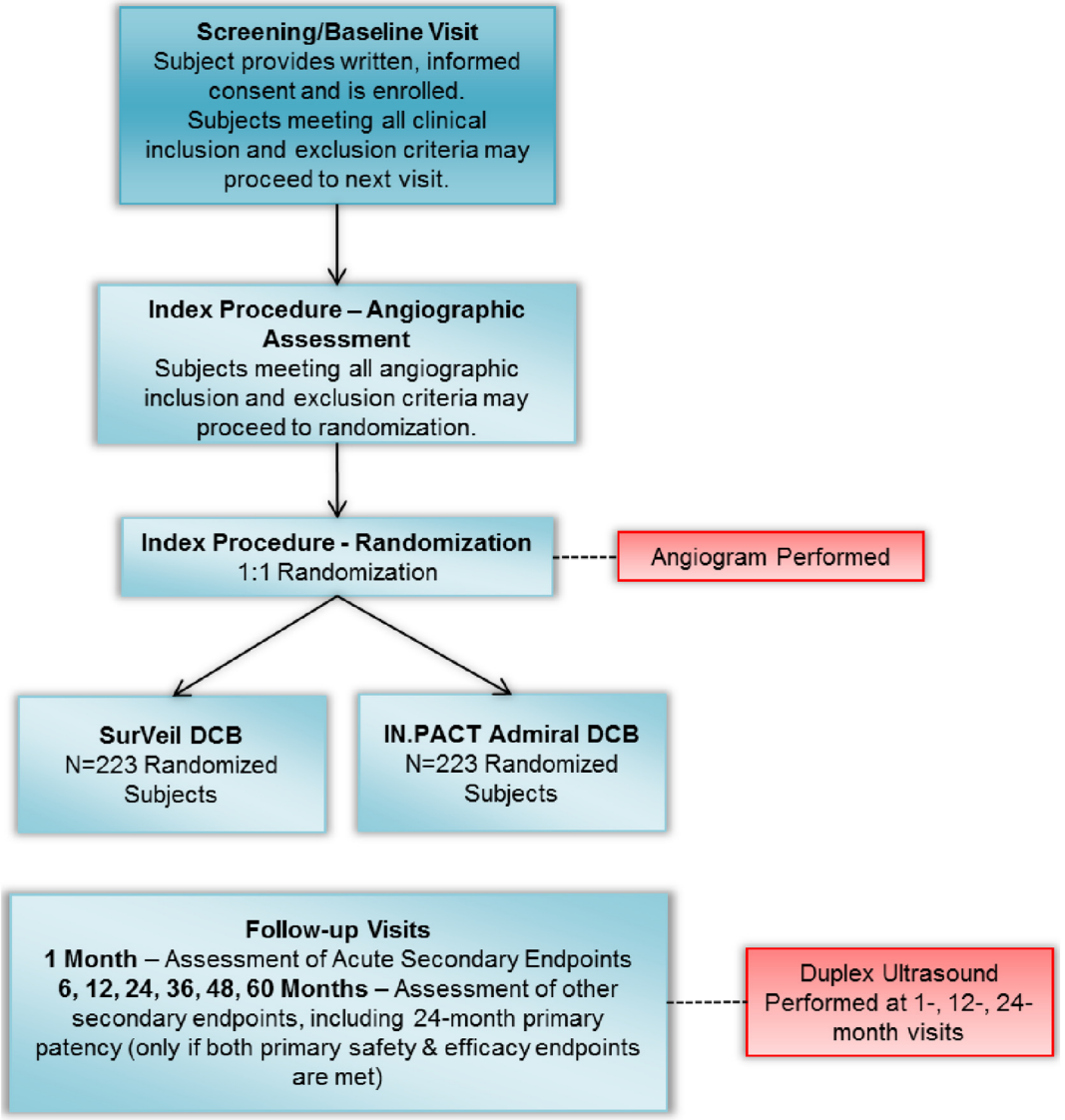
Procedure

Subjects meeting all clinical inclusion criteria and no clinical exclusion criteria will provide written informed consent prior to initiation of any trial-related procedures. Baseline angiography of the vessel(s) will be performed as per angiographic core laboratory procedure guidelines to characterize the target lesion and to confirm angiographic eligibility criteria (Table I). Assessment of angiographic eligibility criteria is based on a visual assessment of the angiogram and/or quantitative angiography. All angiograms, either digital subtraction angiography or cineangiography, will be submitted to an independent angiographic core laboratory for analysis.

Lesion pre-dilatation

Standard PTA balloons will be used for pre-dilatation in accordance with the Instructions for Use (IFU) for the SurVeil DCB and IN.PACT Admiral DCB. Use of embolic

Figure 1



Patient flow and follow-up visits.

capture angioplasty balloons or cutting/scoring balloons and atherectomy devices is not allowed. The uncoated PTA catheters should have a diameter that is 1 mm less than RVD and a length that approximates the length of the lesion. Successful pre-dilatation is defined as having achieved residual stenosis ≤70% and the absence of a flow-limiting dissection. If a subject does not achieve a successful pre-dilatation, the subject is not eligible to be randomized, is considered a screen failure, and is treated in accordance with standard of care.

Randomization

Subjects meeting angiographic eligibility criteria (Table I) will be randomized in a 1:1 fashion to either the SurVeil DCB or the IN.PACT Admiral DCB. Randomization will be stratified by study center and to prevent bias; the blocks and randomization schedules will be pre-defined prior to the first subject being enrolled.

Treatment with SurVeil and IN.PACT DCBs

The appropriate size DCB will be based on visual estimate and/or quantitative angiography. No more than two study devices should be used to treat a single target lesion during the procedure. Balloon(s) will be sized as follows:

- The nominal DCB diameter must match the RVD distal to the target lesion.

Table I. Clinical and angiographic inclusion and exclusion criteria. Subjects must meet all the clinical and angiographic inclusion criteria to participate in the trial. Subjects will be excluded from the trial if any of the clinical and angiographic exclusion criteria met

Clinical Inclusion Criteria
Subject is ≥18 years of age.
Subject has target limb Rutherford classification 2, 3, or 4.
Subject has provided written informed consent and is willing to comply with the study follow-up requirements.
Clinical Exclusion Criteria
Subject has acute limb ischemia.
Subject underwent intervention involving the target vessel within the previous 90 days.
Subject underwent any lower extremity percutaneous treatment in the ipsilateral limb using a paclitaxel-eluting stent or a DCB within the previous 90 days.
Subject underwent PTA of the target lesion using a DCB within the previous 180 days.
Subject has had prior vascular intervention in the contralateral limb within 14 days before the planned index procedure or subject has planned vascular intervention the in contralateral limb within 30 days after the index procedure.
Women who are pregnant, breast-feeding or intend to become pregnant or men who intend to father children during the time of the study.
Subject has life expectancy of less than 2 years.
Subject has a known allergy to contrast medium that cannot be adequately pre-medicated.
Subject is allergic to all antiplatelet treatments.
Subject has impaired renal function (i.e. serum creatinine level ≥ 2.5 mg/dL).
Subject is dialysis dependent.
Subject is receiving immunosuppressant therapy.
Subject has known or suspected active infection at the time of the index procedure.
Subject has platelet count $<100{,}000/mm^3$ or $>700{,}000/mm^3$.
Subject has history of gastrointestinal hemorrhage requiring a transfusion within 90 days prior to the index procedure.
Subject is diagnosed with coagulopathy that precludes treatment with systemic anticoagulation and/or DAPT.
Subject has history of stroke within the past 90 days.
Subject has a history of myocardial infarction within the past 30 days.
Subject is unable to tolerate blood transfusions because of religious beliefs or other reasons.
Subject is incarcerated, mentally incompetent, or abusing drugs or alcohol.
Subject is participating in another investigational drug or medical device study that has not completed primary endpoint(s) evaluation or that clinically interferes with the endpoints from this study, or subject is planning to participate in such studies prior to the completion of this study.
Subject has had any major (e.g. cardiac, peripheral, abdominal) surgical procedure or intervention unrelated to this study within 30 days prior to the index procedure or has planned major surgical procedure or intervention within 30 days of the index procedure.
Subject had previous bypass surgery of the target lesion.
Subject had previous treatment of the target vessel with thrombolysis or surgery.
Subject is unwilling or unable to comply with procedures specified in the protocol or has difficulty or inability to return for follow-up visits as specified by the protocol.
Angiographic Inclusion Criteria
De novo lesion(s) or non-stented restenotic lesion(s) occurring >90 days after prior POBA angioplasty or >180 days after prior DCB treatment.
Target lesion location starts ≥10 mm below the common femoral bifurcation and terminates distally at or above the end of the P1 segment of the popliteal artery.
Target vessel diameter ≥4 mm and ≤7 mm
Target lesion must have angiographic evidence of ≥70% stenosis by operator visual estimate.
Chronic total occlusions may be included only after successful, uncomplicated wire crossing of target lesion via an anterograde approach. Successful crossing of the target lesion occurs when the tip of the guide wire is distal to the target lesion without the occurrence of flow-limiting dissection or perforation and is judged by visual inspection to be within the true lumen. Subintimal dissection techniques may be used if re-entry occurs above the knee and without the use of re-entry devices.
Target lesion must be ≤180 mm in length (one long lesion or multiple serial lesions) by operator visual estimate.
Note: combination lesions must have a total lesion length of ≤180 mm by visual estimate and be separated by ≤30 mm.
Target lesion is located at least 30 mm from any stent, if target vessel was previously stented
Successful, uncomplicated (without use of a crossing device) wire crossing of target lesion. Successful crossing of the target lesion occurs when the tip of the guide wire is distal to the target lesion without the occurrence of flow-limiting dissection or perforation and is judged by visual inspection to be within the true lumen.
After pre-dilatation, the target lesion is ≤70% residual stenosis, absence of a flow limiting dissection and treatable with available device matrix.
A patent inflow artery free from significant stenosis (≥50% stenosis) as confirmed by angiography.
At least one patent native outflow artery to the ankle or foot, free from significant stenosis (≥50% stenosis) as confirmed by angiography.
Angiographic Exclusion Criteria
Target lesion has severe calcification (as defined by the PARC classification of calcification).
Target lesion involves an aneurysm or is adjacent to an aneurysm (within 5 mm).
Target lesion requires treatment with alternative therapy such as stenting, laser, atherectomy, cryoplasty, brachytherapy, or re-entry devices.
Significant target vessel tortuosity or other parameters prohibiting access to the target lesion.
Presence of thrombus in the target vessel.
Iliac inflow disease requiring treatment, unless the iliac artery disease is successfully treated first during the index procedure. Success is defined as ≤30% residual diameter stenosis without death or major complications.
Presence of an aortic, iliac or femoral artificial graft.

Abbreviations: DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; POBA, plain old balloon angioplasty; PTA, percutaneous transluminal angioplasty.

- The nominal DCB length must cover the entire target lesion or area treated by the pre-dilatation balloon, whichever is longer, plus a minimum of 5 mm proximally and 5 mm distally.
- If multiple DCBs are required to treat a lesion, the balloons must overlap by at least 10 mm. DCB angioplasty should be angiographically positioned to ensure coverage of at least 5 mm proximally and distally beyond the margins of the pre-dilatation.
- The balloon to artery ratio must be approximately 1.1:1.

The DCB(s) (SurVeil or IN.PACT Admiral) will be inflated for a minimum of 120 seconds to achieve the desired dilatation. Whenever possible, the randomly assigned DCB catheter should be the final treatment of the vessel, however, post-dilatation will be allowed. All treated patients will be prescribed dual-antiplatelet therapy for 1 month after the index procedure and aspirin (75–100 mg) daily indefinitely thereafter.

Bailout stenting

Prior to bailout stenting, the investigator should attempt prolonged balloon inflations (>2 minutes) in order to limit the amount of bailout stenting required in the study.

Bail out stenting is allowed if:

- Residual stenosis is ≥50% or
- Major (≥Grade D) flow-limiting dissection confirmed by a peak trans-lesional systolic pressure gradient >10 mmHg.

If bailout stenting is required per either of the above criteria, patients should be treated per standard of care use of a superficial femoral artery (SFA)-indicated bare nitinol stent. All subjects who undergo a bailout procedure, including emergency surgery, will be followed per the protocol follow-up schedule. These subjects will be included in all study analyses.

Primary endpoints

The primary efficacy endpoint is primary patency, defined as a composite of freedom from clinically-driven TLR and binary restenosis (restenosis defined as duplex ultrasound [DUS] peak systolic velocity ratio [PSVR] ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs) through 12 months post-index procedure.[27] In cases when there is a discrepancy between angiographic and DUS assessment of patency, angiographic assessment takes precedence.

The primary safety endpoint is a composite of freedom from device- and procedure-related death through 30 days post-index procedure and freedom from major target limb amputation (above the ankle) and clinically-driven target vessel revascularization (TVR) through 12 months post-index procedure.

Statistical methods

The study will be deemed a success if at a minimum, the hypotheses of inferiority of the safety and efficacy of the SurVeil DCB are rejected. The proportions of subjects meeting the primary efficacy and safety endpoints at 12-months post-index procedure and their 95% confidence intervals (CIs) will be reported.

Statistical analyses for the primary efficacy and safety endpoints will be conducted using a Farrington & Manning test for noninferiority of proportions. The SurVeil DCB will be declared noninferior to IN.PACT Admiral DCB with respect to the both the efficacy and safety endpoint if the null hypothesis of inferiority is rejected at a one-sided significance level of 2.5%. Given the possibility that the SurVeil DCB coating will result in superior clinical outcomes, if the null hypothesis of inferiority is rejected, a statistical test for superiority at the one-sided 2.5% will be conducted. The main analysis will be carried out using the intention-to-treat (ITT) analysis set. In addition to the main ITT analysis, supportive analyses will also be carried out using the as treated (AT) and per-protocol (PP) analysis sets.

To assess the effect of missing data on the results of the primary efficacy and safety endpoints, a series of sensitivity analyses will be carried out. First, a tipping point analysis will be carried out. Second, a sensitivity analysis of the primary efficacy and safety endpoints will be carried out using Cox regression. In these analyses, study discontinuation before an event will be treated as a censored observation at the time of dropout.

Primary patency rates and noninferiority margin

In the primary publication of the IN.PACT SFA trial, the 12-month primary patency rates were 82.2% and 52.4% in the IN.PACT Admiral DCB and PTA groups,[21] respectively, and the primary safety rates were 95.7% and 76.6% in these groups, respectively. The observed difference in between the IN.PACT Admiral DCB and PTA groups was 29.8% for the 12-month primary patency rates, and 19.1% for the primary safety endpoint rates. A noninferiority margin of 15.0% for the primary efficacy endpoint and 10% for the primary safety endpoint were chosen to preserve 50% of the treatment effect between DCB and PTA.[28]

Sample size

A sample size of 400 evaluable subjects, or 446 randomized subjects to account for an estimated 10% loss to follow-up, was calculated to provide adequate power for both the primary efficacy and safety endpoints.

Table II. Secondary endpoints. Secondary endpoints will be assessed in both the acute phase of the study and in the follow-up phase of the study

Acute Endpoints:

- Device Success: defined as successful delivery, balloon inflation, deflation and retrieval of the intact study device without burst below rated burst pressure, and achievement of <50% residual stenosis of the target lesion (by core lab-assessed quantitative angiography [QA]) without flow-limiting arterial dissection, using only the study device.
- Technical Success: defined as achievement of a final residual diameter stenosis of <50% (by core lab-assessed QA) without flow-limiting arterial dissection at the end of the procedure.
- Procedure Success: defined as evidence of both acute technical success and absence of Peripheral Academic Research Consortium major adverse events (PARC MAEs; e.g., death, stroke, myocardial infarction, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and or need for urgent/ emergent vascular surgery) within 72 hours of the index procedure.
- Freedom from all-cause death, major target limb amputation and TVR through 30 days.

Follow-up Phase Endpoints:

- Primary patency through 24 months (only if both the primary safety and efficacy hypotheses of noninferiority are met).
- Target vessel patency, defined as freedom from clinically-driven TVR and freedom from binary restenosis (restenosis defined as DUS PSVR ≥2.4 or ≥ 50% stenosis as assessed by independent angiographic and DUS core labs) within 12 and 24 and months (In cases when there is a discrepancy between angiographic and DUS assessment of patency, angiographic assessment takes precedence.)
- Sustained clinical improvement, defined as freedom from major target limb amputation, TVR and worsening target limb Rutherford class within 6, 12, and 24 months
- Clinically-driven TLR within 6, 12, 24, 36, 48, and 60 months
- Historical major adverse events (Historical MAEs), defined as composite of all-cause death, clinically-driven TLR, major target limb amputation, or thrombosis at the target lesion, within 6, 12, 24, 36, 48, and 60 months
- Major target-limb amputation within 6, 12, 24, 36, 48, and 60 months
- Thrombosis at the target lesion within 6, 12, 24, 36, 48, and 60 months
- Change in target limb Rutherford class from baseline to 1, 6, 12, and 24 months
- Change in target limb Peripheral Academic Research Consortium (PARC) class from baseline to 1, 6, 12, and 24 months
- Decrease in target limb resting ABI or toe brachial index (TBI) ≥0.15 from baseline to 6, 12, and 24 months
- Change in Walking Impairment Questionnaire (WIQ) score from baseline to 1, 12, and 24 months
- Change in 6-minute walk test (6-MWT) from baseline to 12 and 24 months
- Change in Peripheral Artery Questionnaire (PAQ) score from baseline to 1, 12, and 24 months

For the efficacy endpoint, assumptions include a true 12-month primary patency rate of 82.2% in both treatment groups, 1:1 randomization, one-sided significance level of 2.5%, and a 15.0% absolute noninferiority margin. Under these assumptions, the power is at least 97.5%.

For the primary safety endpoint, assumptions included a true 12-month primary safety endpoint rate of 95.7% in both treatment groups, 1:1 randomization, one-sided significance level of 2.5%, and a 10.0% absolute noninferiority margin. Under these assumptions, the power is >99%.

Secondary endpoints

Primary patency through 24 months will be compared between treatments if both the primary safety and efficacy hypotheses of noninferiority are met. This hierarchical testing scheme ensures that the study-wide Type I error rate is 0.025 (one-sided) when the key secondary endpoint is tested at one-sided $\alpha = 0.025$. The objective is to assess whether the primary patency rate of subjects in the SurVeil DCB group is noninferior to that of the IN.PACT DCB group, using the Farrington and Manning test for noninferiority. If noninferiority is demonstrated for the 24-month patency rates, a test of superiority will be conducted. In the IN.PACT SFA study, the 24-month primary patency rates were 78.9% and 50.1% in the IN.PACT Admiral DCB and PTA groups,[29] respectively, with an observed difference of 28.8%. Thus, a noninferiority margin of 15.0% is clinically justified, as it preserves ~50% of the treatment effect between DCB and PTA at 2 years.

Additional secondary endpoints will be assessed in both the acute phase of the study and the long-term follow-up phase of the study, as shown in Table II.

Subgroup analyses

Treatment by subgroup interaction will be examined to evaluate the consistency of results across various subgroups if noninferiority is demonstrated for the primary endpoints. A test of interaction will be performed using logistic regression models with the effects of subgroup, randomized treatment, and randomized treatment-by-subgroup interaction to formally assess heterogeneity of treatment effect on the primary endpoint across subgroups, with an interaction P value <0.15 indicating a potential differential effect. Treatment group differences in the primary endpoint rate, along with 95% CIs, will be assessed. The planned subgroups for analysis are age, smokers vs. non-smokers, females vs. males, subjects with vs. without diabetes mellitus, lesion length ≤90 mm vs. >90 mm, calcified vs. non-calcified lesions, de novo vs. restenotic lesions, and subjects with vs. without bailout stenting.

Poolability of data

Treatment center heterogeneity will also be assessed using logistic regression to evaluate the interaction of treatment and site. Poolability of patients within and outside the United States will also be assessed using logistic regression with treatment, region (United States vs. non-United States) and their interaction. For both of these analyses, $P \leq .15$ for the interaction term will indicate that the observed effects may not be homogenous.

Study administration and management

The Institutional Review Board or Ethics Committee at each participating institution must approve the study, and all subjects must provide written informed consent prior. Funding is provided by Surmodics. The Baim Institute for Clinical Research will maintain the complete study database and will perform all key analyses. The Steering Committee, composed of a chair, study principal investigators, sponsor representatives, and other experts, will provide leadership for the study. A blinded, independent Clinical Events Committee (CEC) will be responsible for adjudicating major adverse events (MAEs, as defined in Table II) and other specified clinical endpoints, and for determining their device- and procedure-relatedness. An independent Data.

Monitoring Committee (DMC), composed of a biostatistician and physicians independent from the trial but with expertise in vascular surgery and vascular intervention, will review aggregate and individual subject data related to safety, data integrity, and overall conduct of the trial, on a periodic basis. The DMC may make recommendations regarding modification or early termination of the trial to the Steering Committee and study Sponsor as a result of its monitoring activities.

Discussion

We describe the design and rationale of the TRANSCEND Trial, a large randomized clinical trial assessing the safety and efficacy of the SurVeil DCT as compared to the FDA-approved Medtronic IN.PACT Admiral DCB in subjects with symptomatic PAD due a stenotic lesion within the femoropopliteal artery. The SurVeil DCB uses an excipient that enables sufficient and uniform paclitaxel transfer to the vessel wall while allowing for lower systemic paclitaxel exposure. These features may help to minimize the risk of restenosis and also the occurrence of adverse clinical events.

Drug-coated balloons provide the benefits of PTA, including accessibility, minimal trauma, mechanical dilation of lesions, with the ability to distribute anti-proliferative medications, such as paclitaxel, to PAD lesions without concerns of a permanent stent implant. Significant clinical data demonstrate the safety and efficacy of DCB devices in treating PAD, particularly in the femoropopliteal segment.[13] Three DCBs are currently approved by the FDA for treatment of PAD involving the femoropopliteal artery, the Lutonix 035 paclitaxel-coated balloon catheter, the Medtronic IN.PACT Admiral paclitaxel-coated balloon catheter, and the Spectranetics Stellarex drug-coated angioplasty balloon catheter. The Lutonix DCB catheter was evaluated within the Lutonix Paclitaxel-Coated Balloon for the Prevention of Femoropopliteal Restenosis (LEVANT) 2 trial, in which 476 patients were randomized in a 2:1 ratio to a DCB coated with paclitaxel vs. PTA. At 12 months, primary patency (freedom from binary restenosis or from TLR) was achieved in 65.2% of patients receiving DCB vs. 52.6% of patients receiving PTA ($P = .02$), and 83.9% vs. 79.0%, respectively, were free from primary safety events (noninferiority $P = .005$).[20] In the similarly designed IN.PACT SFA trial, 331 patients were randomized in a 2:1 ratio to a DCB coated with paclitaxel vs. PTA. At 12 months, primary patency was achieved in 82.2% of patients receiving DCB vs. 52.4% of patients receiving PTA ($P < .001$).[21] At 36 months, treatment with the IN.PACT DCB was associated with persistently increased primary patency (69.5%) compared with PTA (45.1%, $P < .001$), and reduced clinically-driven TLR (15.2% vs. 31.1%, respectively, $P = .002$).[30] Within the Prospective, Randomized, Single-Blind, U.S. Multi-Center Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With A Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon (ILLUMENATE) Pivotal Study, the Spectranetics Stellarex DCB was compared to standard angioplasty within 300 patients randomized in a 2:1 fashion. Primary patency was significantly higher with the Stellarex DCB compared to PTA (82.3% vs. 70.9%; $P = .002$).[22] In a meta-analysis of 7 randomized trials including 1230 patients comparing DCBs to uncoated balloon angioplasty in patients with PAD of the femoropopliteal artery, DCBs were associated with reduced TLR (odds ratio [OR] 0.26, 95% CI 0.13–0.56), but no differences in rates of binary restenosis (OR 0.37, 95% CI 0.11–1.26), amputation (OR 2.21, 95% CI 0.23–21.51), or death (OR 0.67, 95% CI 0.31–1.46).[13]

The SurVeil DCB utilizes a design that seeks to improve the efficiency of drug transfer to the target and a manufacturing process that ensures consistency of paclitaxel drug form, crystal size and shape, and uniform distribution of drug coating over the working length of the balloon. These advances are intended to increase the therapeutic dose administered while minimizing systemic exposure. The current trial's comparison of the SurVeil DCB with FDA-approved DCB with the best published rates for maintenance of primary patency at 12 months (the IN.PACT Admiral DCB) will help to determine whether the SurVeil DCB can further optimize efficacy while at the same time providing lower drug-loading on the balloon and lower systemic exposure of paclitaxel.

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Disclosures

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