The Randomized And Controlled Noninferiority Trial to Evaluate Safety and Clinical Efficacy of the SurVeil™ Drug-Coated Balloon iN the Treatment of Subjects with Stenotic Lesions of the Femoropopliteal Artery Compared to the Medtronic IN.PACT® Admiral® Drug-Coated Balloon

TRANSCEND Study

CLINICAL PROTOCOL SUR17-001

Version 3.3

14 August 2020

Investigational Device: Surmodics SurVeil™ Drug Coated Balloon (SurVeil DCB)

Sponsored By

Surmodics, Inc.

9924 West 74th Street

Eden Prairie, MN 55344 USA

DOCUMENT HISTORY

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3.0	[redacted]	[redacted]	[redacted]	[redacted]
3.1	[redacted]	[redacted]	[redacted]	[redacted]
3.2	[redacted]	[redacted]	[redacted]	[redacted]
3.3	[redacted]	[redacted]	[redacted]	[redacted]uest

STUDY PRINCIPAL INVESTIGATORS SIGNATURE PAGE

Protocol No. SUR17-001

I, the undersigned, have read and understood the protocol for the study entitled

The **R**andomized **A**nd Controlled **N**oninferiority Trial to Evaluate **S**afety and **C**linical **E**fficacy of the SurVeil™ Drug-Coated Balloon i**N** the Treatment of Subjects with Stenotic Lesions of the Femoropopliteal Artery Compared to the Medtronic IN.PACT® Admiral® **D**rug-Coated Balloon: TRANSCEND Study

Surmodics, Inc.

I agree with its contents. I will comply with all the protocol requirements. The protocol and any other information provided by Surmodics will serve as the basis for cooperation in the clinical investigation.

Investigator Name (print or type): _____

Investigator Signature: _____

Date: _____

Sponsor Signature and Date: [redacted]

Sponsor Printed Name and Title:

Sponsor Legal Representative Signature and Date: _____

Sponsor Legal Representative Printed Name and Title: _____

_____

SITE INVESTIGATORS SIGNATURE PAGE

Protocol No. SUR17-001

I, the undersigned, have read and understood the protocol for the study entitled

The **R**andomized **A**nd Controlled **N**oninferiority Trial to Evaluate **S**afety and **C**linical **E**fficacy of the SurVeil™ Drug-Coated Balloon i**N** the Treatment of Subjects with Stenotic Lesions of the Femoropopliteal Artery Compared to the Medtronic IN.PACT® Admiral® **D**rug-Coated Balloon: TRANSCEND Study

Surmodics, Inc.

The signature below documents the receipt and review of the TRANSCEND clinical study protocol and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to the local legal and regulatory requirements and applicable United States Federal Regulations, ISO 14155, ICH and GCP guidelines.

Investigator Name (print or type): _____

Investigator's Signature: _____

Date: _____

Site Number: _____

Site Address: _____

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1. Protocol Synopsis

Study Title	**T**he **R**andomized **A**nd Controlled **N**oninferiority Trial to Evaluate **S**afety and **C**linical **E**fficacy of the SurVeil™ Drug-Coated Balloon i**N** the Treatment of Subjects with Stenotic Lesions of the Femoropopliteal Artery Compared to the Medtronic IN.PACT® Admiral® **D**rug-Coated Balloon: **TRANSCEND Study**
Investigational Device	Surmodics SurVeil™ Drug-Coated Balloon (SurVeil DCB)
Comparator Device	Medtronic IN.PACT® Admiral® DCB
Objectives	To demonstrate the safety and efficacy of the SurVeil DCB for treatment of subjects with symptomatic peripheral artery disease (PAD) due to stenosis of the femoral and/or popliteal arteries.
Study Design	Prospective, multi-center, single-blind, randomized, controlled, noninferiority clinical trial The trial will randomize approximately 446 subjects with symptomatic PAD due to stenoses of the femoral and/or popliteal arteries. Subjects meeting eligibility criteria will be randomized 1:1 to treatment with either the SurVeil DCB or the IN.PACT Admiral DCB, and followed for 60 months.
Subject Populations	Subjects with symptomatic PAD due to a stenotic lesion of the femoral and/or popliteal arteries with a reference vessel diameter (RVD) of 4 mm to 7 mm and a total lesion length ≤180 mm.
Subjects and Sites	Up to 446 subjects will be randomized at approximately 60 sites in the United States and approximately 18 sites outside of the United States.
Primary Safety Endpoint	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.

Primary Efficacy Endpoint	The primary efficacy endpoint is primary patency, defined as a composite of freedom from clinically-driven target lesion revascularization (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. In cases when there is a discrepancy between angiographic and DUS assessment of patency, angiographic assessment takes precedence.
Secondary Endpoints	Acute: • 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 Through follow-up: • 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 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 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 PARC class from baseline to 1, 6, 12, and 24 months • Decrease in target limb resting ankle brachial index (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
Statistical Considerations	The proposed investigational device exemption (IDE) study will assess noninferiority of the 12-month primary patency rate in subjects treated with the SurVeil DCB vs. the primary patency rate in subjects treated with the IN.PACT Admiral DCB. *Hypotheses*: The efficacy objective will be assessed through testing the following hypotheses: $H_0: p_S^{\text{Eff}} - p_M^{\text{Eff}} \leq -\delta^{\text{Eff}}$ $H_1: p_S^{\text{Eff}} - p_M^{\text{Eff}} > -\delta^{\text{Eff}}$ where p_S^{Eff} and p_M^{Eff} are the 12-month primary patency rates in the SurVeil group and comparator IN.PACT Admiral group, respectively, and δ^{Eff} is the noninferiority margin. Statistical analyses for the primary endpoint will be conducted using a Farrington & Manning test for noninferiority of proportions; the test will be a one-sided test at $\alpha = 0.025$ *Sample Size Assumptions:* • True 12-month primary patency rate is 82.2% in both treatment groups

	• 1:1 randomization of SurVeil DCB vs IN.PACT Admiral DCB • 15.0% is the absolute noninferiority margin (50% of the difference in primary patency rate between IN.PACT Admiral DCB and PTA[1]) A sample size of 446 (223 randomized to SurVeil DCB group and 223 randomized to IN.PACT Admiral DCB group) randomized subjects, accounting for an assumed 10% lost to follow up, will lead to a power level of 97.5%. If the true primary patency rates are 82.2% in the IN.PACT Admiral DCB arm, and 80% and 78.3% in the SurVeil DCB arm, at least 90% and 80% power, respectively, will be preserved at the planned sample size.
Clinical Inclusion Criteria	Subjects must meet **all** of the following criteria to participate in the trial: CI1. Subject is ≥18 years. CI2. Subject has target limb Rutherford classification 2, 3 or 4. CI3. Subject has provided written informed consent and is willing to comply with study follow-up requirements.
Clinical Exclusion Criteria	Subjects will be excluded from the trial if **any** of the following criteria are met: CE1. Subject has acute limb ischemia. CE2. Subject underwent intervention involving the target vessel within the previous 90 days. CE3. Subject underwent any lower extremity percutaneous treatment in the ipsilateral limb using a paclitaxel-eluting stent or a DCB within the previous 90 days. CE4. Subject underwent PTA of the target lesion using a DCB within the previous 180 days. CE5. Subject has had prior vascular intervention in the contralateral limb within 14 days before the planned study index procedure or subject has planned vascular intervention in the contralateral limb within 30 days after the index procedure. CE6. Women who are pregnant, breast-feeding or intend to become pregnant or men who intend to father children during the time of the study. CE7. Subject has life expectancy less than 2 years. CE8. Subject has a known allergy to contrast medium that cannot be adequately pre-medicated.

[1] Tepe, Laird, Schneider, *et al.* Circulation. 2015;131:495-502.

	CE9. Subject is allergic to ALL antiplatelet treatments. CE10. Subject has impaired renal function (i.e. serum creatinine level ≥2.5 mg/dL). CE11. Subject is dialysis dependent. CE12. Subject is receiving immunosuppressant therapy. CE13. Subject has known or suspected active infection at the time of the index procedure. CE14. Subject has platelet count <100,000/mm^3 or >700,000/mm^3. CE15. Subject has history of gastrointestinal hemorrhage requiring a transfusion within 3 months prior to the study procedure. CE16. Subject is diagnosed with coagulopathy that precludes treatment with systemic anticoagulation and/or dual antiplatelet therapy (DAPT). CE17. Subject has history of stroke within the past 90 days. CE18. Subject has a history of myocardial infarction within the past 30 days. CE19. Subject is unable to tolerate blood transfusions because of religious beliefs or other reasons. CE20. Subject is incarcerated, mentally incompetent, or abusing drugs or alcohol. CE21. 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. CE22. 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. CE23. Subject had previous bypass surgery of the target lesion. CE24. Subject had previous treatment of the target vessel with thrombolysis or surgery. CE25. 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	The target lesion/vessel must meet **all** of the following angiographic criteria for the subject to participate in the trial:

Criteria	AI1. *De novo* lesion(s) or non-stented restenotic lesion(s) occurring >90 days after prior plain old balloon (POBA) angioplasty or >180 days after prior DCB treatment. AI2. 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. AI3. Target vessel diameter ≥4 mm and ≤7 mm. AI4. Target lesion must have angiographic evidence of ≥70% stenosis by operator visual estimate. AI5. 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. AI6. 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. AI7. Target lesion is located at least 30 mm from any stent if target vessel was previously stented. AI8. 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. AI9. After pre-dilatation, the target lesion is ≤70% residual stenosis, absence of a flow limiting dissection and treatable with available device matrix. AI10. A patent inflow artery free from significant stenosis (≥50% stenosis) as confirmed by angiography. AI11. 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	Subjects will be excluded from the trial if the target lesion/vessel meets **any** of the following angiographic criteria: AE1. Target lesion has severe calcification (as defined by the PARC classification of calcification). AE2. Target lesion involves an aneurysm or is adjacent to an aneurysm (within 5 mm). AE3. Target lesion requires treatment with alternative therapy such as stenting, laser, atherectomy, cryoplasty, brachytherapy, or re-entry devices. AE4. Significant target vessel tortuosity or other parameters prohibiting access to the target lesion. AE5. Presence of thrombus in the target vessel. AE6. 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. AE7. Presence of an aortic, iliac or femoral artificial graft.
Subject Follow-up	All randomized subjects will be followed through 60 months post-index procedure with follow-up assessments at 30 days and at 6, 12, 24, 36, 48, and 60 months.

2. Study Administration and Contacts

Sponsor	Surmodics, Inc. [redacted] 9924 West 74th Street Eden Prairie, Minnesota, 55344 USA [redacted]
Principal Investigators	William Gray, MD Lankenau Medical Center [redacted] Kenneth Rosenfield, MD Massachusetts General Hospital [redacted] Marianne Brodmann, MD Medical University Graz, Department of Internal Medicine [redacted]
Protocol Development	Baim Institute for Clinical Research Sammy Elmariah, MD, Medical Director Gheorghe Doros, PhD, Statistical Consulting, Biostatistics
Data Coordinating Center	Baim Institute for Clinical Research 930-W Commonwealth, 3rd Floor Boston, MA 02215-1212 USA [redacted]

[redacted]	[redacted]
Angiographic Core Lab	Yale Angiographic Core Laboratory Alexandra Lansky, MD One Church Street, Suite 330 New Haven, CT 06510 USA [redacted]
Duplex Ultrasound Core Lab	VasCore Gail Hadley, Technical Director 1 Bowdoin Square, 10th Floor Boston, MA 02114 USA [redacted]

3. Table of Contents

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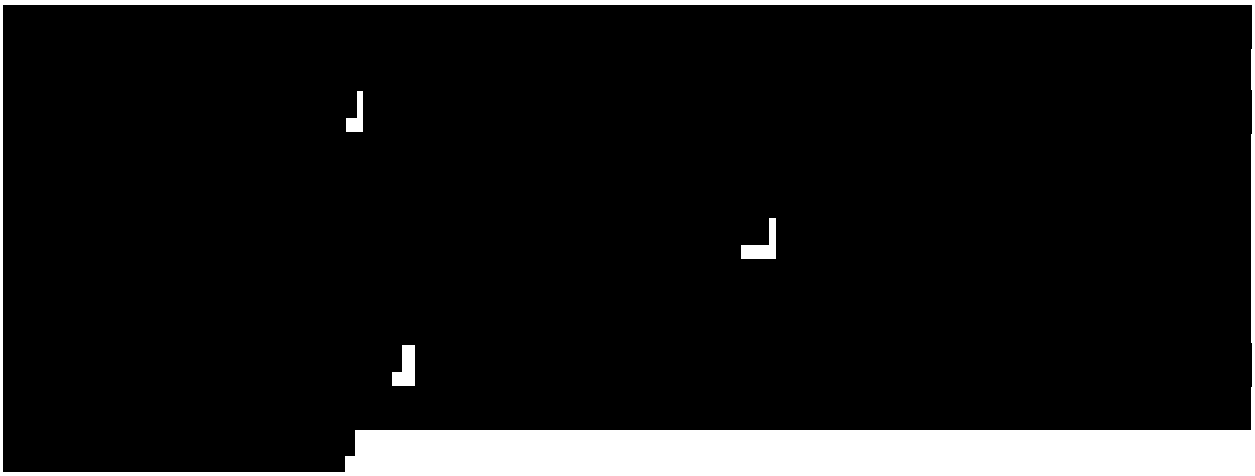
4. Introduction

4.1



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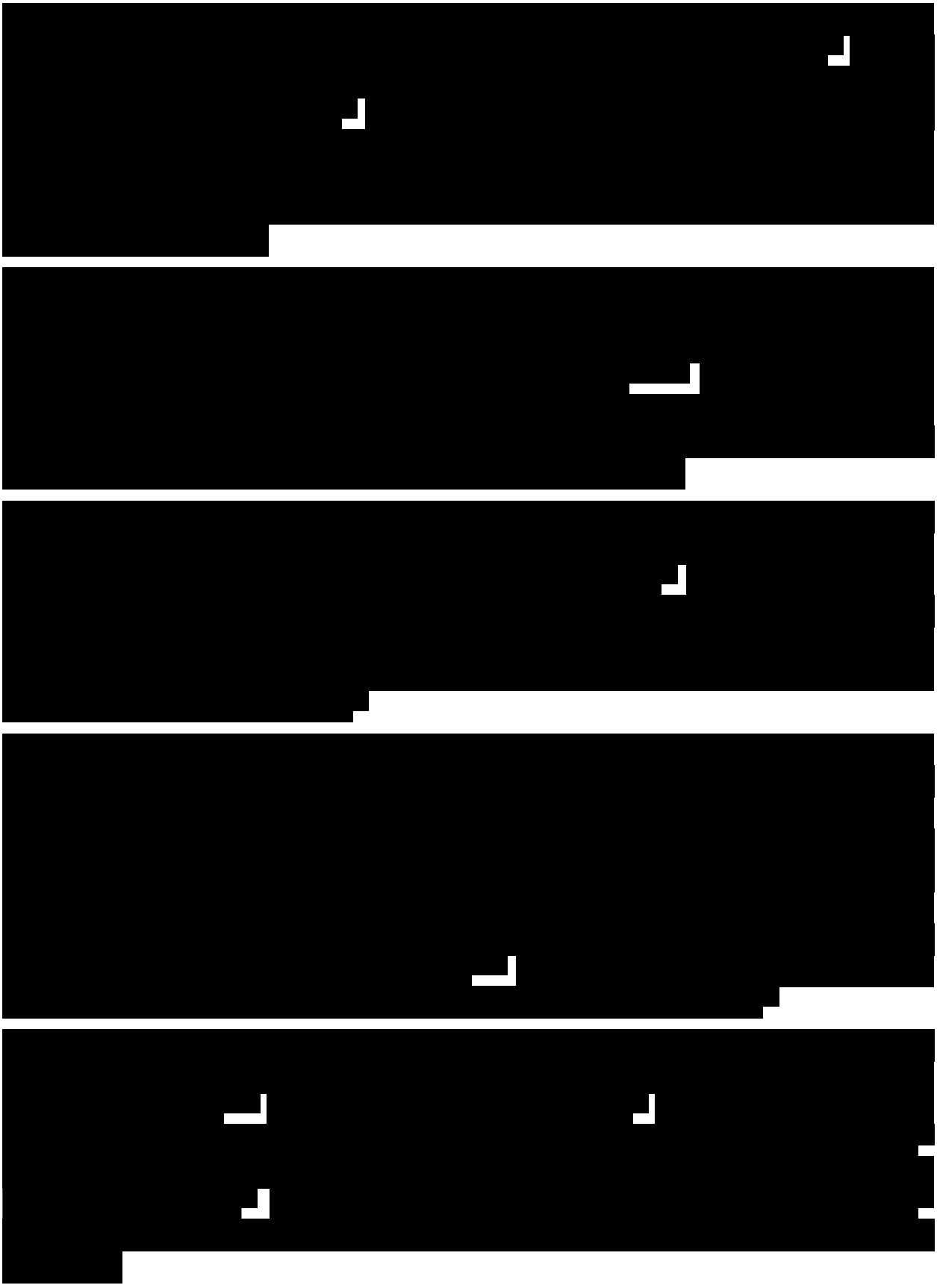

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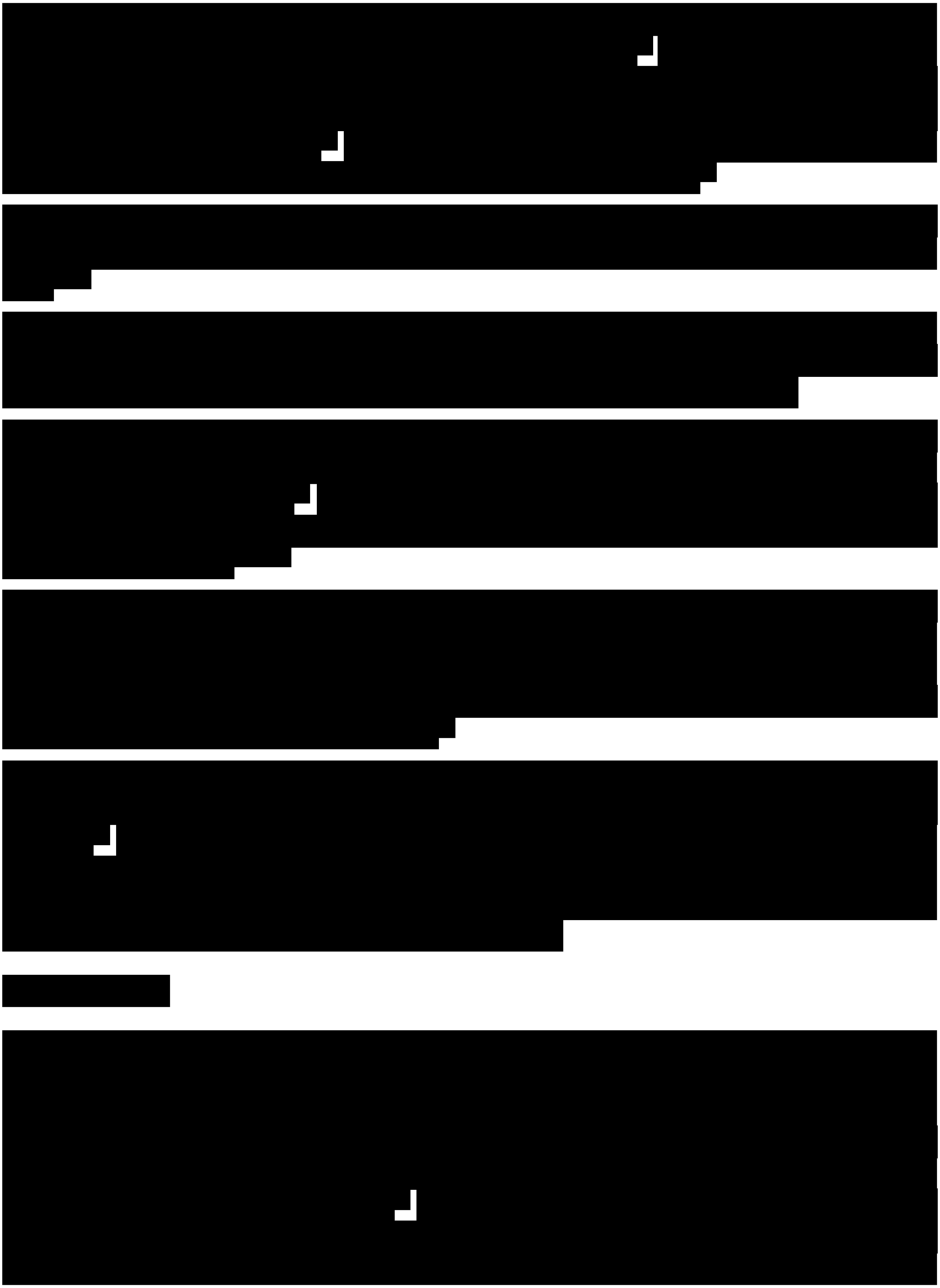

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4.6 Study Rationale

The rationale for the current pivotal study is to further evaluate the safety and efficacy of the SurVeil DCB in subjects with symptomatic PAD due to a stenotic lesion of the femoral and/or popliteal arteries with a RVD of 4 mm to 7 mm and a total lesion length ≤180 mm. Specifically, the SurVeil DCB is being evaluated in terms of its noninferiority to the Medtronic IN.PACT Admiral DCB, which is indicated for use in PTA, after successful pre-dilatation, of *de novo* or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with RVDs of 4-7 mm.

5. Device Description/Indications for Use

The SurVeil DCB (**Figure 1**) is indicated for PTA, after pre-dilatation of *de novo* or restenotic lesions (≤180 mm in length) in femoral and popliteal arteries having reference vessel diameters of 4 mm to 7 mm.

5.1 PTA Catheter Description

The SurVeil DCB Catheter (**Figure 1**) is a standard 0.035" over the wire PTA catheter, 1350 mm working length. [redacted] The shaft tubing size is 5 French and connects the hub to the proximal end of the balloon. [redacted] The shaft of the catheter is coated with Surmodics PhotoLink® lubricious [redacted] coating.

The balloon has a cylindrical section, which defines the length of the balloon, with a nominal diameter and a nominal length and a cone section at each end. [redacted] The catheter tip, with an atraumatic design, acts as the transition from the catheter to the guidewire.

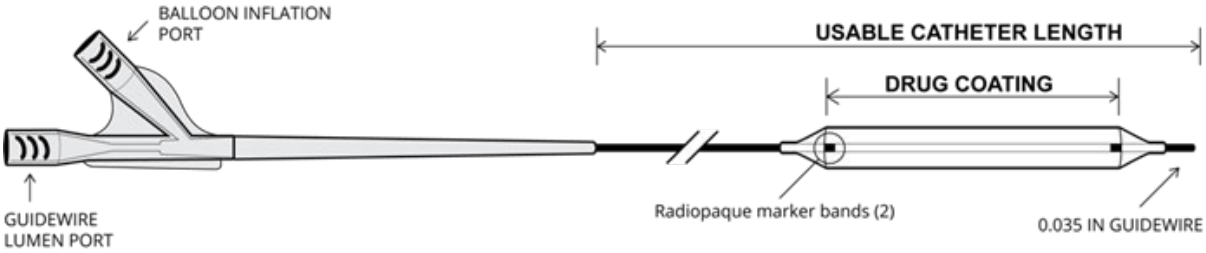


Figure 1. The SurVeil DCB Catheter

5.2 Balloon Drug Coating Description

The balloon is coated with two proprietary coatings. The first layer is a hydrophilic basecoat [redacted] The second layer comprises the drug paclitaxel (See

Table 1) and excipient. The balloon surface has a nominal dose density of paclitaxel of 2.0 µg/mm² (see **Table 2** for nominal total quantity of paclitaxel per balloon).

The excipient in the drug coating is an inactive ingredient that facilitates efficient transfer of paclitaxel to the arterial wall.

Table 1 Paclitaxel Description

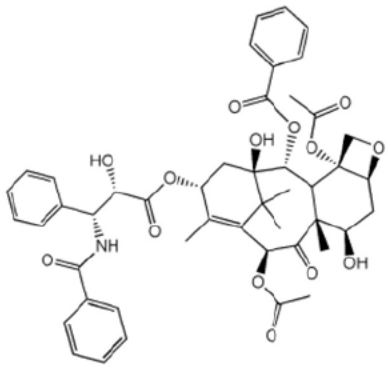
United States Adopted	Paclitaxel
Compendial Name (USP)	Paclitaxel
CAS Registry Number	33069-62-4
Chemical Name	[2a R- [2aα,4β, 4aβ, 6β, 9α (αR*,βR*), 11α, 12α, 12aα, 12bα]]- b-(Benzoylamino)-a-hydroxybenzenepropanoic acid 6, 12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a, 5, 6, 9, 10, 11, 12, 12a, 12b-dodecahydro-4, 11-dihydroxy-4a, 8, 13, 13-tetramethyl-5oxo-7, 11-methano-1Hcyclodeca[3,4]benz [1,2-b]oxet-9-yl ester
Molecular Formula	$C_{47}H_{51}NO_{14}$
Relative Molecular Weight	853.93
Structural Formula	

Table 2. SurVeil Device Supply Matrix and Paclitaxel Content (µg)

Balloon diameter (mm)	Nominal Paclitaxel Content (µg) per Balloon length					
	40 mm	**60 mm**	**80 mm**	**100 mm**	**120 mm**	**150 mm**
4.0	1005	1508	2011	2513	3016	3770
5.0	1257	1885	2513	3142	3770	4712
6.0	1508	2262	3016	3770	4524	--

7.0	1759	2639	3519	--	--	--
Shading indicates sizes available for start of pivotal; additional sizes may be added. Site must confirm availability of appropriately sized device prior to randomization.						

6. Trial Design

6.1 Trial Design

This is a prospective, multi-center, single-blind, randomized, controlled trial to evaluate the noninferiority of the SurVeil DCB in the treatment of subjects with stenotic lesions of the femoropopliteal artery compared to the 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.

The target lesion must be either *de novo* or a non-stented restenotic lesion >90 days from prior POBA angioplasty or >180 days from prior DCB treatment. It may be one long lesion or multiple serial lesions with a RVD of ≥4 mm and ≤7 mm and a total lesion length ≤180 mm.

6.2 Clinical Sites and Subjects

Up to 446 subjects will be randomized at approximately 60 sites in the United States and approximately 18 sites outside of the United States. No one site will be allowed to randomize more than 10% of the total population.

6.3 Subject Status Definitions

Enrolled – Subject who is fully informed about the specifics of the study by authorized site personnel and provides informed consent by properly signing an informed consent form after confirmation of the initial enrollment criteria.

Screen failure – Enrolled subject who withdraws consent prior to randomization or is unsuitable for randomization following clinical and angiographic assessments as described in the study eligibility (inclusion and exclusion) criteria. These subjects will be exited from the study once screen failure is confirmed.

Randomized – Enrolled subject who meets all clinical and angiographic eligibility criteria and has been randomized. These subjects will be followed in accordance with the protocol requirements.

Study exit - Termination of study participation applicable to subjects who have signed an informed consent form. This status can apply to subjects who terminate the study early or to subjects who have completed the entire study.

See **Figure 2** in Section 9.3 for a visual depiction of subject study status.

7. Trial Objective and Endpoints

7.1 Trial Objective

The objective of the study is to demonstrate the safety and efficacy of the SurVeil DCB for the treatment of subjects with symptomatic PAD due to stenosis of the femoral and/or popliteal arteries. 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.

7.2 Primary Safety Endpoint

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.

7.3 Primary Efficacy Endpoint

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) and through 12 months post-index procedure. In cases when there is a discrepancy between angiographic and DUS assessment of patency, angiographic assessment takes precedence.

7.4 Secondary Endpoints

7.4.1 Acute

The following acute secondary endpoints will be assessed:

- 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.

7.4.2 Through Follow-Up

The following endpoints will be assessed through the follow-up period:

- 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

8. Trial Population

8.1 Study Population (Eligibility Criteria)

Subjects with symptomatic PAD presenting for percutaneous revascularization of stenosed femoral and/or popliteal arteries (either *de novo* lesions or non-stented restenotic lesions >90 days from prior POBA angioplasty or >180 days from prior DCB treatment) will be screened according to the protocol inclusion and exclusion criteria. Subjects who have signed the approved consent form are considered to be enrolled. Enrolled subjects who have met 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 investigator is satisfied that the subject has met all of the remaining study eligibility criteria, the subject may be randomized. Enrolled subjects who were not randomized will be considered screen failures and exited from the study.

8.1.1 Clinical Inclusion Criteria

Subjects must meet **all** the following clinical criteria to participate in the trial.

CI1. Subject is ≥ 18 years of age.

CI2. Subject has target limb Rutherford classification 2, 3, or 4.

CI3. Subject has provided written informed consent and is willing to comply with the study follow-up requirements.

8.1.2 Clinical Exclusion Criteria

Subjects will be excluded from the trial if **any** of the following clinical criteria are met.

CE1. Subject has acute limb ischemia.

CE2. Subject underwent intervention involving the target vessel within the previous 90 days.

CE3. Subject underwent any lower extremity percutaneous treatment in the ipsilateral limb using a paclitaxel-eluting stent or a DCB within the previous 90 days.

CE4. Subject underwent PTA of the target lesion using a DCB within the previous 180 days.

CE5. Subject has had prior vascular intervention in the contralateral limb within 14 days before the planned index procedure or subject has planned vascular intervention in the contralateral limb within 30 days after the index procedure.

CE6. Women who are pregnant, breast-feeding or intend to become pregnant or men who intend to father children during the time of the study.

CE7. Subject has life expectancy of less than 2 years.

CE8. Subject has a known allergy to contrast medium that cannot be adequately pre-medicated.

CE9. Subject is allergic to ALL antiplatelet treatments.

CE10. Subject has impaired renal function (i.e. serum creatinine level ≥2.5 mg/dL).

CE11. Subject is dialysis dependent.

CE12. Subject is receiving immunosuppressant therapy.

CE13. Subject has known or suspected active infection at the time of the index procedure.

CE14. Subject has platelet count <100,000/mm^3 or >700,000/mm^3.

CE15. Subject has history of gastrointestinal hemorrhage requiring a transfusion within 90 days prior to the index procedure.

CE16. Subject is diagnosed with coagulopathy that precludes treatment with systemic anticoagulation and/or DAPT.

CE17. Subject has history of stroke within the past 90 days.

CE18. Subject has a history of myocardial infarction within the past 30 days.

CE19. Subject is unable to tolerate blood transfusions because of religious beliefs or other reasons.

CE20. Subject is incarcerated, mentally incompetent, or abusing drugs or alcohol.

CE21. 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.

CE22. 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.

CE23. Subject had previous bypass surgery of the target lesion.

CE24. Subject had previous treatment of the target vessel with thrombolysis or surgery.

CE25. 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.

8.1.3 Angiographic Inclusion Criteria

The target lesion/vessel must meet **all** the following angiographic criteria to participate in the trial.

AI1. *De novo* lesion(s) or non-stented restenotic lesion(s) occurring >90 days after prior POBA angioplasty or >180 days after prior DCB treatment.

AI2. 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.

AI3. Target vessel diameter ≥4 mm and ≤7 mm

AI4. Target lesion must have angiographic evidence of ≥70% stenosis by operator visual estimate.

AI5. 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.

AI6. 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.

AI7. Target lesion is located at least 30 mm from any stent, if target vessel was previously stented

AI8. 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.

AI9. After pre-dilatation, the target lesion is ≤70% residual stenosis, absence of a flow limiting dissection and treatable with available device matrix.

AI10. A patent inflow artery free from significant stenosis (≥50% stenosis) as confirmed by angiography.

AI11. At least one patent native outflow artery to the ankle or foot, free from significant stenosis (≥50% stenosis) as confirmed by angiography.

8.1.4 Angiographic Exclusion Criteria

Subjects will be excluded from the trial if the target lesion/vessel meets **any** of the following angiographic criteria:

AE1. Target lesion has severe calcification (as defined by the PARC classification of calcification).

AE2. Target lesion involves an aneurysm or is adjacent to an aneurysm (within 5 mm).

AE3. Target lesion requires treatment with alternative therapy such as stenting, laser, atherectomy, cryoplasty, brachytherapy, or re-entry devices.

AE4. Significant target vessel tortuosity or other parameters prohibiting access to the target lesion.

AE5. Presence of thrombus in the target vessel.

AE6. 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.

AE7. Presence of an aortic, iliac or femoral artificial graft.

9. Study Procedures

9.1 Schedule of Events

Table 3. Schedule of Events

Study Requirement (Visit Window)	**Screening/ Baseline** (Within 14 Days Prior to Procedure)	**Index Procedure to Discharge** (Day 1)	**1 Month** (Day 30, -2 to +15 Days)	**6 Months** (Day 180 ±30 Days)	**12 Months** (Day 365 ±30 Days)	**24 Months** (Day 730 ±60 Days)	**36 Months**[1] (Day 1095 ±60 Days)	**48 Months**[1] (Day 1460 ±60 Days)	**60 Months**[1] (Day 1825 ±60 Days)	**Unscheduled Visit(s)**[6]
Contact Type	Office Visit		Office Visit	Office Visit	Office or Telephone Visit	Office or Telephone Visit	Telephone or Office Visit	Telephone or Office Visit	Telephone or Office Visit	Office Visit
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Physical Exam[2]	X		X	X	X	X				X
Medications	X	X	X	X	X[10]	X[10]	X	X	X	X
Target Limb Resting ABI (TBI if ABI can't be assessed)	X[3]			X	X	X				X
Rutherford Classification	X		X	X	X[12,10]	X[12,10]				X
PARC Classification	X		X	X	X[10]	X[10]				X
Pregnancy Test[4]	X									
CBC	X		X							
Comprehensive Metabolic Panel[5]	X		X							
PAQ	X		X		X[10]	X[10]				X

Study Requirement (Visit Window)	**Screening/ Baseline** (Within 14 Days Prior to Procedure)	**Index Procedure to Discharge** (Day 1)	**1 Month** (Day 30, -2 to +15 Days)	**6 Months** (Day 180 ±30 Days)	**12 Months** (Day 365 ±30 Days)	**24 Months** (Day 730 ±60 Days)	**36 Months**[1] (Day 1095 ±60 Days)	**48 Months**[1] (Day 1460 ±60 Days)	**60 Months**[1] (Day 1825 ±60 Days)	**Unscheduled Visit(s)**[6]
WIQ	X		X		X[10]	X[10]				X
6-MWT	X				X	X				X
Angiogram		X								X[7]
Randomization		X								
DUS			X[8]		X[9]	X[9]				X
AE/SAE Collection[11]	X	X	X	X	X[10]	X[10]	X	X	X	X

Abbreviations: 6-MWT, 6-minute walk test; ABI, ankle brachial index; AE, adverse event; CBC, complete blood count; PAQ: peripheral artery questionnaire; PARC, Peripheral Academic Research Consortium; SAE, serious adverse event; DUS, duplex ultrasound; WIQ, walking impairment questionnaire.

[1] The 36-, 48-, and 60-month visits may be conducted via a telephone call or at the clinic.
[2] Physical exam (PE) includes weight, height, blood pressure, target limb examination at Baseline/Screening. PE includes exam of access site and target limb at 1 Month. PE includes clinical assessment of target limb for 6, 12, and 24 Months and Unscheduled Visits.
[3] Target limb resting ABI or TBI may be collected up to 90 days prior to the index procedure, provided that there is no change in the subject's clinical symptoms between the ABI/TBI assessment and the baseline visit. If there is a change in the subject's clinical symptoms, the target limb ABI/TBI must be reassessed. ABI or TBI collected as standard of care prior to informed consent may be utilized.
[4] For women of childbearing potential only, per standard of care.
[5] Comprehensive metabolic panel includes kidney and liver function tests.
[6] An unscheduled visit is any visit that is for an ischemic event of the target limb.
[7] Angiogram to be performed only if re-intervention is deemed necessary from clinical symptoms.
[8] 30-Day DUS is intended to establish a post-treatment baseline and help to inform the primary endpoint assessment.
[9] A mobile DUS may be performed.
[10] When conducting a telephone visit, these assessments will be performed.
[11] All AEs (serious and non-serious) will be recorded for the entire study period to the extent required by national and/or local requirements. For United States sites only: After the 12-month visit, ongoing AEs will be followed through to resolution or until the event becomes stable, and only SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.
[12] When conducting a telephone visit, Target limb Rutherford Classification without the use of treadmill may only be performed. If a treadmill has been previously used in the assessment, it must consistently be used throughout the study and therefore would require an office visit.

9.2 Informed Consent

Subjects are to be consented prior to initiating any study-specific procedures that are not considered routine standard of care. The investigator or site personnel, who has been trained on the protocol, will approach individual subjects who are potential candidates for participation. She or he will explain the nature and scope of the study, the procedures to be performed as part of the study, the potential risks and benefits of participation, and will answer questions for the candidate. The study will be explained to the subject in lay terms and adequate time will be allowed for the subject to ask questions. Interested subjects will be invited to participate in the trial and will be asked to provide written informed consent prior to initiation of any trial-related procedure. Subjects will be assured that they may withdraw from the study at any time and for any reason, without repercussion. If the subject agrees to participate, the informed consent must be signed and dated by the subject or their legally authorized representative and by the person who obtained the informed consent. If a participant requires a translated consent, the Ethics Committee (EC) or Institutional Review Board (IRB) policies will apply to the informed consent process. Any additional persons required to sign the informed consent by the local EC/IRB will also do so.

The informed consent form that is used must be approved by the EC/IRB. A dated and signed copy of the informed consent form will be given to the subject or their legally authorized representative and a dated and signed copy will be placed in the research folder.

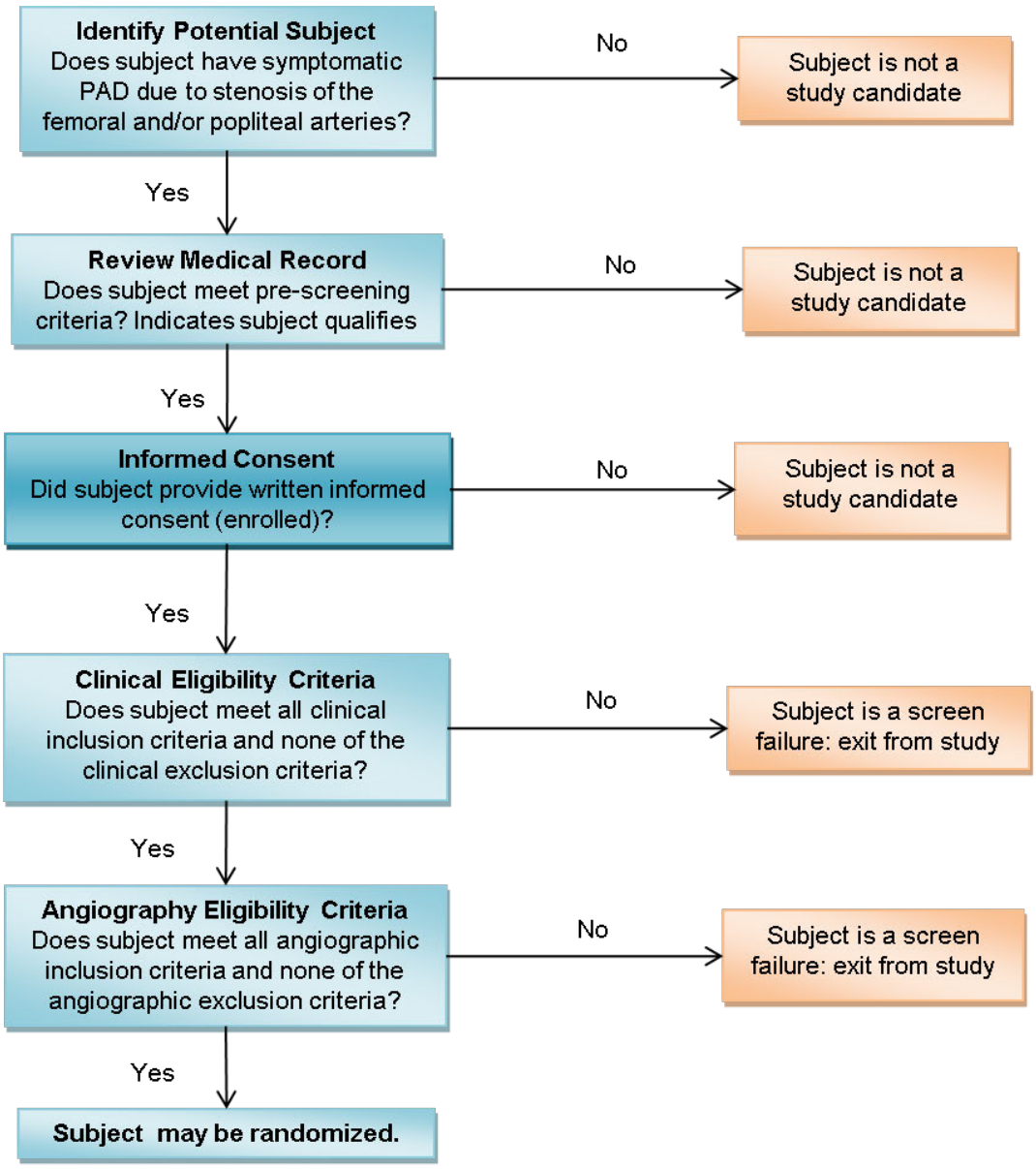
Failure to obtain a signed and dated informed consent form prior to the procedure constitutes a protocol violation, which must be reported in accordance with all applicable regulations.

9.3 Enrollment

Eligible subjects will be enrolled consecutively at each investigative site in this study. **A subject is considered to be enrolled after she or he has signed the informed consent form**. Enrolled subjects who met all the clinical inclusion criteria and none of the clinical exclusion criteria will then be evaluated for angiographic eligibility criteria. If an enrolled subject fails any of the clinical or angiographic eligibility criteria, the investigative site research staff will enter information into the electronic data capture (EDC) system to document this; the subject will be considered a screen failure, will not be randomized, will be exited from the study, and will be followed per site standard of care. Subjects who do not fail the angiography eligibility criteria may be randomized: once angiography is complete and the investigator is satisfied that the subject has met all of the trial eligibility criteria, he/she may then randomize the subject.

Figure 2 depicts subject status:

Figure 2. Subject Status



9.4 Screening/Baseline (Up to 14 Days Prior to Procedure)

As specified in Section 9.2, signed written informed consent must be obtained for all subjects who are potential trial candidates prior to provisional enrollment. Adverse event (AE)/serious adverse event (SAE) collection must begin after the subject has signed the consent form. Additionally, the following evaluations must be completed for all enrolled subjects prior to the procedure, unless otherwise specified:

Within 14 Days Prior to the Trial Procedure:

- Confirmation of clinical eligibility criteria

- Demographics, including date of birth or age at time of procedure, gender, and race/ethnicity (as allowed per local regulations)
- Medical history (general medical, cardiac, peripheral vascular, neurologic and renal history), including, but not limited to, the following:
    - Risk factors (e.g. dyslipidemia, hypertension, diabetes mellitus, tobacco use)
    - Cardiovascular history (e.g. prior myocardial infarction, prior percutaneous coronary intervention, history of congestive heart failure)
    - History of peripheral vascular disease (e.g. prior interventions, stroke, transient ischemic attack)
- Physical examination, including weight, height, blood pressure, target limb examination
- Target limb Rutherford classification
- Target limb PARC classification
- Resting ABI or TBI (see section 9.9.4 for details). Note that resting ABI or TBI may be obtained up to 90 days prior to the index procedure, provided there must be no significant clinical change in the subject's status between the ABI/TBI assessment and the index procedure. If there is a significant change, defined as a change in clinical symptoms, the ABI/TBI must be reassessed. See Appendix B for definition of significant clinical change.
- WIQ
- 6-MWT
- PAQ
- Laboratory tests
    - Complete blood count (CBC); differential is also required if the white blood cell count is NOT within normal limits
    - Comprehensive metabolic panel (that includes kidney and liver function tests)
    - Pregnancy test for women of child-bearing potential with analysis per standard of care (serum and/or urine)
- Adverse event (AE)/serious adverse event (SAE) assessment
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

9.5 Procedure (Day 1)

9.5.1 Subject Preparation and Baseline Angiography

The subject must have met all clinical inclusion and none of the exclusion criteria, including confirmation of all laboratory results, prior to proceeding with the index procedure. Subject preparation and percutaneous access should be performed according to the standard hospital care unless otherwise specified in this investigational plan. The procedure begins once percutaneous access has been established. Standard PTA balloons should be used for pre-dilatation. Use of embolic capture angioplasty balloons or cutting/scoring balloons and atherectomy devices is not allowed. The appropriate size of the balloon to be used should be selected by visual assessment.

Baseline angiography of the vessel(s) will be performed as per the angiographic core laboratory procedure guidelines to characterize the target lesion and to confirm angiographic eligibility criteria. Because the lesion location must start ≥10 mm below the common femoral bifurcation (and terminate distally at or above the end of the P1 segment of the popliteal artery), the common femoral artery cannot be treated. Assessment of angiographic eligibility criteria is based on a visual assessment of the angiogram and/or QA. All angiograms, either digital subtraction angiography or cineangiography, will be submitted to an independent angiographic core laboratory for analysis. Angiograms should be captured before and during the index procedure, and at any unscheduled interventions. Care should be taken to utilize the same angles and views for all angiographic assessments. All angiograms should be submitted as soon as possible to the angiographic core laboratory for analysis per the core laboratory guidelines.

9.5.2 Inflow Lesion Treatment

In order to be randomized, the subject must have a patent inflow artery free from significant stenosis (≥50% stenosis) as confirmed by angiography. Subjects can be randomized after successful treatment of inflow stenosis per standard practice; there is no limit to the number of inflow lesions that can be treated. Successful treatment is defined as ≤30% residual stenosis without death or major vascular complications.

9.5.3 Target Lesion Pre-Dilatation

Refer to the SurVeil DCB and IN.PACT Admiral DCB Instructions for Use (IFU) for detailed pre-dilatation requirements. Pre-dilatation of the target lesion with an uncoated PTA catheter is required for both the SurVeil and IN.PACT Admiral DCBs. The uncoated PTA catheters should have a diameter that is 1mm less than RVD. The length of the uncoated PTA catheter should approximate the length of the lesion. This is in order to limit vessel injury outside the boundaries of the target lesion and prevent “geographic miss” where the pre-dilation balloon

treated area is outside of the DCB treated area. The DCB must be longer than the uncoated PTA catheter that was used.

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.

9.5.4 Randomization

Subjects will be randomized in a 1:1 fashion via the EDC to either the SurVeil DCB or the IN.PACT Admiral DCB.

Prior to randomization, the investigative site should verify that the appropriate sizes of both the IN.PACT Admiral and SurVeil products are available for use in the subject. Each subject will receive one unique randomization number associated with a randomization assignment allocated via EDC. 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.

9.5.5 Subjects Not Randomized

A subject who was enrolled but not randomized due to not meeting all of the eligibility criteria (either clinical or angiographic) will be treated per the investigative site's standard of care. The appropriate electronic case report form (eCRF) should be filled out to indicate that this subject has been exited from the study.

9.5.6 Treatment with the SurVeil DCB or IN.PACT Admiral DCB

Refer to the appropriate device (SurVeil DCB or IN.PACT Admiral DCB) IFU for detailed information on use of the particular device. The investigator should determine the appropriate size DCB based on visual estimate and/or QA and plan to use a maximum of 2 SurVeil DCBs.

DCB sizing must match the RVD and fully cover and extend slightly beyond the lesion length. The operator should not plan to use more than two study devices to treat a single target lesion during the procedure. The investigator should determine the appropriate size of the balloon(s) to be used as follows:

- The nominal DCB diameter must match the RVD distal to the target lesion.
- The nominal DCB length must cover the entire target lesion or area treated by the pre-dilatation balloon 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. The additional DCB should be angiographically positioned to ensure coverage of at least 5 mm proximally and distally beyond the margins of the pre-dilatation lesion.

The balloon to artery ratio must be 1.1:1.

Use a radiopaque ruler to ensure appropriate placement of the DCB catheter. The device(s) should cover the entire lesion.

Balloon inflation pressure should be at or beyond the nominal pressure. Do not exceed rated burst pressure.

The DCB(s) (SurVeil or IN.PACT Admiral) should be inflated for a minimum of 120 seconds to achieve the desired dilatation. If additional dilatation is required, a standard PTA catheter should be used.

If a SurVeil DCB is opened but not used, or if a device deficiency or malfunction occurs during its use, it must be returned to Surmodics or its designee in accordance with the packaging and shipping instructions. The Sponsor is responsible for device deficiencies reporting of the SurVeil DCB to all concerned National Competent Authorities of the EU according to national regulations and in line with MEDDEV 2.7/3 revision 3, May 2015.

9.5.7 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.

Bailout stenting is allowed if:

- residual stenosis is ≥50% (based on in-lab review of angiograms with/without QA) or
- major (≥Grade D) flow-limiting dissection confirmed by a peak translesional systolic pressure gradient >10 mmHg.

If bailout stenting is required per either of the above criteria, the investigator should treat the patient per standard of care including use of a superficial femoral artery (SFA)-indicated bare nitinol stent. The size of the stent should be as short as possible in order to cover the dissection or focal area of residual stenosis and not to cover the entire lesion with the bailout stent. During angiography, care should be taken to utilize the same angles and views that were used during the baseline and DCB procedures.

All subjects who undergo a bailout procedure, including emergency surgery, are required to be followed per the protocol follow-up schedule. These subjects will be included in all study analyses. Any complication leading to a bailout procedure is considered an AE in this study, or an SAE based on the seriousness of the event (see Section 12.3.1).

9.5.8 End of Procedure

Angiography of the vessel(s) must be performed per angiographic core lab guidelines and in the same views that were taken at baseline. FDA-approved/CE-marked closure devices are

allowed. The end of the procedure is defined as the time the guide catheter is removed from the subject. If the subject is returned to the procedure room and a guiding catheter is reinserted and a dilatation is performed, this should be considered a repeat intervention. Please see Section 9.8 for Medication Regimen information.

9.6 Follow-Up Visits

All follow-up visits in the study will be completed per the schedule of events (See Table 3.) including the required exams and assessments at the specified timepoints after the index procedure.

9.6.1 Exceptions for the 12-month and 24-month Follow-up Visits

If travel restrictions and limitations on personal contact with study subjects are due to the Coronavirus pandemic (COVID-19), exceptions will be made to the protocol. This includes a telephone call to the study subject instead of an in-office visit at the time of the 12-month and/or 24-month follow-up visit. Mobile duplex ultrasound (DUS) examinations will also be available during these visits. However, efforts should continue to obtain an in-office visit to perform all of the protocol-required exams and procedures (See Table 3 Schedule of Events) at the earliest opportunity for the investigational site and study subject.

9.6.2 1-Month Visit (30 Days, -2 to + 15 Days)

Subjects will be evaluated at 1-month post-procedure (30 days -2 to +15 days) by an office visit. Evaluations at 1 month include:

- Physical exam includes an examination of the access site and the target limb.
- DUS (the clinical status of the subject should be established prior to performing the DUS)
- CBC; differential is also required if the white blood cell count is NOT within normal limits
- Comprehensive metabolic panel (that includes kidney and liver function tests)
- Target limb Rutherford Classification
- Target limb PARC classification
- WIQ
- PAQ
- AE/SAE assessment
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

9.6.3 6-Month Visit (180 Days +/- 30 Days)

Subjects will be evaluated at 6 months post-procedure (180 days ± 30 days) by an office visit. Evaluations at 6 months include:

- Physical exam includes an examination of the target limb
- Target limb Rutherford classification
- Target limb PARC classification
- Target limb resting ABI or TBI (see section 9.9.4 for details)
- AE/SAE assessment
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

9.6.4 12-Month Visit (365 Days +/- 30 Days)

Subjects will be evaluated at 12 months post-procedure (365 days ± 30 Days) by an office or telephone call visit. Office visit evaluations at 12 months include:

- Physical exam includes an examination of the target limb
- DUS (the clinical status of the subject should be established prior to performing the DUS)
- Target limb Rutherford classification
- Target limb PARC classification
- Target limb resting ABI or TBI (see section 9.9.4 for details)
- WIQ
- PAQ
- 6-MWT
- AE/SAE assessment
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

  Note: For telephone call visit, see Table 3 for Schedule of Events for exams and assessments to be performed.

9.6.5 24-Month Visit (730 Days +/- 60 Days)

Subjects will be evaluated at 24 months post-procedure (730 days ± 60 days) by an office or telephone call visit. Office visit evaluations at 24 months include:

- Physical exam includes an examination of the target limb
- DUS (the clinical status of the subject should be established prior to performing the DUS)
- Target limb Rutherford classification
- Target limb PARC classification
- Target limb resting ABI or TBI (see section 9.9.4 for details)
- WIQ
- PAQ
- 6-MWT
- AE/SAE assessment* (All AEs and SAEs will be recorded for the entire study period to the extent required by national and/or local requirements. For United States sites only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable, and only new SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.)
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

  Note: For telephone call visit, see Table 3 for Schedule of Events for exams and assessments to be performed.

9.6.6 36-Month Visit (1095 Days +/-60 Days)

The 36-month visit may be performed via a telephone call with the subjects. Evaluations at 36 months post-procedure (1095 days ± 60 days) include:

- AE/SAE assessment (All AEs and SAEs will be recorded for the entire study period to the extent required by national and/or local requirements. For United States sites only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable, and only new SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.)
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

9.6.7 48-Month Visit (1460 Days +/-60 Days)

The 48-month visit may be performed via a telephone call with the subjects. Evaluations at 48 months post-procedure (1460 days ± 60 days) include:

- AE/SAE assessment (All AEs and SAEs will be recorded for the entire study period to the extent required by national and/or local requirements. For United States sites

only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable, and only new SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.)
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

9.6.8 60-Month Visit (1825 Days +/-60 Days)

The 60-month visit may be performed via a telephone call with the subjects. Evaluations at 60 months post-procedure (1825 days ± 60 days) include:

- AE/SAE assessment (All AEs and SAEs will be recorded for the entire study period to the extent required by national and/or local requirements. For United States sites only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable, and only new SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.)
- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications

9.7 Unscheduled Visits

Any visit that is for an ischemic event of the target limb should be classified as an unscheduled visit.

The following assessments should be performed at unscheduled visits:

- Physical exam (assessment of the target limb).
- DUS (the clinical status of the subject should be established prior to performing the DUS) per core laboratory guidelines. All images should be submitted to the core laboratory as soon as possible.
- Target limb Rutherford classification
- Target limb PARC classification
- Target limb resting ABI or TBI
- WIQ
- PAQ
- 6-MWT
- AE/SAE assessment (All AEs and SAEs will be recorded for the entire study period to the extent required by national and/or local requirements. For United States sites only: After the 12-month follow-up visit, continuing AEs will be followed through to

resolution or until event becomes stable, and only new SAEs, including PARC MAEs, Historical MAEs, and clinical study endpoints, will be recorded.)

- Current medication regimen including anti-platelet/anti-coagulant, and paclitaxel-related medications
- Angiography is to be performed **only if re-intervention is deemed necessary from clinical symptom**s: If the subject undergoes a catheterization, all procedural angiograms should be recorded at the same angles and views as taken during the index procedure, where possible. All images should be taken per core laboratory guidelines and should be submitted to the core laboratory as soon as possible.

9.8 Medication Regimen

Unless clinically contraindicated, all subjects should receive the medication regimen listed in **Table 4**. All cardiovascular and diabetic medications administered (including use of antiplatelet/anti-coagulant therapy) should be recorded in the eCRF from 24 hours pre-procedure through the 12-month follow-up assessment. Use of antiplatelet/anticoagulant therapy and paclitaxel-related medications will be recorded throughout the full follow-up period.

Table 4. Medication Regimen

Timing	Medication	Regimen
Prior to Procedure	Acetylsalicylic acid (aspirin)	75-325 mg daily (within 24 hours prior to procedure).
	Clopidogrel or Prasugrel/Ticagrelor	Loading dose of 300 mg within 24 hours prior to index procedure or immediately post-procedure (within 30 minutes). No loading dose required for subjects on clopidogrel therapy (subject has taken three or more 75-mg doses of clopidogrel within 72 hours prior to procedure). Subjects on prasugrel or ticagrelor therapy (e.g. if subject is allergic to or intolerant of clopidogrel, or with prior cardiac indication for one of these medications) within 24 hours are not required to receive a loading dose.
During Procedure	Heparin	Per routine hospital practice, it is recommended to maintain activated clotting time of ≥250 seconds (or ≥200 seconds if a glycoprotein IIb/IIIa receptor blocker is administered) throughout the interventional portion of the procedure.

	Glycoprotein IIb/IIIa Inhibitor	At investigator's discretion.
	Bivaliruden	At investigator's discretion.
Post-Procedure[1]	Acetylsalicylic acid (aspirin)	75-100 mg daily indefinitely.
	Clopidogrel or Prasugrel/Ticagrelor	75 mg per day for a minimum of 1 month. For subjects on chronic prasugrel or ticagrelor therapy, post-procedure treatment with the same agent (5 mg or 10 mg prasugrel daily **or** 90 mg ticagrelor twice daily) is allowed for a minimum of 1 month.

[1] In cases where a stent is placed (bailout stenting), please refer to the stent manufacturer's Instructions for Use for dosing instructions

9.9 Imaging and Other Clinical Assessments

9.9.1 Angiogram

All angiograms will be performed per angiographic core lab guidelines. Care should be taken to utilize the same angles and views that were assessed at baseline for all subsequent assessments.

9.9.2 Duplex Ultrasound (DUS)

All DUS will be performed by personnel who have been trained on the protocol and also on the DUS core laboratory guidelines. The quality of the DUS images are critical for assessing study endpoints. The DUS core laboratory will be monitoring images closely during the duration of the study to ensure DUS images are captured correctly.

9.9.2.1 Mobile Duplex Ultrasound

If the investigational site is interested in using mobile duplex ultrasound as an option to obtain DUS exams for subjects who are not able to attend an in-office visit, a third party mobile diagnostic company has been contracted by the sponsor. (United States sites only). Subjects will be reconsented per local IRB requirements prior to obtaining the mobile DUS exam. Mobile DUS technicians will be qualified and trained on the study to perform the DUS exams according to the imaging protocol. The DUS exam images and completed worksheets will be provided to the specific investigational site and to the DUS Core Lab. The DUS core lab will review and interpret the DUS images.

9.9.3 Target Limb Rutherford and PARC Evaluations

Target limb Rutherford classification and target limb PARC classification can be determined with or without a treadmill, but at a minimum, each subject should have the evaluations performed in the same manner over the course of the entire study. For example, if a treadmill is used for the baseline visit Rutherford and PARC evaluations for a subject, a treadmill should then be used for all subsequent Rutherford and PARC evaluations for that same subject.

Exception: When conducting a telephone visit, Target limb Rutherford Classification without the use of treadmill may only be performed. If a treadmill has been previously used in the assessment, it must consistently be used throughout the study and therefore would require an office visit.

9.9.4 Ankle Brachial Index

A resting ABI should be performed on the target limb per hospital standard practice. If an ABI cannot be assessed, a TBI can be used. If a TBI is used, future visits will need to have a TBI recorded as well.

9.9.5 6-Minute Walk Test, Walking Impairment Questionnaire, and Peripheral Artery Questionnaire

The 6-MWT, WIQ, and PAQ will be performed for each subject.

10. Blinding Plan

In this single-blind study, all randomized subjects will be blinded.

All core laboratory personnel (DUS, angiogram), all members of the Clinical Events Committee (CEC), and a study statistician will be blinded to the subject's treatment.

11. Subject Accountability and Withdrawal

11.1 Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the study personnel or institution. If a subject decides to withdraw, they will be asked to participate in a limited capacity by allowing their medical status to be followed by telephone contact, medical chart review, or by other agreed upon method. If a subject decides not to continue participation in a limited capacity, all study tests and procedures will be stopped and an inquiry will be made about the cause of withdrawal; however, study data collected prior to their withdrawal may be reviewed and publicly available records may be consulted prior to or after withdrawal.

The investigative site must account for and document all subjects enrolled in the study, including those withdrawn from the study or lost to follow-up. All subjects will be encouraged to remain in the trial through 60 months. If a subject withdraws from the clinical investigation, the reason(s) shall be reported on the eCRF.

Reasons for withdrawal include, but are not limited to:

- Subject does not receive a device
- Physician discretion
- Subject choice to withdraw consent
- Loss to follow-up
- Death

Randomized subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total trial subjects. Additional study data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent. Data collected up to the point of subject withdrawal will be used for analysis. If a subject withdraws due to medical safety considerations because of an AE, the AE must be followed by medical attention to satisfactory resolution and all study data related to the subject will be reported.

11.2 Loss to Follow-Up

A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include 3 attempts to make contact with the subject (or their legally authorized representative) via telephone and if contact via telephone is not successful, a certified letter from the investigator must be sent to the subject's last known address. Should both telephone and mail efforts to contact the subject be unsuccessful, the subject's primary physician should be contacted. All contact efforts to obtain follow-up information must be documented in both the subject's medical records and on the eCRFs. Subjects are not eligible to be exited as lost to follow-up until after the 12-month follow-up visit. After the 12-month follow-up visit, if a minimum of two consecutive study visits have been missed, after making two attempts by phone and one by certified mail at each time point, lost to follow-up may be an acceptable reason for exit.

12. Adverse Events

Starting at the time of informed consent signing and at each subsequent evaluation (scheduled or unscheduled), the investigator will determine if any AEs have occurred in any subject. Subjects are encouraged to report AEs freely or in response to general, non-directed questioning. The subject may volunteer information that appears to be an AE anytime during

the study. If an AE is determined to have occurred, the investigator should obtain all the required information and document findings on the eCRF.

12.1 Adverse Event Definitions

12.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: Abnormal laboratory findings will be considered AEs, only if determined by the investigator to be clinically significant

NOTE 4: For users or other persons, this definition is restricted to events related to investigational medical devices.

Any current condition that is recorded as a pre-existing condition in the physical examination section, unless there is a change in nature, severity, or degree of incidence, is not an AE.

All AEs will be followed until the event becomes stable or through to resolution, independent of duration or follow-up window.

12.1.2 Serious Adverse Event (SAE)

A SAE is an AE that leads to:

1. Death
2. A serious deterioration in the health of the subject that either resulted in:
    a. life-threatening illness or injury or
    b. a permanent impairment of a body structure or a body function or
    c. in-patient hospitalization or prolongation of existing hospitalization or
    d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
3. Fetal distress, fetal death, or congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. A planned

hospitalization is one that is scheduled prior to the subject signing the informed consent for the study.

SAEs include device deficiencies that might have led to an SAE if

a. suitable action had not been taken or
b. intervention had not been made or
c. circumstances had been less fortunate. These are handled under the SAE reporting system.

Please note, any investigational device deficiencies must be reported to Baim Institute for Clinical Research.

12.1.3 Adverse Device Effect (ADE)

An adverse device effect (ADE) is an AE that is related to the investigational medical device.

NOTE 1: This definition includes AEs resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event that is a result of a use error or from intentional abnormal use of the investigational medical device.

12.1.4 Anticipated Adverse Event

Any undesirable health related experience occurring to a subject whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the clinical protocol, predefined in the clinical protocol and/or IFU that is identified or worsens during a clinical study. Anticipated AEs are identified in the IFU and can be found in Section 14.2.

12.1.5 Device Deficiency, Device Malfunction & User Error

The investigators are instructed to report all device deficiencies, device malfunctions and user errors during the study. The following are the descriptions of each instance:

Device Failure: A device failure occurs when the device is used in compliance with the IFU, but does not perform as described in the IFU and also negatively impacts treatment of the study subject

Device Deficiency (ISO14155:2011): Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequate labeling.

Device Malfunction (ISO 14155:2011): Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or clinical study protocol.

Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1: Use error includes slips, lapses, and mistakes.

NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

12.1.6 Serious Adverse Device Effect (SADE)

An SADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

12.1.7 Unanticipated Adverse Device Effect (UADE) and Unanticipated Serious Adverse Device Effect (USADE)

12.1.7.1 UADE per the United States Code of Federal Regulations (CFR)

Pertinent to investigative sites conducting this study within the United States: An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

12.1.7.2 USADE per the International Organization for Standardization (ISO)

Pertinent to investigative sites conducting this study outside the United States: An unanticipated serious adverse device effect (USADE) is defined in ISO14155:2011 3.42 as "Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

12.2 Adverse Event Documentation

All AEs must be documented on the appropriate eCRF and will be characterized by the following criteria:

- Seriousness
- Intensity or Severity

- Relatedness to device and procedure
- Outcome
- Treatment or action taken

All AEs (serious and non-serious) will be reported for the entire study period to the extent required by national and/or local requirements. For United States investigative sites only: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable, and only SAEs, including Historical MAEs, and clinical study endpoints, will be recorded.

12.2.1 Intensity or Severity

The intensity or severity or each AE, as assessed by the investigator, will be recorded using the following definitions:

Mild	Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with a subject's usual activity, but the subject is still able to function
Severe	Events that interrupt a subject's usual daily activity and generally require a systemic drug therapy or other treatment

12.2.2 Relatedness to Study Device or Procedure

The investigator will evaluate if the AE or SAE is related to the investigational device or study procedure. The investigator will use the following definitions for this assessment:

Table 5. Adverse Event Relatedness Categories

Not Related	Relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to, or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body site or an organ not expected to be affected by the device or procedure;

	• the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that- o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

12.2.3 Outcome/Event Status

The clinical outcome of the AE or SAE at the time of the last observation will be characterized as follows:

- Recovered/resolved
- Recovered/resolved with sequelae
- Ongoing
- Death

12.3 Adverse Event Reporting

12.3.1 Serious Adverse Events

Reporting of SAEs includes reporting of any SAE, any investigational medical device deficiency that might have led to an SAE and any new finding/update in relation to already reported events.

It is the responsibility of each investigator to report all SAEs to the sponsor or its designee within 24 hours using the appropriate eCRF, and in accordance with applicable national regulations. Report of a subject death must be submitted using the eCRF along with a brief statement of the pertinent details, and the death records/certificate or autopsy report, if available/performed. Every effort should be made to report the SAEs leading to the subject death using the eCRF.

The Sponsor or its designee will evaluate the SAE for UADE and perform analysis of the event. The Sponsor or its designee will prepare the safety documentation to be submitted to investigators, National/local regulatory authorities, and IRB/ECs according to national/local regulations and IRB/EC requirements.

12.3.2 Unanticipated Adverse Device Effects

If a complication occurs that the site investigator believes may be a potential UADE, the site should immediately contact the sponsor or its authorized representative to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a subject, the site should immediately notify the sponsor.

The site investigator shall submit to the sponsor or its authorized representative a report of any UADE occurring during an investigation as soon as possible, but in no event later than 24 hours after the Investigator first learns of the effect. All UADEs must be documented by the site investigator including the date of onset, a complete description of the event, causality assessment, possible reason(s) for the event, severity, duration, actions taken, and outcome.

Copies of all supporting documents should be submitted concurrently with the SAE via the eCRF.

A report from the Sponsor will be submitted to the National/local regulatory authorities and to all reviewing IRB/ECs and participating Investigators. Reports will be submitted to the National/local regulatory authorities within 10 working days after the Sponsor first receives notice of the effect. The Sponsor will submit other reports as required by the National/local regulatory authorities.

12.3.3 Notification of Events

Table 6. Investigator Reporting Responsibilities

Type of Report/Event	Prepared by Investigator for	Time of Notification
• Serious adverse event (SAE) • Serious adverse device effect (SADE) • Unanticipated adverse device effect (UADE)	Sponsor (or designee)	**Written** –As soon as possible, but no later than 24 hours after investigator is first aware of the event.
Withdrawal of IRB approval or other action on part of the IRB that affects the study	Sponsor (or designee)	**Written** – Within 5 working days of IRB decision.
Progress Reports	IRB	At regular intervals, but in no event less than annually.
Progress Reports	EC	As required per National/local regulations
Deviations from investigational plan	Sponsor (or designee) and IRB/EC	**Emergency** – As soon as possible, but no later than 5 working days after the deviation occurs. **Non-emergency** – Prior approval by Sponsor and if deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, IRB/EC, National/local regulatory authorities, and FDA as an IDE supplement.
Inappropriate informed consent	Sponsor (or designee) and IRB/EC	Within 5 working days of use of the investigational device.
Device Deficiency, Device Malfunction or User Error	Sponsor (or designee) and IRB/EC	Within 5 working days.
Other	As required	Upon request by the IRB/EC or FDA/National/local regulatory authorities, provide accurate, complete, and current information about any aspect of the study.

It is understood that complete information about an event may not be known at the time the initial report is submitted. The investigator must assess, to the best of their ability, the relationship of the event to the study device and should make every attempt to obtain as much information as possible concerning the event. Additional information pertaining to an event to be reported within 24 hours of becoming aware of the event should be submitted to the Baim Institute for Clinical Research as it becomes available.

Table 7. Sponsor Reporting Responsibilities

Type of Report/Event	Prepared by Sponsor for	Time of Notification
Unanticipated adverse device effect (UADE)	Investigators	**Written** - Within 10 Calendar Days, or as required by National/local regulations
Unanticipated adverse device effect (UADE)	National/local regulatory authorities and IRB/EC	**Written** - Within 10 Working Days, or as required by National/local regulations
Withdrawal of IRB/EC approval or other action on part of the IRB/EC that affects the study	Investigators and National/local regulatory authorities	**Written** – Within 5 working days, or as required by National/local regulations
Withdrawal of FDA/Competent Authority approval	Investigators, IRB/EC, and National/local regulatory authorities	**Written** – Within 5 working days, or as required by National/local regulations
Device Recall	Investigators and National/local regulatory authorities	**Written** – Within 30 working days, or as required by National/local regulations
Progress Reports	Investigators and National/local regulatory authorities	**Written** – At regular intervals, but in no event less than annually.
Inappropriate Informed Consent	National/local regulatory authorities	**Written** – Within 5 working days of notification, or as required by National/local regulations
Study Closure	Investigators and National/local regulatory authorities	**Written** – Within 10 working days of completion or termination of study, or as required by National/local regulations
Final Report	Investigators and National/local regulatory authorities	**Written** – Within 6 months of study closure, or as required by National/local regulations

13. Study Committees

13.1 Data Monitoring Committee (DMC)

[redacted] The Committee will include a biostatistician and physicians independent from the trial with expertise in vascular surgery and vascular intervention.

The DMC will be responsible for monitoring the trial performance and the safety of enrolled subjects. Prior to the start of subject enrollment, the Committee will approve a DMC Charter and Standard Operating Procedures (SOPs). The Committee will meet on a schedule and with a frequency necessary to support the DMC's safety review function and will review trial performance and safety data on a regular schedule and on an as-needed basis if necessary, and make any recommendations it thinks appropriate to the Sponsor and to the Steering Committee regarding modification or early termination of the trial. All final decisions, however, regarding trial modifications, rest with Surmodics, as advised by the Steering Committee. No formal statistical rule for stopping the trial will be defined in this trial and no formal interim analysis is planned. Meeting outcomes will be documented in the resulting letter of recommendation from the DMC, and noted in the IDE annual progress reports.

13.2 Clinical Events Committee (CEC)

CEC members are chosen based on their clinical expertise and have no association with any trial for which they adjudicate events. As appropriate, the CEC is blinded to treatment assignment during all deliberations. Three voting members comprise a quorum. This committee is comprised of 3-5 physicians with experience in clinical trial event adjudication, including physicians with expertise in vascular surgery and/or vascular intervention. Committee physicians meet regularly throughout the study to adjudicate events in an ongoing fashion.

[redacted] CEC review of events will be planned as events become available for adjudication. Adjudication results will be available electronically after the adjudication is complete.

As documentation of the CEC meeting and each event under review, the Baim Institute for Clinical Research will provide to Surmodics relevant supporting documentation and/or adjudication results.

The CEC will be responsible for adjudicating MAEs (PARC and Historical), specified clinical endpoints and determining their device- and procedure-relatedness. Prior to the start of subject enrollment, the CEC will approve a charter and criteria for event evaluation. Explicit rules outlining the minimum amount of data required, and the algorithm followed to classify study endpoint–related clinical events will be established and provided in the charter.

13.3 Steering Committee

A steering committee will be composed of the study principal investigators, the steering committee chairperson, representatives of the sponsor, and may also include other experts. The Steering Committee participates in sponsor-requested meetings to review study progress and conduct, and to provide feedback to the sponsor on an *ad hoc* basis.

13.4 Publication Committee

The publication committee will be defined during the course of the study. Committee membership will include representatives of the steering committee. The goal of the committee is to ensure that the study results are published. The publication committee is responsible for reviewing proposals for publication, overseeing the development of manuscripts and abstracts, and identifying and appointing author(s)/writer(s).

14. Risk Benefit Analysis

14.1 [redacted]

[redacted]

[redacted]

14.2 Potential Risks of SurVeil DCB

Risks associated with the SurVeil DCB include risks associated with a standard peripheral balloon dilatation catheterization procedure. These risks may include, but are not limited to, the following:

Puncture related:

- Arterio-venous fistula
- Bleeding
- Femoral nerve compression with associated neuropathy
- Groin area bruising and discomfort
- Local hematoma
- Local hemorrhage
- Local infections
- Local or distal thromboembolic episodes
- Pseudoaneurysm
- Total occlusion or thrombosis

Dilatation related:

- Acute re-occlusion necessitating surgical intervention
- Aneurysm or rupture of the artery
- Dissection in the dilated artery wall
- Perforation of the artery wall
- Prolonged spasms
- Restenosis of the dilated artery

Angiography related:

- Allergic reaction to contrast solution
- Arrhythmias
- Death
- Drug reactions
- Endocarditis

- Kidney failure
- Low blood pressure
- Pain and tenderness
- Pyrogenic reaction
- Respiratory failure
- Sepsis/infection
- Short-term hemodynamic deterioration
- Stroke
- Systemic embolization

Potential risks that may be unique to the SurVeil DCB catheter:

- Allergic/immunologic reaction
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- Myalgia/arthralgia
- Myelosuppression
- Peripheral neuropathy

There may be other potential risks that are unforeseen at this time. The occurrence of the above-listed risks may lead to the need for a repeat procedure, emergency blood vessel surgery, amputation or death.

For more detailed information on the risks of treatment with the SurVeil DCB, including a complete list of warnings, precautions and potential AEs, please refer to the IFU, which is provided with the product.

14.3 Potential Benefits

There are no guaranteed benefits from participation in this trial; however, it is possible that treatment with the SurVeil DCB may reduce the potential for restenosis of the treated lesion, thereby reducing the need for repeat interventions.

Moreover, in this clinical investigation all subjects will have a more intense medical follow-up compared to standard practice, which can be beneficial to the long-term clinical outcome of study subjects.

Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. Efficacy and safety data collected on the SurVeil DCB will contribute to expanding the knowledge of use of DCBs in peripheral interventions. Surmodics believes the risk for significant injury or death is low and the potential benefits of decreased restenosis and need for re-intervention are likely, but these potential risks and benefits have yet to be quantified.

14.4 Anticipated Adverse Device Effects

The anticipated adverse device effects are listed in Section 14.2. These events are typical for other commercially available peripheral balloon dilatation devices.

14.5 Residual Risk

There were no intolerable risks remaining in the risk analysis. The remaining risks have been mitigated as far as reasonably practicable.

14.6 Risks Associated with Participation in the Clinical Trial

The risks associated with participation in this study will be similar to those associated with use of commercially available peripheral balloon dilatation devices. The risks of participation in this study will be minimized by careful subject and site selection, as well as by implementing monitoring procedures to ensure proper conduct and management of the study.

Meta-analyses of randomized controlled trials of paclitaxel-coated balloons and paclitaxel-eluting stents used to treat peripheral arterial disease in the femoropopliteal arteries have identified an increased risk of late mortality at 2 years and beyond. The magnitude and mechanism for the increased risk in mortality is currently unclear. The analyses also demonstrated reduced revascularization rates with the drug-containing products. The impact of future device exposure is unknown as is the impact of other drug-containing devices. Physicians should discuss the benefits and risks of all available treatment options with patients.

14.7 Possible Interactions with Concomitant Treatments

Concomitant treatment with this device has not been investigated. Therefore the interaction of this device with concomitant treatments remains unknown.

14.8 Risk Mitigation

To minimize the potential risks associated with study procedures, all efforts will be made to select investigators who are experienced and skilled in using peripheral interventional devices. Additionally, at study initiation all investigators will be trained on the SurVeil IFU and the protocol. All enrolling investigators will be instructed on appropriate subject selection in an effort to minimize the risk of recruiting ineligible subjects to the study.

Subjects will be monitored closely throughout the study duration and will be evaluated at pre-specified time points to assess their clinical status.

14.9 Risk / Benefit Rationale

The conclusions from the risk analyses performed on the SurVeil DCB are:

- The device is appropriate for the intended use.
- The potential benefits of the device outweigh the risks.
- All applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the subject.
- The use of the device is designed to protect the health and safety of the subject, user, and environment.

15. Data Collection and Verification

15.1 Data Collection, Verification and Retention

All required data for this trial will be collected on standardized eCRFs. The investigator or investigational site will maintain, at the investigative site, in original format, all essential study documents and source documentation that support the data collected on the study subjects in compliance with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), ISO14155:2011, and any local regulatory guidelines. Sites that are able to send complete source documents to the Baim Institute will be encouraged to do so: the EDC system allows a direct upload of documentation, which mitigates the site burden and reduces delays. This will not replace monitoring visits on site, but can be used to accelerate the review of the subject data.

Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal completion of or discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with Surmodics or in compliance with other local regulations. To avoid error, the investigator should contact Surmodics before the destruction of any records and reports pertaining to the trial to ensure they no longer need to be retained. In addition, Surmodics should be contacted if the investigator plans to leave the investigational site so arrangements can be made for the transfer of records.

15.2 Protocol Deviations

A protocol deviation is defined as any instance during the conduct of the study in which the investigator or other site personnel changed or failed to adhere to the study design or procedures specified by the protocol. Examples of protocol deviations may include:

a. enrollment of a study subject who does not meet all of the inclusion/exclusion criteria specified in the protocol;

b. failure to obtain a key safety procedure or lab test; or

c. enrollment of a patient during a lapse in IRB/EC approval of the study.

All relevant protocol deviations should be submitted by the site on the applicable eCRF, and will be reviewed and assessed for their impact on subject safety by Surmodics or its designee.

Investigative sites are expected to comply with the study protocol except where necessary to protect the life or physical well-being of a subject in an emergency (in cases of medical emergency, the Baim Institute for Clinical Research should be notified within 24 hours of the occurrence of the event).

All protocol deviations will be tracked and entered into the EDC system. Surmodics or its designee is responsible for assuring the site investigator is aware of all protocol deviations at their site, reporting to regulatory agencies as appropriate, and for determining if the trial needs to be terminated at a particular site due to the number or type of protocol deviations. Investigative sites should report deviations to their IRBs/ECs per their procedures.

Protocol deviations for inability to perform office visits, exams or procedures due to COVID-19 pandemic should be completed and a notation of “COVID-19” in the CRF for each deviation.

16. Device Supply and Management

Tracking of the investigational product used in this study will be consistent with 21 CFR Part 821 and ISO 14155:2011, and in accordance with location-specific requirements. Devices must be stored in a locked location at the investigative site.

Surmodics will provide the investigational device (SurVeil DCB) to all participating sites. Control devices (IN.PACT Admiral DCBs) will not be provided by the study; sites should use their own inventory in this case.

Device management will be captured through EDC and on the device accountability log. The site will record device usage in the EDC as soon as possible after opening any DCB (both test and control devices) used in this study, including the description and the dimensions of the device. If a SurVeil DCB is opened but not used, or if a device deficiency or malfunction occurs during its use, it must be returned to Surmodics or its designee in accordance with the packaging and shipping instructions.

Based on pre-specified thresholds, resupply of study device will be triggered electronically.

17. Statistical Methods

The proposed study is a prospective, multi-center, randomized, controlled trial designed to assess the noninferiority of the SurVeil DCB in the treatment of subjects with stenotic lesions of the femoropopliteal artery, compared to the IN.PACT Admiral DCB, with respect to the primary efficacy endpoint of 12-month primary patency, defined as freedom from clinically-driven TLR and binary restenosis (restenosis defined as DUS PSVR ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs), and with respect to the primary safety endpoint, defined as 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 TVR through 12 months post-index procedure. 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 the confidence intervals of these rates in each group will be reported.

The main analysis of primary efficacy and safety endpoints will be based on multiple imputation. Details on the imputation model will be included in the Statistical Analysis Plan (SAP).

17.1 Assessment of Primary Efficacy Endpoint

The primary efficacy endpoint is primary patency, defined as a composite of freedom from clinically-driven TLR and binary restenosis (restenosis defined as DUS PSVR ≥2.4 or ≥50% stenosis as assessed by independent angiographic and DUS core labs) and through 12 months post-index procedure. In cases when there is a discrepancy between angiographic and DUS assessment of patency, angiographic assessment takes precedence. The primary efficacy objective will be assessed through testing the following hypotheses:

$\boldsymbol{H_0}$: The proportion of subjects who meet the efficacy endpoint in the SurVeil DCB group through 12 months post-index procedure is clinically inferior to the proportion of subjects who meet the efficacy endpoint in the IN.PACT Admiral DCB group

$$H_0: p_S^{\mathrm{Eff}} - p_M^{\mathrm{Eff}} \leq -\delta^{\mathrm{Eff}}$$

$\boldsymbol{H_1}$: The proportion of subjects who meet the efficacy endpoint in the SurVeil DCB group through 12 months post-index procedure is clinically noninferior to the proportion of subjects who meet the efficacy endpoint in the IN.PACT Admiral DCB group

$$H_1: p_S^{\mathrm{Eff}} - p_M^{\mathrm{Eff}} > -\delta^{\mathrm{Eff}}$$

where $p_S^{\mathrm{Eff}}$and $p_M^{\mathrm{Eff}}$are the 12-month primary patency rates in the SurVeil DCB group and comparator IN.PACT Admiral DCB group, respectively, and δ^{Eff} is the noninferiority margin.

Statistical analyses for the primary efficacy endpoint 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 efficacy endpoint if the null hypothesis of inferiority is rejected at a one-sided significance level of 2.5%. Subsequently, if the null hypothesis of inferiority is rejected, a statistical test for superiority

$$H_0: p_S^{\text{Eff}} - p_M^{\text{Eff}} \leq 0$$

$$H_1: p_S^{\text{Eff}} - p_M^{\text{Eff}} > 0$$

at the one-sided 2.5% will be conducted. If the superiority hypothesis is also met, the Surveil DCB will be declared superior to IN.PACT Admiral DCB with respect to the efficacy endpoint. 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.

17.1.1 Primary Patency Rates and Noninferiority Margin

The FDA-approved/CE marked Medtronic IN.PACT Admiral DCB will be used as the comparator for the SurVeil DCB. In the Medtronic Premarket Approval (PMA) study, the 12-month primary patency rates were 82.2% and 52.4% in the IN.PACT Admiral DCB and PTA groups,[40] respectively. The observed difference in the 12-month primary patency rates between the IN.PACT Admiral DCB and PTA groups was 29.8%. Based on 50% of the difference in primary patency between IN.PACT Admiral DCB and PTA, a noninferiority margin of 15.0% is clinically justified as it preserves the 50% of the treatment effect between DCB and PTA.

17.1.2 Sample Size Calculations

The assumptions for this analysis are:

- True 12-month primary patency rate is 82.2% in both treatment groups
- 1:1 randomization of SurVeil DCB vs. IN.PACT Admiral DCB
- 15.0% is the absolute noninferiority margin (50% of the difference in primary patency rate between IN.PACT Admiral DCB and PTA)
- Statistical analysis will be conducted using a Farrington & Manning test for noninferiority of proportions; the test will be a one-sided test at α=0.025
- Sample Size: N=400 (200 in the SurVeil DCB group and 200 in the IN.PACT Admiral DCB group) evaluable subjects or 446 (223 in the SurVeil DCB group and 223 in the IN.PACT Admiral DCB group) randomized subjects to account for an assumed 10% loss to follow-up

Under these assumptions, the power is at least 97.5%. If the true primary patency rates are 82.2% in the IN.PACT Admiral DCB group and 78.3% or higher in the SurVeil DCB group,

at least 80% power will still be preserved at the planned sample size. Power calculations were performed with SAS software, version 9.3 (SAS Institute, Cary, NC).

Sample Size Calculation Assuming a One-sided 2.5% Type I Error Bound

Comparator	Non-inferiority Margin	Sample Size						Patency Rate		Power
		Evaluable			Enrolled*			SurVeil	IN.PACT	
		Total	SurVeil	IN.PACT	Total	SurVeil	IN.PACT			
IN.PACT Admiral, **1:1 Randomization**	15.0% **	400	200	200	446	223	223	82.2%	82.2%	97.5%
								80.0%	82.2%	90.0%
								78.3%	82.2%	80.0%

* Enrolled sample size assumes 10% loss to follow-up at 12 months.
** The 15.0% margin is 50% of the difference between Medtronic IN.PACT Admiral DCB and PTA patency rates.

17.2 Assessment of the Primary Safety Endpoint

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 and clinically-driven TVR through 12 months post-index procedure.

The primary safety objective will be assessed through testing the following hypotheses:

$\boldsymbol{H_0}$: The proportion of subjects who meet the safety endpoint in the SurVeil DCB group through 12 months post-index procedure is inferior to the proportion of subjects who meet the safety endpoint in the IN.PACT Admiral DCB group

$$H_0: p_S^{\text{Saf}} - p_M^{\text{Saf}} \leq -\delta^{\text{Saf}}$$

$\boldsymbol{H_1}$: The proportion of subjects who meet the safety endpoint in the SurVeil DCB group through 12 months post-index procedure is clinically noninferior to the proportion of subjects who meet the safety endpoint in the IN.PACT Admiral DCB group

$$H_1: p_S^{\text{Saf}} - p_M^{\text{Saf}} > -\delta^{\text{Saf}}$$

where p_S^{Saf} and p_M^{Saf} are the 12-month primary safety rates in the SurVeil DCB group and comparator IN.PACT Admiral DCB group, respectively, and δ^{Saf} is the noninferiority margin.

Statistical analyses for the primary safety endpoint 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 safety endpoint if the null hypothesis of inferiority is rejected at a one sided significance level of 2.5%.

Subsequently, if the null hypothesis of inferiority is rejected, a statistical test for superiority

$$H_0: p_S^{\text{Saf}} - p_M^{\text{Saf}} \leq 0$$

$$H_1: p_S^{\text{Saf}} - p_M^{\text{Saf}} > 0$$

at the one-sided 2.5% will be conducted. If the superiority hypothesis is also met, the Surveil DCB will be declared superior to IN.PACT Admiral DCB with respect to the safety endpoint. The main analysis will be carried out using the ITT analysis set. In addition to the main ITT analysis, supportive analyses will also be carried out using the AT and PP analysis sets.

17.2.1 Primary Safety Endpoint Rates and Noninferiority Margin

The FDA-approved/CE marked Medtronic IN.PACT Admiral DCB will be used as the comparator for the SurVeil DCB. In the primary publication of the IN.PACT SFA trial, the primary safety rates were 95.7% and 76.6% in the IN.PACT Admiral DCB and PTA groups, respectively.[40] The observed difference in primary safety endpoint rates between the IN.PACT Admiral DCB and PTA groups was 19.1%. Based on 50% of the difference in primary safety endpoint between IN.PACT Admiral DCB and PTA, a noninferiority margin of 10.0% is clinically justified, as it preserves the 50% of the treatment effect between the DCB and PTA. This is the same noninferiority margin utilized in the IN.PACT SFA study.

17.2.2 Sample Size Calculations

The assumptions for this analysis are:

- True 12-month primary safety endpoint rate is 95.7% in both treatment groups
- 1:1 randomization of SurVeil DCB vs. IN.PACT Admiral DCB
- 10.0% is the absolute noninferiority margin (50% of the difference in primary safety endpoint rate between IN.PACT Admiral DCB and PTA)
- Statistical analysis will be conducted using a Farrington & Manning test for noninferiority of proportions; the test will be a one-sided test at α=0.025
- Sample Size: N=400 (200 in the SurVeil DCB group and 200 in the IN.PACT Admiral DCB group) evaluable subjects or 446 (223 in the SurVeil DCB group and 223 in the IN.PACT Admiral DCB group) randomized subjects to account for an assumed 10% loss to follow-up

Under these assumptions, the power is at > 99%. If the true primary safety endpoint rates are 95.7% in the IN.PACT Admiral DCB group and 92.7% or higher in the SurVeil DCB group, at least 80% power will be preserved at the planned sample size. Power calculations were performed with SAS software, version 9.3 (SAS Institute, Cary, NC).

Sample Size Calculation Assuming a One-Sided 2.5% Type I Error Bound

Comparator	Non-Inferiority Margin	Sample Size						Primary Safety Rate		Power
		Evaluable			Enrolled*			SurVeil	IN.PACT	
		Total	SurVeil	IN.PACT	Total	SurVeil	IN.PACT			
IN.PACT Admiral,	10.0% **	400	200	200	446	223	223	95.7%	95.7%	99.5%
								93.6%	95.7%	90.0%

1:1 Randomiza-tion								92.7%	95.7%	80.0%

* Enrolled sample size assumes 10% loss to follow-up at 12 months.
** The 10.0% margin is 50% of the difference between Medtronic IN.PACT Admiral DCB and PTA primary safety endpoint rates.

17.3 Handling of Missing Data in the Analysis of Primary Efficacy and Safety Endpoints

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. The reasons for missing data will be described in detail and evaluated for assessment of possible bias. The missing data is expected to be <10% at 12 months.
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. For the primary efficacy endpoint, it is assumed that for all IN.PACT Admiral DCB subjects with missing primary patency status, the loss of primary patency did not occur. For SurVeil DCB subjects with missing data, it will be first assumed that the loss of primary patency occurred for exactly one such subject; then the primary analyses will be re-run to assess if noninferiority is met under this assumption. Then it will be assumed the primary patency loss occurred for exactly two SurVeil DCB subjects with missing data, and the primary noninferiority analysis will be rerun. The process will continue sequentially in this manner until all SurVeil DCB subjects with missing data are considered to have lost primary patency. Of interest is the "tipping point", or i.e., the number of imputed SurVeil DCB subjects not meeting primary patency where noninferiority is not met in this analysis. A similar analysis will be carried out for the primary safety endpoint.

Second, a sensitivity analysis of the primary efficacy and safety endpoints will be carried out using Cox regression. In this analyses, study discontinuation before an event will be treated as a censored observation at the time of dropout.

17.4 Assessment of Secondary Endpoints

The main analysis of the secondary endpoints will be carried out using the ITT analysis set. In addition to the main ITT analysis, supportive analyses will also be carried out using the AT and PP analysis sets.

Primary patency through 24 months will be compared between treatments only 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 α=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:

$\boldsymbol{H_0}$: The proportion of subjects with primary patency in the SurVeil DCB group through 24 months is clinically inferior to that of the IN.PACT DCB group.

$\boldsymbol{H_1}$: The proportion of subjects with primary patency in the SurVeil DCB group through 24 months is clinically noninferior to that of the IN.PACT DCB group.

The Farrington and Manning test for noninferiority of proportions at a one-sided significance level of α=0.025 will be used to test the hypothesis. The primary patency rate at 24 months, along with the 95% confidence intervals of these rates in each group, will be reported. If noninferiority is demonstrated for the 24-month patency rates between the SurVeil DCB and IN.PACT Admiral DCB groups, a test of superiority of the SurVeil DCB compared to the IN.PACT Admiral DCB will be conducted.

In the Medtronic Premarket Approval (PMA) study, the 24-month primary patency rates were 78.9% and 50.1% in the IN.PACT Admiral DCB and PTA groups,[41] 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.

Descriptive analysis of the following additional Secondary Endpoints will be performed, comparing the two treatment groups.

17.4.1 Secondary Endpoints (Acute)

- 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 QA) without flow-limiting arterial dissection, using only the study device.
- Technical Success: defined as achievement of a final residual diameter stenosis of <50% without flow-limiting arterial dissection at the end of the procedure.
- Procedure Success: defined as evidence of both acute technical success and absence of 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.

The incidence estimates for each endpoint above will be reported along with a 95% confidence interval for the SurVeil and the IN.PACT Admiral groups. Fisher's exact test at a two-sided significance level of 0.05 will be used to compare the results between the SurVeil and IN.PACT Admiral groups.

17.4.2 Secondary Endpoints (Through 60 Months Follow-Up)

In addition to primary patency through 24 months, as listed above, other secondary endpoints through follow-up include:

- 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 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 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

The incidence estimates for each endpoint above will be reported along with a 95% confidence interval for the SurVeil and the IN.PACT Admiral groups at the specified time points. Fisher's exact test at a two-sided significance level of 0.05 will be used to compare the incidence of each endpoint between the SurVeil and IN.PACT Admiral groups at each specified time point. In addition, Kaplan-Meier estimates will be provided at 6, 12, and 24 months, unless otherwise indicated:

- Change in target limb Rutherford class from baseline to 1, 6, 12, and 24 months
- Change in target limb PARC class from baseline to 1, 6, 12, and 24 months
- Decrease in resting target limb ABI or TBI ≥0.15 from baseline to 6, 12, and 24 months
- Change in WIQ score from baseline to 1, 12, and 24 months
- Change in 6-MWT from baseline to 12 and 24 months
- Change in PAQ from baseline to 1, 12, and 24 months

Descriptive statistics (means, standard deviations and 95% confidence intervals) for each of the above endpoints will be reported in each treatment group and at the specified time points. The differences between the Surveil DCB and the IN.PACT Admiral DCB in the above endpoints at the specified time points will be evaluated using a two-sample t-test or the nonparametric Wilcoxon rank-sum test at a two-sided significance level of 0.05.

17.5 Study Populations

The study will use the following analysis data sets:

Screen Failure Analysis Population

The Screen Failure analysis set is defined as all subjects who were enrolled but not randomized.

Intention-to-Treat (ITT) Analysis Population

The ITT analysis set will comprise all subjects who were randomized. Subjects will be analyzed according to their randomized group assignment. The ITT analysis set will be used for the primary efficacy and safety analyses.

As Treated (AT) Analysis Population

The AT analysis set will include only those subjects treated with either an investigational or control device, and the comparison will be based on the actual device used, not the randomized assignment. The AT analysis set will be used for sensitivity and supporting analyses for the primary safety and efficacy analyses.

Per-Protocol (PP) Population

The PP analysis set is defined as all randomized subjects who were treated with the assigned study balloon, who have sufficient follow-up data (at least 335 days of follow-up or experienced the primary endpoint), and who had no major protocol eligibility violations (i.e. inclusion/exclusion criteria violations that could impact the primary endpoint). Subjects will be compared based on the actual device used. The PP analysis set will be used for sensitivity and supporting analyses for the primary safety and efficacy analyses.

17.6 Subgroup Analysis

The following subgroups will be analyzed, in order to assess for heterogeneity of clinical endpoints:

- Age
- Smokers vs. non-smokers
- Females vs. males
- Subjects with diabetes mellitus vs. subjects without diabetes mellitus
- Lesion length ≤90 mm vs. >90 mm in length
- Calcified vs. non-calcified lesions
- *De novo* vs. restenotic lesions
- Subjects with bailout stenting vs. subjects without bailout stenting

The treatment group difference (SurVeil DCB vs. IN.PACT Admiral DCB) in the primary endpoint rate and the two-sided 95% confidence interval of the difference will be presented within each subgroup. A test of interaction on the primary endpoint 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. An interaction p-value <0.15 will indicate a potential differential effect of treatment across the subgroup; the nature of any such effect (e.g., quantitative vs. qualitative) will further be investigated by inspecting the treatment differences within the relevant subgroups. The purpose of this analysis is not to formally assess noninferiority within each subgroup, but simply to assess consistency of results across the various subgroups. Subjects with an event or with appropriate follow-up will be included in this analysis.

17.7 Poolability of Data Across Sites and Regions (United States vs. Outside the United States)

In evaluating the center treatment effect heterogeneity, centers with 9 or fewer subjects randomized will be combined by geographic region into aggregate sites, not to exceed 20 subjects per aggregate site. Logistic regression will be employed, with treatment, site, and the interaction of treatment and site as covariates. Statistical significance (0.15 level) of the interaction term will indicate that the observed effects are not homogeneous across sites.

Since the study plans to recruit patients from the United States as well as from outside the United States, a poolability analysis will be conducted to determine if data from these two regions are poolable. For both the primary and safety endpoints, a logistic regression with treatment, region (United States vs. non- United States) and their interaction as covariates will be employed. Statistical significance (0.15 level) of the interaction term will indicate that the observed effects are not homogeneous between the two regions and may potentially negate poolability of the two regions for the primary analysis or may require assessment of the endpoint rate adjusting for region variability. In that case, further inspection of the "by-region" primary endpoint rates and possible discussion with the FDA will determine if regions may still be pooled for the primary analysis and if adjustment for region variability is required (for example, if it is agreed between the sponsor and the FDA that the statistically significant region effect is not clinically meaningful, it is possible that the regions may still be pooled for the primary endpoint analysis, and without adjustment for region variability).

17.8 Assessment of Adverse Events

Descriptive statistics will be used to identify the frequencies and 95% confidence intervals of AEs in each treatment group. Fisher's exact tests at a two-sided significance level of 0.05 will be used to compare the AEs proportions.

18. Regulatory Compliance

18.1 Statement of Compliance

This study will be conducted in accordance with applicable regulations and/or guidance per country or region including ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects, Good Clinical Practice, the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

18.2 Investigator Responsibilities

The role of the site investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The principal investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155:2011, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

18.2.1 Investigator Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

18.3 Sponsor Responsibilities

Surmodics, the sponsor, has the overall responsibility for the conduct of the study, including assurance that the study meets and is conducted within the regulatory requirements specified by each reviewing regulatory authority. In this study, the Surmodics will have certain direct responsibilities and will delegate other responsibilities to designees such as the Baim Institute for Clinical Research and core laboratories. Surmodics and its designees will ensure adherence to requirements regarding sponsor general duties, selection of investigators, monitoring, supplemental applications, maintaining records and submitting reports.

18.4 Institutional Review Board/Ethics Committee

The investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol and informed consent form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

18.5 Study Amendments

All changes to the protocol must be documented in the format of an amendment with justification statements. All amendments must be submitted to the IRB/EC and regulatory authority for review and approval. Following approval, the protocol amendment will be distributed to all protocol recipients at the study site.

18.6 Informed Consent

Written informed consent is required from all subjects or their legally authorized representative. The investigator is responsible for ensuring that informed consent is obtained prior to the use of any investigational devices or study-required procedures and/or testing that is outside of standard of care. A copy of the consent form must be forwarded to Surmodics or their designee for review and approval prior to submitting to the IRB/EC.

The obtaining and documentation of informed consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155:2011, any applicable national regulations, and local EC and/or Regulatory authority body, as applicable. The informed consent must be approved by Surmodics or its designee, the investigative site's IRB/EC, or central IRB, if applicable, prior to study use.

Failure to obtain subject consent will be reported to the applicable regulatory body per their requirements (e.g., FDA requirement is within 5 business days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and national/local regulatory authorities (e.g. IRB/EC), as appropriate.

18.7 Subject Confidentiality

Subject confidentiality will be maintained throughout the study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code (identification number and subject name code) will be used that allows identification of all data reported for each subject.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated as confidential and that the subject's privacy is guaranteed.

For investigative sites within the United States, "Protected Health Information" will be treated and maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy rule. For investigative sites within the European Union, data protection for individuals will be maintained in compliance with the Directive 95/46/EC, and as of 25MAY2018, in compliance with the General Data Protection Regulation (Regulation 2016/679), with regard to the processing of personal data and on the free movement of such data.

The duration of storage time of personal data at the investigational sites will be in accordance with national regulations (see Section 15.1).

18.8 Use of Electronic Signatures

The Sponsor will be responsible for certification to the FDA that electronic signatures in their system are intended to be the legally binding equivalent of traditional handwritten signatures, as specified in 21 CFR, Part 11.100 (c).

18.9 Site Monitoring

Qualified monitors from Surmodics or designee will conduct on-site and remote monitoring visits to ensure that all investigators conduct the study in compliance with the protocol and the investigators' agreements. The site will receive notification prior to each monitoring visit during the course of the study. The investigator and/or sub-investigator and other appropriately trained study staff are expected to be available on the day of the visit in case any questions might arise.

The progress of the study will be monitored by:

- Ensuring the completed eCRF matches source documents, and resolution of any discrepancies. Direct access to complete source documents and medical records, including electronic medical records, must be made available during monitoring visits for verification of eCRF data. Source documents will be reviewed to verify the data recorded on the eCRF, including AE data, based on the study-specific monitoring plan.

- Periodic on-site visits and remote monitoring of data will be done based on the study-specific monitoring plan.
- Frequent telephone or email communications between the investigator/site and the assigned site monitors.

Periodic on-site and remote monitoring visits will be made in accordance with the approved monitoring plan at all active study sites throughout the clinical study to assure that the investigator's obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the sponsor and the IRB, device and device inventory are controlled, and the investigator is properly executing all agreed activities. Additional detail will be provided in the study Monitoring Plan.

Surmodics and designee will evaluate circumstances where an investigator deviates from the clinical protocol. Surmodics or its designees retain the right to remove either the investigator or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements. Surmodics or designee will perform the monitoring responsibilities per their SOPs.

On one or more occasions, the investigative site may be inspected or audited by Surmodics, its designee, or a third party such as a regulatory agency. The investigator will be informed in advance of this visit.

A representative or designee of Surmodics may accompany the monitor to the site.

19 Suspension, Termination, and Close-Out

19.1 Procedure for Suspension or Early Termination

The sponsor may suspend or prematurely terminate either this clinical investigation in an individual investigation site or the entire clinical investigation.

A site investigator, IRB/EC, or regulatory authority may suspend or prematurely terminate participation in this clinical investigation at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, the sponsor will suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed.

The sponsor will consider terminating or suspending the participation of a particular investigational site or investigator if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication.

If suspension or premature termination occurs:

- The sponsor will remain responsible for providing resources to fulfill the obligations from this protocol and existing agreements for following the subjects enrolled in the clinical investigation, and
- The site investigator or authorized designee will promptly inform the enrolled subjects at his/her investigation site

If the trial is terminated, Surmodics must comply with all applicable government regulations and the protocol-required subject follow-up. Should discontinuation of the study occur, the investigator must return all clinical study materials (including devices) to the Sponsor, and provide a written statement to the IRB/EC explaining the reasons for the premature termination. All applicable clinical investigation documents shall be subject to the same retention policies, as detailed in Section 15.1.

19.2 Procedure for Resuming the Clinical Investigation After Temporary Suspension

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor will inform the relevant parties of the rationale and provide them with the relevant data supporting this decision.

Concurrence will be obtained from the IRBs/ECs and, where appropriate, regulatory authorities before the clinical investigation resumes.

If subjects have been informed of the suspension, the site investigator or authorized designee will inform them of the reasons for resumption.

19.3 Routine Close-Out

Routine close-out activities will be conducted to ensure that the site investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved, and all parties are notified.

20 Publication Policy

The Sponsor acknowledges the importance of publication of information collected or generated by the trial. Publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors (ICMJE).

The Sponsor will establish a publication committee (as described in Section 13.4) and the committee membership may include the Principal Investigator, other Investigators from the study, and representatives of Surmodics, Inc. (e.g. statistician, clinical research specialist, etc.). The committee will establish a publication strategy.

21 References

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113:e463-654.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;127:e6-e245.
3. Murabito JM, Evans JC, D'Agostino RB, Sr., Wilson PW, Kannel WB. Temporal trends in the incidence of intermittent claudication from 1950 to 1999. Am J Epidemiol 2005;162:430-7.
4. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation 1997;96:44-9.
5. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.
6. Murphy TP, Ariaratnam NS, Carney WI, Jr., et al. Aortoiliac insufficiency: long-term experience with stent placement for treatment. Radiology 2004;231:243-9.
7. McDermott MM, Guralnik JM, Ferrucci L, et al. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. Circulation 2008;117:2484-91.
8. Bradbury A. In: BASIL Investigators' Meeting Vascular Society.
9. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
10. Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. J Vasc Surg 2010;51:69S-75S.
11. Slovut DP, Lipsitz EC. Surgical technique and peripheral artery disease. Circulation 2012;126:1127-38.
12. Flu HC, Ploeg AJ, Marang-van de Mheen PJ, et al. Patient and procedure-related risk factors for adverse events after infrainguinal bypass. J Vasc Surg 2010;51:622-7.
13. Nicoloff AD, Taylor LM, McLafferty RB, Moneta GL, Porter JM. Patient recovery after infrainguinal bypass grafting for limb salvage. J Vasc Surg 1998;27:256-63.
14. 2011 ACCF/AHA Focused Update of the Guideline for the Management of patients with peripheral artery disease (Updating the 2005 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011;124:2020-45.
15. Tendera M, Aboyans V, Bartelink ML, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of

extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851-906.
16. Sarode K, Spelber DA, Bhatt DL, et al. Drug delivering technology for endovascular management of infrainguinal peripheral artery disease. JACC Cardiovasc Interv 2014;7:827-39.
17. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G, Viva Physicians I. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69:910-9.
18. Zeller T. Drug coated balloons: hope or hype? Available at: http://evtoday.com/2012/08/drug-coated-balloons-hope-or-hype/. Accessed October 13, 2014. Endovascular Today 2012.
19. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in native coronary artery. N Engl J Med 2003;349:1315-23
20. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005;294:1215-23.
21. Dake MD, Ansel GM, Jaff MR, et al. Durable Clinical Effectiveness With Paclitaxel-Eluting Stents in the Femoropopliteal Artery: 5-Year Results of the Zilver PTX Randomized Trial. Circulation 2016;133:1472-83; discussion 83.
22. Loh JP, Barbash IM, Waksman R. The current status of drug-coated balloons in percutaneous coronary and peripheral interventions. EuroIntervention 2013;9:979-88.
23. Scheinert D, Scheinert S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol 2005;45:312-5.
24. Laird JD. Limitations of percutaneous transluminal angioplasty and stenting for the treatment of disease of the superficial femoral and popliteal arteries. J Endovasc Ther 2006;13(Suppl II):II.
25. Waksman R, Pakala R. Drug-eluting balloon: the comeback kid? Circ Cardiovasc Interv 2009;2:352-8.
26. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202.
27. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435-41.
28. Hunt B. In: BASIL Investigators' Meeting Vascular Society.
29. Kayssi A, Al-Atassi T, Oreopoulos G, Roche-Nagle G, Tan KT, Rajan DK. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs. Cochrane Database Syst Rev 2016:CD011319.
30. Seedial SM, Ghosh S, Saunders RS, et al. Local drug delivery to prevent restenosis. J Vasc Surg 2013;57:1403-14.
31. Fanelli F, Cannavale A, Boatta E, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial. J Endovasc Ther 2012;5:571-80.

32. Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial. Circ Cardiovasc Interv 2012;5:831-40.
33. Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008;358:689-99.
34. Werk M, Langner S, Reinkensmeier B, et al. Inhibition of restenosis in femoropopliteal arteries: paclitaxel-coated versus uncoated balloon: femoral paclitaxel randomized pilot trial. Circulation 2008;118:1358-65.
35. Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty. JACC Cardiovasc Interv 2014;7:10-9.
36. Byrne RA, Joner M, Alfonso F, Kastrati A. Drug-coated balloon therapy in coronary and peripheral artery disease. Nat Rev Cardiol 2014;11:13-23.
37. Freyhardt P, Zeller T, Kroncke TJ, et al. Plasma levels following application of paclitaxel-coated balloon catheters in patients with stenotic or occluded femoropopliteal arteries. Rofo 2011;183:448-55.
38. Micari A, Cioppa A, Vadala G, et al. Clinical evaluation of a paclitaxel-eluting balloon for treatment of femoropopliteal arterial disease: 12-month results from a multicenter Italian registry. JACC Cardiovasc Interv 2012;5:331-8.
39. Micari A, Cioppa A, Vadala G, et al. 2-year results of paclitaxel-eluting balloons for femoropopliteal artery disease: evidence from a multicenter registry. JACC Cardiovasc Interv 2013;6:282-9.
40. Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015;131:495-502.
41. Laird JR, Schneider PA, Tepe G, et al. Durability of Treatment Effect Using a Drug-Coated Balloon for Femoropopliteal Lesions: 24-Month Results of IN.PACT SFA. J Am Coll Cardiol 2015;66:2329-38.
42. Lutonix I, October 10, 2014. (Accessed February 27, 2017, at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418455.htm)
43. Jaff MR, Rosenfield K, Scheinert D, et al. Drug-coated balloons to improve femoropopliteal artery patency: Rationale and design of the LEVANT 2 trial. Am Heart J 2015;169:479-85.
44. Rosenfield K, Jaff MR, White CJ, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med 2015;373:145-53.
45. Lyden, S. ILLUMENATE Pivotal Stellarex DCB IDE Study 12-Month Results. In: Transcatheter Cardiovascular Therapeutics, 2016.
46. Metzger C. US Trial Update: Levant 2. In: Transcatheter Cardiovascular Therapeutics. San Francisco, CA; 2013.
47. Cassese S, Byrne RA, Ott I, et al. Paclitaxel-coated versus uncoated balloon angioplasty reduces target lesion revascularization in patients with femoropopliteal arterial disease: a meta-analysis of randomized trials. Circ Cardiovasc Interv 2012;5:582-9.

Appendix A. Acronyms and Abbreviations

Abbreviation/Acronym	Complete Term
6-MWT	6-Minute walk test
ABI	Ankle brachial index
ADE	Adverse device event
AE	Adverse event
AR	Adverse reaction
BARC	Bleeding Academic Research Consortium
BASIL	Bypass Surgery versus Angioplasty in Severe Ischemia of the Leg
BMS	Bare metal stent
CBC	Complete blood count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CLI	Critical limb ischemia
CRO	Clinical research organization
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DCC	Data coordinating center
DES	Drug-eluting stent
DMC	Data monitoring committee
DUS	Duplex ultrasound
EC	Ethics committee
EDC	Electronic data capture
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Early feasibility study
FDA	Food and Drug Administration
FEP	Fluorinated ethylene propylene
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IFU	Instructions for use
IRB	Institutional review board
ISO	International Organization for Standardization
LLL	Late lumen loss
MAE	Major adverse event
MI	Myocardial infarction
PAD	Peripheral artery disease

Abbreviation/Acronym	Complete Term
PAQ	Peripheral Artery Questionnaire
PARC	Peripheral Academic Research Consortium
PEB	Paclitaxel-eluting balloon
POBA	Plain old balloon angioplasty
PSVR	Peak systolic velocity ratio
PTA	Percutaneous transluminal angioplasty
QA	Quantitative angiography
RVD	Reference vessel diameter
SADE	Serious adverse device effect
SAE	Serious adverse event
SFA	Superficial femoral artery
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TASC	TransAtlantic Inter-Society Consensus Classification
TBI	Toe brachial index
TLR	Target lesion revascularization
TVR	Target vessel revascularization
UADE	Unanticipated adverse device effect
US	United States
USADE	Unanticipated serious adverse device effect
WBC	White blood cell
WIQ	Walking Impairment Questionnaire

Appendix B. Definitions

ADVERSE DEVICE EFFECT

An ADE is defined as any AE that is related to the use of the investigational medical device.

> **NOTE 1**: This definition includes AEs resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
>
> **NOTE 2**: This definition includes any event that is a result of a use error or from intentional abnormal use of the investigational medical device.

ADVERSE EVENT

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the investigational medical device.

> **NOTE 1:** This definition includes events related to the investigational medical device or the comparator.
>
> **NOTE 2:** This definition includes events related to the procedures involved.
>
> **NOTE 3:** Abnormal laboratory findings will be considered AEs, only if determined by the investigator to be clinically significant**.**
>
> **NOTE 4**: For users or other persons, this definition is restricted to events related to investigational medical devices.

ANKLE BRACHIAL INDEX

Ankle systolic pressure/brachial systolic pressure (ABI), measured by constructing a ratio from the peak systolic pressure measured during the deflation of the ankle cuffs during DUS detection to the systolic brachial pressure.

ANTICIPATED ADVERSE EVENT

Any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the clinical protocol, predefined in the clinical protocol and/or IFU, and/or product label that is identified or worsens during a clinical study.

ARTERIAL THROMBOSIS OF THE TREATED SEGMENT ON ANGIOGRAPHY

A total occlusion documented by DUS and/or angiography at the treatment site with or without symptoms. Thrombosis may be categorized as acute (<1 day), subacute (1-30 days) and late (>30 days). The presence of thrombus at the target lesion must be noted as an AE in the eCRF.

BLEEDING ACADEMIC RESEARCH CONSORTIUM (BARC)[1] DEFINITION FOR BLEEDING

Bleeding complications are defined according to the BARC classification of bleeding events

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Overt bleeding plus hemoglobin drop of 3 to <5 g/dL (provided hemoglobin drop is related to bleed)

Any transfusion with overt bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed compromising vision

Type 4: CABG-related bleeding

[1] Mehran R, Rao SV, Bhatt DL, *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-47.

Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period
Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CLINICALLY-DRIVEN TARGET LESION REVASCULARIZATION

Clinically-driven TLR is any repeat intervention of the target lesion (plus 10 mm proximal and distal to the index device) or surgical bypass of the target lesion performed due to target lesion diameter stenosis ≥50% and either evidence of clinical or functional ischemia (e.g., recurrent/progressive life-limiting intermittent claudication, claudication unresponsive to medical therapy, critical limb ischemia) or recurrence of the clinical syndrome for which the initial procedure was performed. If the target lesion is occluded and bypass is done to another artery below the knee, this should be considered TLR.

CLINICALLY-DRIVEN TARGET VESSEL REVASCULARIZATION

Clinically-driven TVR is any repeat intervention of the target vessel or surgical bypass of the target vessel performed due to target vessel diameter stenosis ≥50% and either evidence of clinical or functional ischemia (e.g., recurrent/progressive life-limiting intermittent claudication, claudication unresponsive to medical therapy, critical limb ischemia) or recurrence of the clinical syndrome for which the initial procedure was performed. If the target vessel is occluded and bypass is done to another artery below the knee, this should be considered TVR.

DEATH

All-cause mortality.

DEVICE DEFICIENCY (ISO14155:2011)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance. This may include malfunctions, use error, or inadequate labeling.

DEVICE FAILURE

A device failure occurs when the device is used in compliance with the IFU, but does not perform as described in the IFU and also negatively impacts treatment of the study subject.

DEVICE MALFUNCTION (ISO 14155:2011)

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU or clinical study protocol.

DEVICE SUCCESS

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.

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) **CLASSIFICATION**[2]

Grade A: Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.

Grade B: Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.

Grade C: Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.

Grade D: Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.

Grade E: Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.

Grade F: Filling defect accompanied by total coronary occlusion.

EMBOLIC EVENTS OF TARGET LIMB

Embolism with concomitant suggestive clinical signs and symptoms, located separate from and distal to the target lesion. Classified by probability:

• Definite: Angiographic evidence of distal embolization with a new intraluminal filling defect and/or abrupt occlusion of a run-off vessel distal to a lesion that is clearly not attributable to wire trauma or dissection, irrespective of the time from the index procedure.

• Probable: Suggestive clinical signs and symptoms of distal embolization occurring ≤30 days after the index procedure, in the absence of angiographic evidence.

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[2] Detre, K., R. Holubkov, S. Kelsey, M. Bourassa, D. Williams, D. Holmes, Jr., G. Dorros, D. Faxon, R. Myler, K. Kent, *et al*. One-year follow-up results of the 1985-1986 National Heart, Lung, and Blood Institute's Percutaneous Transluminal Coronary Angioplasty Registry. Circulation. 1989;80(3):421-8.

• Possible: Suggestive clinical signs and symptoms of distal embolization occurring >30 days after the index procedure in the absence of angiographic evidence.

INDEX PROCEDURE

The index procedure is the randomized study procedure occurring on day 1, in which subjects are randomly assigned to receive either a SurVeil DCB or an IN.PACT Admiral DCB.

MAJOR ADVERSE EVENT, PARC[3]

A PARC MAE is death, stroke, myocardial infarction, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and/or need for urgent/emergent vascular surgery.

MAJOR ADVERSE EVENT, HISTORICAL

A historical MAE is all-cause death, clinically-driven TLR, major target limb amputation (above the ankle), or thrombosis at the target lesion.

MAJOR LIMB AMPUTATION

Above the ankle amputation.

MAJOR VASCULAR COMPLICATIONS

Major vascular complications include the following:

- Hematoma at access site >100 mm
- False aneurysm requiring surgical or percutaneous intervention
- Arterio-venous fistula requiring surgical or percutaneous intervention
- Retroperitoneal bleed associated with significant hemodynamic and/or clinical sequelae
- Any transfusion (any transfusion required will be reported as a vascular complication unless the clinical indication is clearly something other than a catheterization complication)
- Vascular surgical repair of the vascular access site

[3] Patel MR, Conte MS, Cutlip DE, *et al*. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC).J Am Coll Cardiol. 2015;65(9):931-41.

PARC[4] CALCIFICATION CLASSIFICATION

Focal: <180˚ (1 side of vessel) and less than one-half of the total lesion length

Mild: <180˚ and greater than one-half of the total lesion length

Moderate: ≥180˚ (both sides of the vessel at same location) and less than one-half of the total lesion length

Severe: >180˚ (both sides of the vessel at same location) and greater than one-half of the total lesion length

PARC CLINCAL SYMPTOM CLASSIFICATION

- Asymptomatic
- Mild claudication/limb symptoms (no limitation in walking)
- Moderate claudication/limb symptoms (able to walk without stopping >2 blocks or 200 meters or 4 minutes)
- Severe claudication/limb symptoms (only able to walk without stopping <2 blocks or 200 meters or 4 minutes)
- Ischemic rest pain (pain in the distal limb at rest, felt to be due to limited arterial perfusion)
- Ischemic ulcers on distal leg
- Ischemic gangrene

PATENT RUN-OFF

At least one patent native outflow artery from the popliteal to the ankle, free from significant (≥50%) stenosis as confirmed by angiography or ultrasound that has not previously been revascularized.

PRIMARY PATENCY

Defined as a composite of freedom from clinically-driven TLR and binary restenosis (restenosis defined as DUS PSVR ≥2.4 or by ≥50% stenosis as assessed by independent angiographic and DUS core labs) and through 12 months post-index procedure. In cases when there is a discrepancy between angiographic and DUS assessment of patency, angiographic assessment takes precedence.

PROCEDURE SUCCESS

[4] Patel MR, Conte MS, Cutlip DE, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC).J Am Coll Cardiol. 2015;65(9):931-41.

Evidence of both acute technical success and absence of major adverse events (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.

REFERENCE VESSEL DIAMETER

RVD is defined as the average of normal segments within 10 mm proximal and distal to the target lesion from two orthogonal views using QA.

RESTENOSIS

Defined as DUS PSVR ≥2.4 or by ≥50% stenosis as assessed by independent angiographic and DUS core labs. PSVR is a ratio of the peak systolic velocity (PSV) at the lesion relative to the PSV of a normal segment in a proximal reference vessel. The PSVR consequently cannot be calculated in the presence of an abnormal proximal PSV, as can occur in the setting of inflow disease, cardiac disease, or cardiac arrhythmias. In the presence of abnormal reference PSV, the core lab uses the following additional secondary criteria to identify restenosis of the target lesion (≥50% in severity):

- Focal increase in the absolute PSV at the area of visible plaque
- Post-stenotic turbulence (PST) and/or change in the waveform shape and/or drop in velocity distal to the stenosis
- Review of the B-mode images

RUTHERFORD CLASSIFICATION

0: Asymptomatic, no hemodynamically significant occlusive disease

1: Mild Claudication

2: Moderate Claudication

3: Severe Claudication

4: Ischemic rest pain

5: Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia

6: Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable

SERIOUS ADVERSE DEVICE EFFECT

An ADE that results in any of the consequences characteristic of a SAE is considered a SADE.

SERIOUS ADVERSE EVENT

A SAE is an AE that leads to:

1. Death,
2. Serious deterioration in the health of the subject that either resulted in:
    a. Life-threatening illness or injury, or
    b. Permanent impairment of a body structure or a body function, or
    c. In-patient hospitalization, or prolongation of existing hospitalization, or
    d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
3. Fetal distress, fetal death or a congenital abnormality or birth defect.

    NOTE 1: This includes device deficiencies that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

    NOTE 2: Planned hospitalization for pre-existing condition, or a procedure required by the clinical study plan, without a serious deterioration in health, is not considered to be an SAE. A planned hospitalization is one that is scheduled prior to the patient signing the informed consent for the study.

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

A SUSAR is an AR that is both serious and unexpected.

TARGET LESION

A lesion that is to be treated during the index procedure.

TARGET LESION REVASCULARIZATION

TLR is any repeat intervention of the target lesion (plus 10 mm proximal and distal to the index device) or surgical bypass of the target lesion performed for restenosis or other complication involving the target lesion. If the target lesion is occluded and bypass is done to another artery below the knee, this should be considered TLR. In the assessment of TLR, angiograms should be assessed by the angiographic core laboratory and made available to the clinical endpoints committee for review.

TARGET LIMB AMPUTATIONS

All amputations at the target limb including both above the ankle (Major) amputations and below the ankle (Minor) amputations.

TARGET VESSEL REVASCULARIZATION

TVR is any repeat intervention of the target vessel or surgical bypass of the target vessel performed for restenosis or other complication involving the target vessel. If the target vessel

is occluded and bypass is done to another artery below the knee, this should be considered TVR. In the assessment of TVR, angiograms should be assessed by the angiographic core laboratory and made available to the clinical endpoints committee for review.

TARGET VESSEL

Superficial femoral and popliteal arteries, defined as the arterial segment from the bifurcation between the superficial and *profunda femoris* arteries (proximal anatomical landmark) to the distal segment of the popliteal artery at the origin of anterior tibial artery (distal anatomical landmark).

TECHNICAL SUCCESS

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.

THROMBOSIS

A total occlusion documented by DUS and/or angiography at the treatment site with or without symptoms. Thrombosis may be categorized as acute (<1 day), subacute (1-30 days) and late (>30 days). The presence of thrombus at the target lesion must be noted as an AE in the eCRF.

UNANTICIPATED ADVERSE DEVICE EFFECT

An UADE is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of a subject.

UNEXPECTED AE

Any AE that is not consistent in specificity or severity with the current investigator's brochure/protocol, including all amendments, is considered unexpected.

UNSCHEDULED VISIT

An unscheduled visit is any visit that is for an index procedure-related AE or for revascularization of the target limb.

USE ERROR

An act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. (Note 1: Use error includes slips, lapses and mistakes. Note 2: An unexpected physiological response of the subject does not in itself constitute a use error.)

WALKING IMPAIRMENT QUESTIONNAIRE

Instrument to measure walking distance, walking speed, and stair-climbing limitations in patients with PAD in the outpatient setting.[5]

WOMAN OF CHILDBEARING POTENTIAL

A woman of childbearing potential is any postmenarchal female who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman >45 years old in the absence of other biological or physiological causes. In women <55 years old, menopause must be confirmed by a serum follicle-stimulating hormone level of >40 mIU/mL.

WORSENING OF ANKLE BRACHIAL INDEX

A deterioration in the ABI by ≥0.15 from baseline.

WORSENING RUTHERFORD CLINICAL CATEGORY

A deterioration (an increase) in the Rutherford Category by more than 1 category from the earliest post-procedural measurement.

[5] Jain, A., K. Liu, L. Ferrucci, M. Criqui, L. Tian, J. Guralnik, H. Tao, and M. McDermott. 2012. The Walking Impairment Questionnaire stair-climbing score predicts mortality in men and women with peripheral arterial disease. J Vasc Surg 55:1662-73.