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Clinical Investigation of the GORE® Drug-Coated PTA Balloon Catheter (GORE® DCB Catheter) for CE Mark Approval

Protocol Number: DCB 15-02
14Feb2017

W. L. Gore & Associates, Inc.
Medical Products Division

PROTOCOL MODIFICATION SUMMARY

List of Changes in: Clinical Investigation of the GORE® Drug-Coated PTA Balloon Catheter (GORE® DCB Catheter) for CE Mark Approval Revision 2 (DCB 15-02)

The following administrative changes have been made to the protocol:

- Minor typographical and punctuation errors have been corrected in Section 9.1.2.
- In addition, the following changes have been made to the protocol:

Changes incorporated during September 2016 BfArM and Ethics Committee submission cycle:

Section	Changes to Protocol	Rationale
Section 9.1.2 – Adverse Event Classification, Serious Adverse Event	Added Note 3, to include the German Serious Adverse Event definition according to §2 No. 5 MPSV.	Required addition for BfArM approval Modifications made in Sept 2016 during first cycle of BfArM responses
Section 9.1.4 – Serious AE reporting	Added the last paragraph to include the quarterly summary evaluation of all SAEs per BfArM's new process.	Required addition for BfArM approval Modifications made in Sept 2016 during first cycle of BfArM responses

Changes incorporated during February 2017 BfArM and Ethics Committee submission cycle to include ISO 14155:2011 compliance items:

Section	Changes to Protocol	Rationale
Entire document	Added or corrected the register mark for GORE	Consistency in referencing Gore's register mark
Title Page	Added 10 Feb 2017 date after Protocol Number	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant
Protocol Modification Summary	Added Protocol Modification Summary after Title Page	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant

Section	Changes to Protocol	Rationale
Protocol Summary	Authorized Representative Added Updated Primary Objective and added Secondary Objective and hypothesis removed Study Endpoints section: Primary and Secondary Endpoints clarified Number of Sites section: added reference to the maintenance of the investigator list Added Coordinating Investigator section Added Expected Time of Each Study Subject to Complete the Study and Total Expected Duration of the Study sections Added Early Safety Enrollment Section Updated Independent Review section with addresses for contractors and detail for CEC / DSMB	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant Detail added to match body of Protocol
List of Abbreviations	Added DSMB	Omitted in earlier version by mistake
Section 1.2	Added updated information on TACS II guideline Table 3 updated with new information	New information became available
Section 1.3	Updated indication and manufacturer	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant

Section	Changes to Protocol	Rationale
Sections 1.4 and 1.5	Sections added	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant
Sections 2.1 and 2.2	Updated Primary Objective and added Secondary Objective	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant
Section 3.1	Added information about comparator and OPC Provided statement that Sponsor would maintain an updated investigator list Added safety review after 10 subjects enrolled	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant Modifications made in Feb 2017 at request of BfArM Reviewer
Section 3.2.2	Split primary endpoints info performance and safety endpoints	Details added in Feb 2017 for clarity
Section 4.1	Provided clarification to patient population and subject population and rationale for treatment	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant
Section 4.2	Added new inclusion #6 - Patient is not a candidate for conservative therapy or has undergone conservative therapy that was not successful. Changed original #6 to #7	Modification made in Feb 2017 at the request of BfArM reviewer
Section 4.3	Exc #9: Added abbreviation for POBA Exc #18: Changed 72 hours to 30 days Exc #27: Changed to Patients with active vasculitis Added new Exc #28 – Patients with active tumor disease related to cancer	Added in Feb 2017 for clarification Modifications made in Feb 2017 at request of BfArM reviewer

	Changed original Exc #'s 28 & 29, to #'s 29 & 30 respectively	
Section 5	Added information including factors that may compromise the outcome of the study	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant
Section 5.1	Updated figure 2 to reflect 10 patient safety cohort	Modification made in Feb 2017 at request of BfArM Reviewer
Section 5.2	Table 4 modified to include 14 day follow up for 10 subject safety follow up and added pharmacokinetic testing for plasma paclitaxel levels for these same 10 subjects	Modifications made in Feb 2017 at request of BfArM Reviewer
Section 5.4	Added new baseline evaluations collected after informed consent: pharmacokinetic testing for plasma paclitaxel level for first 10 subjects only	Modifications made in Feb 2017 at request of BfArM Reviewer
Section 5.6	Added a statement about the reason for pre-dilation prior to use of the Gore device indicating that the Gore device is the second dilation	Modifications made in Jan 2017 during first cycle of Freiburg Ethics Committee responses
Section 5.6	Clarified standard of care treatments Added Post-procedure evaluation: Pharmacokinetic testing for plasma paclitaxel level – immediately after procedure, 1 hour post procedure, and 3 hours post procedure for first 10 subjects only Added Discharge evaluation: Pharmacokinetic testing for plasma paclitaxel level – at 24 hours or at discharge whichever is sooner for the first 10 subjects only	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant Modifications made in Feb 2017 at request of BfArM Reviewer

Section	Changes to Protocol	Rationale
Section 5.8	Added 14 day follow up information	Modifications made in Feb 2017 at request of BfArM Reviewer
Section 6.2	Monitoring, provided more clarity and included a minimum number of visit	Modifications made in Jan 2017 during first cycle of Freiburg Ethics Committee responses
Section 6.7	Presence of Sponsor, clarified that it was for observation of the procedure under the PI supervision	Modifications made in Jan 2017 during first cycle of Freiburg Ethics Committee responses
Section 6.3	Updated device information to reflect rationale for number of devices used and collection of data regarding devices	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 compliant
Section 6.9	Updated period of time to maintain records for BfS	Modifications made in Feb 2017as result of new information
Section 6.10	Publication Plan, provided more detail about the publication committee and timing of potential publications	Modifications made in Jan 2017 during first cycle of Freiburg Ethics Committee responses
Section 7	Added information regarding the Clinical Data Management Plan	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 7.1	Inserted additional review by Quality Assurance	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 7.2	Added statement about periodic data review	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 8.1	Added competitive device reference to AEs and rates and other known risk	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant

Section	Changes to Protocol	Rationale
Section 8.2	Added statements on sponsor's risk management activities Added bullet related to concomitant medical treatments	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 8.2.1	Section added to cover early safety monitoring process	Modifications made in Feb 2017 at request of BfArM Reviewer
Section 8.4	Risk to Benefit Rationale, corrected last statement Added additional information regarding risk management activities	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant Correcting prior error
Section 9.1.1	Added definition of Adverse Device Effect	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 9.1.2	Added definition of Serious Adverse Device Effect	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 9.3	CEC/DSMB, provided more detail and termination language	Modifications made in Jan 2017 during first cycle of Freiburg Ethics Committee responses
Section 10.1	Moved hypothesis from summary to Statistical Analysis section	Modified in Feb 2017 for clarification
Section 10.4.4	Provided information regarding both the performance endpoint and safety endpoint	Modified in Feb 2017 for clarification
Section 10.4.6	Added sub-group analysis	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 11.2	Clarified additional requirements relative to compliance responsibilities	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant

Section 11.3	Removed reference to legal authorized representative and added emergency contact detail	Modifications made in Feb 2017 at the request of BfArM to be ISO 14155:2011 Compliant
Section 11.8	Included termination criteria per ISO 14155:2011 and actions to be taken at termination	Modifications made in Jan 2017 during first cycle of Freiburg Ethics Committee responses
Section 12	Added reference 30	Modified in Feb 2017 to identify new reference

PROTOCOL SUMMARY

Study Title	Clinical Investigation of the GORE® Drug-Coated PTA Balloon Catheter (GORE® DCB Catheter) for CE Mark Approval
Protocol Number	DCB 15-02
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 1505 North Fourth Street Flagstaff, Arizona 86004 U.S.A.
Authorized Representative	Graeme Shepherd W. L. Gore & Associates (UK) Ltd Mariner Drive • Dundee Technology Park Dundee, DD2 1 JA SCOTLAND
Study Design	Prospective, multi-center, single-arm study characterizing outcomes in subjects with Peripheral Artery Disease (PAD) lesions treated with percutaneous transluminal angioplasty (PTA) using the GORE® DCB Catheter.
Study Objective	The primary objectives of the clinical investigation are to evaluate the performance and the safety of the GORE® DCB Catheter in the treatment of de novo and restenotic atherosclerotic lesions in the superficial femoral and popliteal arteries (SFA/PA) of patients with symptomatic PAD. The secondary objectives of the clinical investigation are to assess procedural success and the long term performance and safety of the GORE® DCB Catheter.
Study Endpoints	<u>Primary Endpoints</u> • The primary performance endpoint: six month late lumen loss (LLL) defined as the difference in minimum lumen diameter of the Target lesion between the time points immediately post-intervention and the 6-month follow-up angiography or at the time of a Clinically Driven Target Lesion Revascularization (CD TLR), whichever is earlier. • The primary safety endpoint: A composite 30-day safety endpoint is freedom from Major Adverse Events (MAE), defined as i) death, ii) Clinically-Driven Target Vessel Revascularization (CD TVR), or iii) amputation above the metatarsals, resulting from a vascular event, in the treated leg (Target limb amputation).

	Secondary Endpoints at Procedure • Acute Device Success • Acute Procedural Success • Technical Success • Treated region thrombosis • % of subjects that require Provisional Stenting Secondary Endpoints for all follow-up assessments: • Primary patency (freedom from clinically-driven TLR and freedom from restenosis as determined by duplex ultrasound (DUS) peak systolic velocity ratio (PSVR) ≤ 2.4 or angiographic stenosis < 50%) • Freedom from MAE • Freedom from TVR • Freedom from CD-TVR • Freedom from TLR • Freedom from CD-TLR • Rutherford improvement • Ankle-Brachial Index (ABI) improvement • Quality of life change • Assisted primary patency • Secondary patency
Subject Population	Patients with de novo or restenotic superficial femoral/popliteal artery lesions; stenosis ≥70%; lesion length 30 - 150 mm; reference vessel diameter 4 - 6 mm; Rutherford 2 - 4.
Number of Subjects	52 subjects
Number of Sites	Up to 10 study sites in Germany The Sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. This list shall be kept separately from this Protocol.
Coordinating Investigator	Prof. Dr. med Thomas Zeller Universitäts-Herzzentrum Bad Krozingen Südring 15 79189 Bad Krozingen, Germany
Expected Time to Complete Enrollment	~ 6 months
Expected Time of each Study Subject to Complete the Study	~24 months
Total Expected Duration of the Study	~ 30 months
Significant Inclusion/Exclusion Criteria	Significant Inclusion Criteria: • PAD patients with Rutherford Class 2 - 4

	• De novo or restenotic lesions, including total occlusions of the SFA/PA • 1 lesion which may include one or more regions of luminal narrowing ≥70% with a total combined lesion length between 30 - 150mm and a reference vessel diameter of 4 – 6mm • 1 patent tibial or peroneal artery Significant Exclusion Criteria: • Surgical or endovascular access in the Target limb/vessel within the previous 30 days • Prior treatment of the Target lesion with PTA within 90 days or any prior treatment with drug-coated balloon • Prior treatment of the Target vessel with stenting or bypass • Iliac artery inflow lesions that cannot be successfully treated during the Index procedure • Acute or subacute thrombus or arterial aneurysm in Target limb • Severe calcification that renders the Target lesion non-dilatable • Acute or chronic renal dysfunction (serum creatinine ≥2.5 mg/dL)
Schedule of Events:	
Baseline Screening Assessments	• Demographics • Medical History (including height and weight) • Blood Work – RBC, WBC, Platelets, Creatinine • Rutherford Classification • ABI • Lesion Characteristics (by angiography at time of intervention) • Quality of Life Questionnaires (EQ-5D, PAQ) • Antiplatelet and Anticoagulant therapy
Study Procedure	• Angiography • Balloon Inflation • Provisional Stenting • Adverse Events
Early Safety Enrollment	• The first 10 subjects will be enrolled at a single institution by the Coordinating Investigator. Pharmacokinetic testing for plasma paclitaxel levels will be collected. Safety data will be reviewed prior to continuing study enrollment at all sites.
Follow-up Assessments	1-, 6-, 12-, and 24-month follow-up evaluations: • Medications – antiplatelet and anticoagulants only • Adverse Events • Rutherford Classification

	• ABI • Quality of Life Questionnaires (EQ-5D, PAQ) • CDUS 6- month follow-up evaluation: Angiography of Target limb
Independent Review	Ultrasound, Angiography Core Labs: coreLab Black Forest GmbH Südring 15 79189 Bad Krozingen, Germany Clinical Research Monitoring: InnoRa GmbH Robert-Koch-Platz 4 10115 Berlin, Germany Combined Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB): • Independent of Sponsor, coordinated by non-Sponsor Administrator • Members shall not be participating investigators in the study • Sponsor will provide operational support

LIST OF ABBREVIATIONS

ABI	Ankle-Brachial Index
AE	Adverse Event
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (The Federal Institute for Drugs and Medical Devices)
BfS	Bundesamt für Strahlenschutz (The Federal Office for Radiation Protection)
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CDUS	Color Flow Duplex Ultrasound
CDMS	Clinical Data Management System
CE	Conformité Européenne
CEC	Clinical Events Committee
CFA	Common Femoral Artery
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
cm	Centimeters
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
ePTFE	Expanded Polytetrafluoroethylene
EU	European Union
FDA	Food and Drug Administration (United States)
FEP	Fluorinated Ethylene Propylene
Fr	French (sizing)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIT	Heparin-Induced Thrombocytopenia
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IVUS	Intravascular Ultrasound
MAE	Major Adverse Event
MedDRA	Medical Dictionary for Regulatory Activity
MI	Myocardial Infarction
mm	Millimeters
OUS	Outside United States

PAD	Peripheral Artery Disease
PG	Performance Goal
PHI	Protected Health Information
PI	Principal Investigator
PA	Popliteal Artery
PSV	Peak Systolic Velocity
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
SAE	Serious Adverse Event
SFA	Superficial Femoral Artery
TIA	Transient Ischemic Attack
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
U.S.	United States
UADE	Unanticipated Adverse Device Effect

1. Introduction

1.1. Disease

Lower extremity peripheral artery disease (PAD) is a condition in which blood flow in the lower limb arteries has been partially or entirely blocked, most commonly as a result of atherosclerotic lesions within the vessel lumen.[1] PAD is a common condition, and affects millions of individuals worldwide.[1-3] In addition to being closely associated with risk factors such as smoking, diabetes mellitus, and race,[1,4] PAD becomes increasingly likely with advancing age. PAD affects between 3% and 14% of the general population, but may be present in over 30% of those greater than 70 years of age.[5-7]

As PAD progresses, the disease may cause intermittent claudication during activity, and, in more severe cases, pain at rest or loss of tissue in the feet and legs. If not adequately addressed, PAD is associated with significant morbidity, and may ultimately result in disability, loss of the affected limb, and death.[8] The progression of PAD is commonly described using Rutherford and Fontaine clinical categories as described in Tables 1 and 2.

Table 1: Rutherford Clinical Categories[9]

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic—no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
I	1	Mild claudication	Completes treadmill exercise†; AP after exercise >50 mmHg but at least 20 mmHg lower than resting value
	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise† *and* AP after exercise < 50 mmHg
II*	4	Ischemic rest pain	Resting AP <40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mmHg
III*	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP <60 mmHg, ankle or metatarsal PVR flat or barely pulsatile: TP <40 mmHg
	6	Major tissue loss—extending above TM level, functional foot no longer salvageable	Same as category 5

AP, Ankle pressure; *PVR*, pulse volume recording; *TP*, toe pressure; *TM*, transmetatarsal.

*Grades II and III, categories 4, 5, 6, are embraced by the term *critical* limb ischemia.

†Five minutes at 2 mph on a 12% incline

Table 2: Rutherford Categories vs Fontaine Categories

Table 1. Fontaine or Rutherford classification systems of peripheral arterial disease

Fontaine classification		Rutherford classification		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischaemic rest pain	II	4	Ischaemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

1.2. Historical Treatments

A number of options exist for the treatment of PAD. These interventions can be grouped into four general categories: (a) behavioral modification, such as smoking cessation or increased exercise; (b) pharmacologic management of certain risk factors, including dyslipidemia and hypertension; (c) revascularization using minimally invasive endovascular techniques, and (d) revascularization using open surgical methods such as endarterectomy or bypass.[4,8,10,11] The appropriate choice of therapy is heavily dependent upon the severity and location of disease.[4,11]

Due to the regular motion and unique combination of mechanical forces to which the superficial femoral artery (SFA) and popliteal artery (PA) are subjected, these vessels are predisposed to the formation of atherosclerotic plaque, even after receiving an initial treatment.[5,12] Physicians must carefully consider the challenges specific to these arteries, as well as the severity of disease present, in determining which intervention is most appropriate. In the TASC II document outlining management strategies for PAD, Norgren et al.[13] proposed a uniform system of classification for femoropopliteal lesions. In this system, lesions are assessed based on length, complexity, and location within the vessel(s), and assigned a designation from Type A (least severe) to Type D (most severe). In 2011, Tenderra et al[30] updated the guideline recommendations for endovascular treatment as a first option for Type A, B, and C lesions, and surgical bypass for Type D lesions (Table 3). A primary endovascular approach may also be considered in TASC D lesions in patients with severe comorbidities and the availability of an experienced interventionist.[30]

Table 3: TASC II Recommendations for Treatment of Femoropopliteal Disease

Lesions		Recommended treatments
Type A lesions	• Single stenosis ≤10 cm in length • Single occlusion ≤5 cm in length	Endovascular therapy is the treatment of choice.
Type B lesions	• Multiple lesions (stenoses or occlusion), each ≤5 cm • Single stenosis or occlusion ≤15 cm not involving the infra geniculate popliteal artery	Endovascular therapy is the preferred treatment.

	• Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass • Heavily calcified occlusion ≤5 cm in length • Single popliteal stenosis	
Type C lesions	• Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification • Recurrent stenoses or occlusions that need treatment after two endovascular interventions	Endovascular therapy is the preferred treatment.
Type D lesions	• Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery) • Chronic total occlusions of popliteal artery and proximal trifurcation vessels	Surgery is the treatment of choice.

Although surgical revascularization is very effective, endovascular treatment is a first-line treatment for SFA/PA disease, due both to the reduction in significant risk of complications and to the increasing effectiveness of less invasive endovascular procedures.[1,9] Endovascular revascularization can be accomplished using a number of procedural options, including percutaneous transluminal angioplasty (PTA) or the implantation of an endoluminal stent.[14]

PTA is a well-established minimally invasive treatment for disease in the superficial femoral and popliteal arteries (SFA/PA). With restenosis rates of 40-60% after 6 to 12 months, many patients require additional percutaneous or surgical interventions to address their recurrent symptoms.[16-18] Alternative treatments to inhibit restenosis are needed. Drug-coated balloons have shown lower late lumen loss and Target lesion revascularization rates compared to uncoated balloons as noted in the FEMPAC, THUNDER, PACIFIER and In.Pact SFA trials.[19-21]

Paclitaxel has been approved for human use for over 20 years in cancer therapy at a dose much more than 10 times higher than the dose coating currently used in available drug-coated balloons.[22] Treating peripheral arterial disease with a paclitaxel-coated balloon may provide better long term patency compared to uncoated balloons without leaving any permanent implant behind.

1.3. Study Device Description

W. L. Gore & Associates, Inc. (Gore) has developed and manufactures the GORE® Drug-Coated PTA Balloon Catheter (GORE® DCB Catheter) to offer clinicians an alternative percutaneous transluminal angioplasty device indicated for use in treating patients with obstructive disease of peripheral blood vessels.

The GORE® DCB Catheter consists of an over-the-wire balloon catheter with a drug-coated nylon/ePTFE composite balloon at the distal tip (Figures 1). The composite balloon consists of a nylon layer on the innermost surface of the balloon and an ePTFE layer on the outermost surface of the balloon and serves as a coating substrate. The composite balloon is coated with a formulation that includes the drug paclitaxel, coated at a concentration of 3.5µg/mm^2, and the excipients stearic acid and tromethamine (tris). The device component physically dilates the vessel lumen by PTA, and the drug component is intended to reduce the proliferative response that is associated with restenosis.

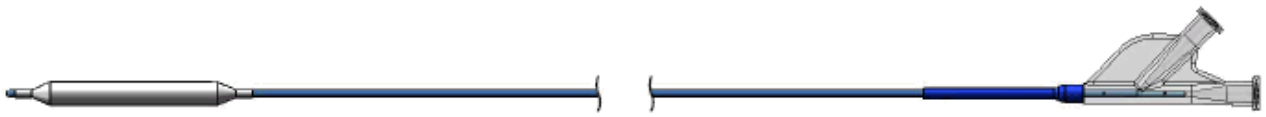


Figure 1. GORE® Drug-Coated PTA Balloon Catheter

The GORE® DCB Catheter consists of a proximal hub, dual lumen shaft, and a distal dilation balloon (Figure 1). The central lumen extends to the distal tip and is used for flushing and guidewire introduction with a diameter of 0.035". The balloon inflation lumen is used to inflate and deflate the balloon. Two radiopaque platinum-iridium markers indicate the working length of the balloon and facilitate fluoroscopic visualization of the balloon during delivery and placement.

The configurations of the GORE® DCB Catheter that will be studied during the clinical investigation in Europe are 4, 5, and 6mm in diameter and 40, 80,120, 150mm in length.

The composite balloon of the GORE® DCB Catheter is coated with a mixture of paclitaxel (active ingredient) and two excipients (inactive ingredients). Descriptions of the active and inactive ingredients are provided below.

Active Ingredient (Paclitaxel)

The GORE® DCB Catheter coating contains paclitaxel, an anti-proliferative pharmaceutical agent that specifically binds to and stabilizes microtubules. By blocking microtubule depolymerization, paclitaxel inhibits smooth muscle cell and fibroblast proliferation and migration as well as secretion of extracellular matrix. The combination of these effects results in the inhibition of neointimal hyperplasia and therefore restenosis.

Inactive Ingredients (Excipients)

The GORE® DCB Catheter contains two excipients or inactive ingredients. Information regarding the two excipients that are mixed with the paclitaxel and applied to the composite balloon is provided below:

- Tromethamine (tris) is widely used as a component of buffer solutions and is also a common inactive ingredient in many intravenous and intravascular pharmaceutical solutions/injections.
- Stearic acid is widely used as a surfactant and softening agent in the production of cosmetics such as shampoos, soaps and shaving cream products and in the preparation of dietary supplements. Stearic acid is a common inactive ingredient in many pharmaceutical preparations, including oral capsules/tablets, topical solutions/ointments/creams, vaginal tablets/creams, and subcutaneous implants.

Gore is the legal manufacturer of the GORE® DCB Catheter.

1.4. Pre-Clinical Data

Gore has performed the following pre-clinical testing on the GORE® DCB Catheter – i) *in vitro* testing; ii) biocompatibility testing per ISO 10993-1; iii) *in vivo* animal studies. See the Investigators Brochure (IB) for detailed descriptions and results of these studies.

1.5. Clinical Data

The GORE® Drug-Coated PTA Balloon Catheter has not been evaluated clinically. However, a number of commercially available drug-coated balloon catheters relevant to the proposed clinical study, have been evaluated. See the IB for adverse event information from these studies.

2. Study Objectives

2.1. Primary Objective(s)

The primary objectives of the GORE® DCB Catheter clinical investigation is to evaluate the performance and the safety of the GORE® DCB Catheter in the treatment of de novo and restenotic atherosclerotic lesions in the superficial femoral and popliteal arteries (SFA/PA) of patients with symptomatic PAD.

2.2. Secondary Objective(s)

The secondary objectives of the GORE® DCB Catheter clinical investigation is to assess procedural success and the long term performance and safety of the GORE® DCB Catheter in the treatment of de novo and restenotic atherosclerotic lesions in the superficial femoral and popliteal arteries (SFA/PA) of patients with symptomatic PAD.

3. Study Design

3.1. Description of Study Design

Previous DCB studies that were intended to supply clinical data for CE marking have used uncoated PTA as a comparator for the test DCB. Given the prominent role that uncoated PTA balloons continue to play in the endovascular management of PAD lesions, peer-reviewed published data from uncoated PTA balloons were used as the starting point for calculation of a performance goal.

Establishing the safety and performance of the GORE® DCB Catheter by comparison with a performance goal is appropriate given the maturity and similarity of the procedure, device, and technology to currently CE marked DCBs. Additionally, there has been an accumulation of a large volume of applicable, high quality clinical data in recent years. The clinical studies that supplied data for performance goal calculation demonstrate considerable homogeneity.

This study is a prospective, multi-center, single-arm study characterizing outcomes in subjects with PAD lesions treated with percutaneous transluminal angioplasty (PTA) using the GORE® DCB Catheter.

A maximum of ten (10) Clinical Investigative Sites (referred to as “Sites” in the remainder of this document) in Germany will participate in this study. The Sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. This list shall be kept separately from this Protocol. Fiftytwo (52) patients will be enrolled in this study with a limit of twelve (12) Subjects enrolled per Site. The anticipated accrual rate is approximately nine (9) Subjects per month, across all sites, for a total accrual period of approximately 6–8 months.

Patients may be enrolled into the study provided all inclusion and no exclusion criteria are met as specified in Section 4. Subjects will be evaluated through hospital discharge and return for follow-up visits at 30 days, 6 months, 12 months, and 24 months post treatment.

Total estimated duration of the study is approximately 30 months.

Bias will be controlled by strict adherence to the study protocol. Sites will be monitored for compliance with study protocol, including subject eligibility criteria.

The study will be conducted in a staged manner. The first 10 subjects will be enrolled at a single institution by the Coordinating Investigator. Pharmacokinetic testing for plasma paclitaxel levels will be collected and safety data reviewed prior to continuing study enrollment at all sites. Enrollment will continue at all sites following CEC/DSMB review and recommendation to continue, and the German competent authority acceptance of that recommendation. See section 8.2.1 for more detail.

3.2. Study Endpoints

3.2.1. Definitions

Acute Device Success: Successful delivery, inflation, deflation, and retrieval of the intact GORE® DCB Catheter without burst less than the rated burst pressure.

Acute Procedural Success: Procedural success without stenting is defined as <50% residual stenosis (investigator's estimation) at the conclusion of the Index procedure without Major Adverse Event prior to discharge or at 24 hours whichever is earlier. Procedural success with Provisional Stenting is defined as <30% residual stenosis (investigator's estimation) at the conclusion of the Index procedure with Provisional Stenting without Major Adverse Event prior to discharge or at 24 hours whichever is earlier.

Ankle Brachial Index (ABI): The highest ankle systolic pressure measured in the Target limb divided by the highest brachial systolic pressure in either arm.

Clinically-Driven Target Lesion Revascularization (CD TLR): Revascularization occurring within the Target lesion(s), after conclusion of the Index procedure, with at least one of the following: i) evidence of new symptoms, or ii) drop of ABI $\geq$20% or >0.15 compared with post procedure ABI, or iii) Target lesion diameter stenosis of $\geq$50% as determined by duplex ultrasound or angiography (images will be reviewed by an imaging core lab). CD TLR will be adjudicated by a CEC / DSMB.

Clinically-Driven Target Vessel Revascularization (CD TVR): Revascularization of the Target vessel, after conclusion of the Index procedure, with at least one of the following: i) evidence of new symptoms, or ii) drop of ABI $\geq$20% or greater than >0.15 compared with post procedure ABI, or iii) Target vessel diameter stenosis of $\geq$50% as determined by duplex ultrasound or angiography (images will be reviewed by an imaging core lab). CD TVR will be adjudicated by a CEC / DSMB.

Dissection (NHLBI Classification):

Type A: minor radiolucent areas within the lumen during contrast injection with little or no persistence of contrast after the dye has cleared.

Type B: parallel tracts or a double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance.

Type C: appear as contrast outside the lumen ("extraluminal cap") with persistence of contrast after dye has cleared from the lumen.

Type D: spiral (“barber shop pole”) luminal filling defects, frequently with excessive contrast staining of the dissected false lumen.

Type E: appear as new, persistent filling defects within the lumen.

Type F: those that lead to total occlusion of the lumen without distal antegrade flow.

Index procedure: Initial treatment of the Target lesion with a GORE® DCB Catheter.

Late Lumen Loss (LLL): The difference in minimum lumen diameter of the Target lesion between the time points immediately post-intervention angiography and the 6 month follow-up angiography or at the time of a Clinically Driven Target Lesion Revascularization (CD TLR), whichever is earlier.

Major Adverse Event (MAE): i) death, ii) Clinically Driven Target Vessel Revascularization (CD TVR), or iii) Major Amputation.

Major Amputation: Removal of the lower limb above the metatarsals, resulting from a vascular event, in the Target limb.

NHLBI Classification: National Heart, Lung and Blood Institute classification of dissection.

Patency: Freedom from total occlusion.

Primary Assisted Patency: Blood flow maintained with or without reintervention in the originally treated Target lesion(s), including the proximal and distal margins covered by the GORE® DCB Catheter.

Primary Patency: Freedom from CD TLR and freedom from restenosis as determined by Color Doppler Ultrasound (CDUS) peak systolic velocity ratio (PSVR) ≤ 2.4. In cases where PSVR cannot be determined, or is determined to be inaccurate by the independent ultrasound core laboratory, reduction in luminal diameter within the treated region must be ≤50% as adjudicated by the core laboratory.

Provisional Stenting: Placement of a stent at the Target lesion at the time of the Index procedure after acute device success due to visually estimated residual stenosis ≥ 50% or flow-limiting dissection.

Rutherford Category [28]**:**

Category 0 – Asymptomatic, no hemodynamically significant occlusive disease

Category 1 – Mild claudication

Category 2 – Moderate claudication

Category 3 – Severe claudication

Category 4 – Ischemic rest pain

Category 5 – Minor tissue loss, non-healing ulcer, focal gangrene with diffuse pedal ischemia

Category 6 – Major tissue loss, extending above trans-metatarsal level, functional foot no longer salvageable

Secondary Patency: Freedom from surgical bypass of the treated region.

Target lesion: The atherosclerotic lesion treated during the Index procedure.

Target Lesion Revascularization (TLR): After conclusion of the Index procedure, any reintervention of the Target lesion by means of a percutaneous vascular intervention, surgical bypass, thrombolysis, or other invasive means, as adjudicated by the CEC / DSMB.

Target limb: The infrainguinal portion of the limb on which the index procedure is performed.

Target vessel: The SFA/PA in the Target limb.

Target Vessel Revascularization (TVR): After conclusion of the Index procedure, any reintervention of the Target vessel by a percutaneous vascular intervention, surgical bypass, thrombolysis, or other invasive means, as adjudicated by the CEC / DSMB.

Technical Success: Acute Device Success and investigator visual estimate of <50% diameter residual stenosis of the Target lesion during the Index procedure without Provisional Stenting.

Treated region: Region containing the Target lesion(s) covered by the study device(s), during the Index procedure.

Treated region thrombosis: an occlusion at the treated region attributable to thrombus formation that is rapidly evolving as confirmed by the sudden onset of symptoms within 14 days of imaging, and documented by duplex ultrasound and angiography of the index vessel.

3.2.2. Primary Endpoints

- Performance: Six month late lumen loss (LLL) as determined by the angiography core lab.
- Safety: A composite 30-day safety endpoint of freedom from Major Adverse Events (MAE), defined as i) death, ii) Clinically-Driven Target Vessel Revascularization (CD TVR), or iii) amputation above the metatarsals, resulting from a vascular event, in the treated leg (Target limb amputation)

3.2.3. Secondary Endpoints

- Acute Device Success
- Acute Procedural Success
- Technical Success
- Treated region thrombosis
- % of subjects that require Provisional Stenting
- Freedom from MAEs at 1, 6, 12, and 24 months post-Index procedure as adjudicated by the CEC / DSMB
- Freedom from TVR at 1, 6, 12, and 24 months post-Index procedure as adjudicated by the CEC / DSMB

- Freedom from CD-TVR at 1, 6, 12, and 24 months post-Index procedure as adjudicated by the CEC / DSMB
- Freedom from TLR at 1, 6, 12, and 24 months post-Index procedure as adjudicated by the CEC / DSMB
- Freedom from CD-TLR at 1, 6, 12, and 24 months post-Index procedure as adjudicated by the CEC / DSMB
- Rutherford category change from pre-Index procedure to 1, 6, 12, and 24 months post-Index procedure
- ABI change from pre-Index procedure to 1, 6, 12, and 24 months post-Index procedure
- Quality of life change from pre-Index procedure to 1, 6, 12, and 24 months post-Index procedure
- Primary patency at 1, 6, 12, and 24 months post-Index procedure
- Assisted primary patency at 1, 6, 12, and 24 months post-Index procedure
- Secondary patency at 1, 6, 12, and 24 months post-Index procedure

4. Study Population

4.1. Description of Population

Patient Population – patients with symptomatic PAD of the SFA/PA.

Study Subject Population - those patients with symptomatic PAD of the SFA/PA meeting the following inclusion and exclusion criteria will be eligible for screening for participation in this study.

The study has been designed with standard eligibility criteria to enroll subjects for whom the study device is intended to treat. Only patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be enrolled.

4.2. Inclusion Criteria

To be considered candidates for this study, patients must meet all of the following criteria:

1. At least 20 years of age at the time of informed consent signature.
2. Subject is willing to provide a signed Informed Consent Form.
3. PAD patients with Rutherford Class 2 - 4 in the target limb, with no active ulceration or tissue loss due to arterial disease in either leg. Walking distance limitation should not be caused by the contralateral leg or concomitant diseases, e.g. pain in the hip joint.
4. Reasonable expectation of survival of at least 1 year after the Index procedure.
5. Patient is capable of complying with the Protocol requirements, including follow-up visits.
6. Patient is not a candidate for conservative therapy or has undergone conservative therapy that was not successful.
7. Vasculature in the target limb meeting angiographic inclusion criteria. To be eligible for inclusion in the study, patients must meet all of the following criteria, assessed angiographically prior to the Index procedure:

   7(a). De novo or restenotic lesions, of the SFA/PA. The lesions must be located in the region beginning at the origin of the superficial femoral artery and ending ≤2 cm below the tibial plateau and ≥1 cm above the origin of the tibial/peroneal trunk.

   7(b). One Target lesion, which may include an area of the vessel with one or more regions of luminal narrowing ≥70% where the multiple single lesions are separated by ≤2 cm between the lesions, visually estimated by the physician.

   7(c). Total occlusions are allowed.

   7(d). Cumulative lesion length 30 - 150 mm, visually estimated by the physician.

   7(e). Reference vessel diameter of 4 - 6 mm, visually estimated by the physician.

   7(f). At least one patent tibial artery or peroneal artery (<50% stenosis angiographically) from the origin to the ankle of the target limb that does not require planned intervention at the time of the Index procedure or within 12 months of enrollment.

   7(g). Only one index limb is to be treated in the study.

   7(h). Guidewire has successfully traversed the Target lesion and is within the true lumen (reentry devices are not allowed).

   7(i). Target lesion has been successfully pre-dilated (no major flow limiting dissections or residual stenosis after pre-dilation >50%, visually estimated by physician) with a plain balloon 1 mm below the reference vessel diameter and a minimum of one (1) minute balloon inflation.

4.3. Exclusion Criteria

Patients will be excluded from the study if they meet one or more of the following criteria:

1. Prior enrollment in this study.
2. Surgical or endovascular access of the Target limb/vessel within the previous 30 days. [NOTE: Target limb catheterizations done for the purposes of planning the Index procedure are allowed within 30 days of the Index procedure if no treatment is performed. Catheterization or access of the Target limb for treatment of inflow disease is allowed during the Index procedure.]

3. Prior treatment of the Target lesion with PTA within 90 days.
4. Prior treatment of the Target lesion with drug-coated balloon.
5. Prior treatment of the Target vessel with stenting.
6. Prior treatment of the Target vessel with bypass.
7. Iliac artery inflow lesions that cannot be successfully treated during the Index procedure.
8. Known outflow lesions requiring treatment during the Index procedure.
9. Other than plain old balloon angioplasty (POBA), procedures required at the time of the Index procedure to facilitate the deployment of the study device and to treat the Target limb.
10. Significant disease in all three Infrapopliteal vessels (as determined by the Investigator).
11. Acute or subacute thrombus or arterial aneurysm (>1.5 x healthy adjacent vessel diameter) in the Target limb.
12. Severe calcification that renders the Target lesion non-dilatable.
13. Acute or chronic renal dysfunction (serum creatinine level ≥2.5 mg/dl or patients on dialysis) at the time of the Index procedure.
14. Untreated pre-procedural hemoglobin <10 g/dL.
15. Coagulopathy manifested by platelet count <100,000 or INR >2.0 (INR is only required in patients who have taken warfarin within 2 weeks of enrollment).
16. Contraindication to PTA treatment with a paclitaxel-coated balloon.
17. Known hypersensitivity or contraindications to nitinol, aspirin, heparin, clopidogrel, ticlopidine or paclitaxel, and sensitivity to contrast media not amenable to premedication.
18. Myocardial infarction within 30 days prior to the Index procedure.
19. Planned surgical or endovascular procedure of the target limb ± 30 days of Index procedure.
20. Planned amputation of the target limb.
21. Septicemia (including bacteremia) or uncontrolled infection.
22. Any co-morbid condition that precludes compliance with this protocol.
23. Women who are known or suspected to be pregnant or intend to become pregnant at the time of the informed consent.
24. Women who are breast feeding.
25. Men who intend to father children.
26. Concomitant medical illness associated with a life-expectancy of less than one year.
27. Patients with active vasculitis.
28. Patients with active tumor disease related to cancer.
29. Patients who are concurrently participating in an investigational study when such participation could confound the treatment or outcomes of this study.
30. Any other factor identified by the investigator that would disqualify the prospective subject from participation in the study.

5. Study Procedures/Evaluations

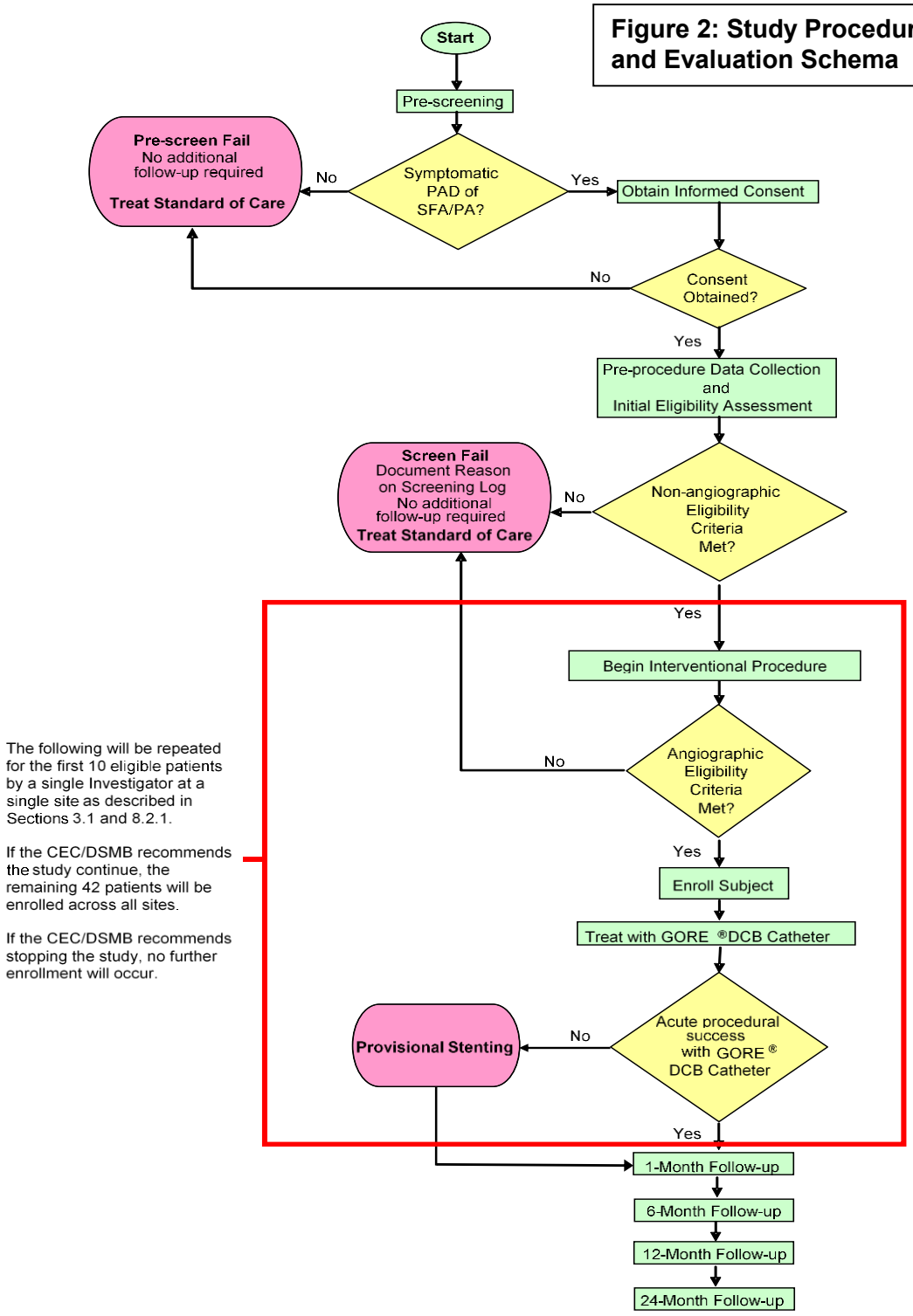
For this study it is expected that the sites will follow this protocol, to ensure scientifically sound evaluation of outcomes. Key items include but are not limited to:

- All protocol requirements are to be followed.
- Only POBA procedures at the time of the Index procedure are to be performed to facilitate the deployment of the study device and to treat the Target limb.
- Patients with prior treatment of the Target lesion with PTA within 90 days are not to be enrolled.
- Patients that have had prior treatment of the Target lesion with drug-coated balloon, with stenting, or with bypass are not to be enrolled.
- All required follow-up visits are to be performed.
- The 6 months angiography for all enrolled subjects is to be performed.
- The required images are to be sent in an analyzable format to the CoreLab.
- All used and unused Gore devices are to be returned, as directed.

There are no additional, known or foreseeable factors that may compromise the outcome of the clinical study or the interpretation of results.

5.1. Study Procedures and Evaluation Schema (Figure 2)

Figure 2: Study Procedures and Evaluation Schema



5.2. Table 4: Schedule of Events

	Screening & Pre-procedure	Procedure	Post-procedure / Discharge	14 day Follow-up[2]	1-, 12-, and 24-month Follow-up	6-month Follow-up	Unscheduled Visit or Reintervention
Informed consent	X						
Demographics and medical history	X						
Antiplatelet and anticoagulant medications	X	X	X		X	X	X
Rutherford category	X				X	X	X
ABI	X				X	X	X
Blood tests (CBC, creatinine)	X						
Pregnancy test (if applicable)	X						
Quality of life questionnaires	X				X	X	X
Angiogram		X			O	X	O/X[1]
Adverse events		X	X	X[2]	X	X	X
Duplex ultrasound	X				X	X	X
Pharmacokinetic testing for plasma paclitaxel level	X[2,3]		X[2,3]				

X = required; O = To be collected when available; X[1] = required for reinterventions
X[2] = required for the first 10 subjects enrolled only
X[3] = plasma collected at the following time points: pre-procedure, immediately post procedure, 1 hour post procedure, 3 hours post procedure and at 24 hours post procedure or at discharge whichever is sooner

5.3. Informed Consent Process

All patients must provide informed consent prior to any study related procedures being performed. The case history (*i.e.*, source documents/Subject chart) for each Subject shall document that such informed consent was obtained. The EC-approved consent form will be signed and personally dated by the Subject, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for their records.

5.4. Pre-Screening / Screening

The pre-screening procedure will involve reviewing existing patient health information to identify patients with symptomatic PAD who may be eligible for study enrollment. Patients who may be eligible for enrollment based upon pre-screening will be provided with an EC-approved ICF describing this study, as well as any additional information required to make an informed decision about their participation. No study procedures or evaluations outside of routine standard of care may be performed before obtaining written informed consent from the patient. All patients who sign an ICF will be considered entered into the screening phase of the study.

Once informed consent has been given by the patient, complete baseline data should be collected prior to initiation of the Index procedure. Baseline data may include existing health information collected following routine standard of care.

The following baseline evaluations will be used to determine whether the patient meets non-angiographic eligibility criteria for the study. These evaluations will be conducted at the pre-procedure screening visit(s) or, if collected following routine standard of care, must have been completed prior to informed consent being given, per timelines defined below for each item:

Within 7 days prior to Index procedure:

- Urine Pregnancy test (if applicable): Pregnancy testing may be waived if a reasonable and prudent explanation is provided such as infertility, surgical sterilization, or post-menopausal status. Urine Pregnancy test, if performed, will be conducted within 7 days prior to Index procedure.

Within 30 days of Informed Consent:

- Demographics
- Medical history (including height and weight)
- Antiplatelet and anticoagulant medications
- Rutherford category
- Blood tests (RBC, WBC, Platelets, and Creatinine): If creatinine is measured multiple times prior to the Index procedure, the measurement closest to the Index procedure date will be used to qualify the patient for the study.
- Color Duplex Ultrasound

Within 90 days of Informed Consent:

- ABI (routine standard of care collected within 90 days of Index Procedure)

The following baseline evaluations must be collected after informed consent is provided by the patient and prior to the Index procedure:

- Quality of life questionnaires (EQ-5D, PAQ)
- Baseline pharmacokinetic testing for plasma paclitaxel level for first 10 subjects only

A screening and enrollment log will be kept at each Site. Every patient providing informed consent will be entered in the log, and the date of written consent will be recorded. Final enrollment status and reasons for screen failure, where applicable, will also be entered for all patients providing informed consent.

5.5. Enrollment

After the baseline data has been collected, and the patient is found to meet all non-angiographic eligibility criteria (Inclusion criteria 1-6 and Exclusion criteria 1-30), the angiographic criteria will be assessed. For the items that can only be confirmed angiographically on the day of treatment; the Target vessel and Target lesion will be assessed angiographically during the start of the interventional procedure, to determine whether they meet angiographic eligibility criteria (Inclusion criteria 7a-7i).

The patient is considered enrolled following successful pre-dilation of the lesion, and when the GORE® DCB Catheter enters the patient's vasculature.

5.6. Procedure

Preparation of patients for the Index procedure should include initiation of an appropriate dosage of antiplatelet medication prior to the procedure, consistent with best medical practices and institutional standards. It is recommended that the following perioperative anticoagulation therapy be applied: loading dose of aspirin of 300 to 500 mg and a thienopyridine-class antiplatelet medication of 300 mg within 24 hours of the Index procedure or 2 hours post-procedure. Heparin must be administered at the time of the Index procedure in a dose of at least 5000IU.

A radiopaque ruler, marker pigtail, external measurement tape, or the calibration measurement from the imaging software must be used for all angiographic imaging.

The balloon delivery system may be accessed from either ipsilateral antegrade or contralateral retrograde approach. A popliteal retrograde approach is allowed especially when an occluded lesion is treated.

If needed, interventional treatment of the ipsilateral iliac artery for an in-flow and / or contralateral iliac artery for a catheter delivery will be performed during the Index procedure. If attempted, this procedure must be successful in restoring in-flow prior to proceeding to the SFA/PA for balloon treatment. Such treatment will be consistent with best medical practices and institutional standards.

Prior to balloon deployment, the vasculature of the Target limb will be visualized angiographically, and the dimensions of the Target vessel and Target lesion will be determined and recorded. Angiographic eligibility criteria will be assessed at this time; angiographic eligibility must include successful pre-dilation of the Target lesion.

Pre-dilation of the Target lesion is intended to dilate the vessel segment to be treated, in order to prepare it for the dilation with the GORE® DCB Catheter and to assist the passage of the GORE® DCB Catheter through the vessel segment. The pre-dilation balloon should be 1 mm below reference vessel diameter, for vessel preparation.

In order to avoid creating a region of vessel injury that is outside the boundaries of the area to be treated by the GORE® DCB Catheter (i.e. geographical miss), limit the longitudinal length of the pre-dilatation balloon to the Target lesion. If pre-dilation is unsuccessful, the patient is not eligible for study enrollment, and will be treated as per standard of care. Treatment of the Target lesion prior to GORE® DCB Catheter use is restricted to PTA with conventional angioplasty balloon catheters. Cutting, drug eluting, or other specialized balloons may not be used. Debulking of lesions is, likewise, not allowed. Additionally, using QVA or IVUS will be recommended to confirm vessel diameter measurements.

The following data will be collected prior to use of GORE® DCB Catheter:

- Target lesion and Target vessel morphology
- Vascular access specifications
- Baseline angiographic images of the Target vessel, Target lesion, and runoff vessels
- Nominal diameter and length of balloons used in pre-dilation of the Target lesion

- Maximum Balloon pressures
- Balloon inflation time
- Outcome of the pre-dilation
- Angiographic images confirming pre-dilation success

If angiographic eligibility (Inclusion criteria 6a – 6i) is confirmed, the GORE® DCB Catheter use should be conducted in accordance with the Instructions for Use (See Appendix 1). Appropriate sizing for the balloon, introducer sheath, and guidewire are presented in Table 5. Enrollment in the study is complete when the GORE® DCB Catheter enters the patient's vasculature.

Table 5: GORE® DCB Catheter Sizing Table

Balloon Diameter (mm)[1, 2]	Balloon Working Length (mm)[1, 2]				Catheter Working Length (cm)	Introducer Sheath Size (Fr)	Recommended Guidewire (inch)
	40	80	120	150			
4	X	X	X	X	135	6	0.035
5	X	X	X	X	135	6	0.035
6	X	X	X	X	135	6	0.035

[1] Rated Burst Pressure ≥ 14 atm for all diameters and lengths.
[2] Nominal Inflation Pressure is 6 atm for all diameters and lengths.

The proximal and distal ends of the lesion will be identified using angiography prior to balloon deployment, and proper placement of the balloon will be monitored and confirmed using fluoroscopy.

The drug, Paclitaxel, is coated on the surface of the GORE® DCB Catheter, which during dilatation comes into close contact with the vessel wall allowing the transfer of the drug to the adjacent tissue. Each GORE® DCB Catheter can only be used once for drug delivery. The dose has been selected on the basis of the animal experiments and the clinical experience with conventional drug coated balloons.

Inflate the GORE® DCB Catheter for minimum 60 seconds at an inflation pressure that completely eliminates any balloon waisting and is at or above nominal pressure, but does not exceed the rated burst pressure (RBP) for that diameter balloon. Select the appropriate length device to completely cover the Target lesion (extending approximately 10 mm beyond the proximal and distal edge of the Target lesion). For longer lesions, multiple GORE® DCB Catheters may be used, with at least a 10 mm overlap between balloons.

Post dilation is allowed per operator discretion. Provisional Stenting of the Target lesion is reserved for patients with a persistent ≥50% residual stenosis (visually estimate) or >10 mmHg trans-lesional gradient, or flow-limiting dissection after repeated post dilation of a minimum of 3 minutes. If treatment will require a provisional stent, a bare metal stent should be utilized for the Provisional Stenting. The bare metal stent that is selected should be long enough to cover the area that was suboptimally dilated, but to avoid geographic miss, the bare metal stent that is selected should be at least 5 mm shorter than the area treated by the GORE® DCB Catheter.

Immediately following the procedure, vascular sheaths can be removed according to usual hospital practice and vascular closure devices may be used at the discretion of the Investigator in accordance with the manufacturer's directions.

With the exception of the GORE® DCB Catheter, the equipment used, imaging performed and medical devices used, during the index procedure, are standard of care. Each site will be responsible for using and maintaining the equipment and medical devices in accordance with the manufacturer's directions and their institutional practices.

Procedural complications arising after enrollment of an eligible subject should be treated as per investigator discretion and standard of care.

The following data will be collected after the GORE® DCB Catheter and any post dilation balloons are use:

- Outcome of balloon deployment
- Nominal Balloon sizes/dimensions
- Maximum Balloon pressures
- Balloon inflation times
- Residual stenosis and/or pressure gradient
- Adverse event (AE) information
- Information on treatment of inflow disease
- Provisional stenting information – reason for Provisional stenting, manufacturer brand and size, post dilation location within original balloon segment, deployment issues with the stent
- Final angiographic images of treated lesion
- Pharmacokinetic testing for plasma paclitaxel level – immediately after procedure, 1 hour post procedure and 3 hours post procedure for first 10 subjects only

The following data will be collected prior to discharge:

- Antiplatelet and anticoagulant medications
- AE information
- Pharmacokinetic testing for plasma paclitaxel level – at 24 hours or at discharge whichever is sooner for the first 10 subjects only

All required angiographic images should be collected in accordance with the core lab imaging guidelines. Copies of required images will be submitted as described in Section 6.4.

Dual antiplatelet therapy will be required for 1 month post-procedure and can be extended for longer periods in case of Provisional Stent placement. The use of aspirin and a thienopyridine-class antiplatelet medication is recommended, unless discontinuation or modification of this therapy is deemed medically necessary by a Site Investigator or a Sub-Investigator. After 1 month post-procedure, aspirin is recommended at least 6 months.

5.7. Repeat Interventions

Study subjects requiring TVR/TLR after the Index procedure will continue to be followed at the specified study follow-up intervals until study completion. Appropriate reintervention therapies may be selected at the discretion of the Site Investigator or Sub-Investigator, although chosen therapies must be commercially available in Germany and may not be specifically contraindicated for use for such repeat intervention. The GORE® DCB Catheter may not be used in reintervention procedures.

A CDUS is required prior to any subsequent angiography of the index limb, and the images must be submitted to the core lab (and to Sponsor if requested). Angiographic images of the treated lesion before and after reintervention are required, and shall be submitted to the core lab (and to Sponsor if requested) as described in Section 6.4.

5.8. Follow-Up

The first 10 consecutive subjects enrolled will complete a 14 day follow-up telephone call to assess any adverse event status.

These 10 study subjects and all other study subjects enrolled will return to the Site for four scheduled follow-up visits throughout the course of the study. These visit intervals, as well as the acceptable time window for each visit, are listed in Table 6.

Table 6: Follow-up Intervals and Associated Visit Windows

Follow-up Visit	Acceptable Visit Window
1 month	30 ± 7 days
6 months	182 ± 30 days
12 months	365 ± 45 days
24 months	730 ± 45 days

The following data will be collected at the 1-, 6-, 12-, and 24- month follow-up intervals:

- Antiplatelet and anticoagulant medications
- Rutherford category
- ABI
- Quality of life questionnaires (EQ-5D, PAQ)
- AE information
- Duplex ultrasound
- Angiography (required for the 6 month interval, when available for all other follow-up intervals)

All images and associated data, including duplex ultrasound and angiographic imaging, should be collected in accordance with the imaging guidelines provided by the core lab. Copies of all images and associated data will be submitted to the core lab (and to Sponsor if requested) as described in Section 6.4.

5.9. Subject Withdrawal from the Study

Subjects can withdraw from this study at any time. In addition, if the investigator determines that continued participation may adversely affect the health of a subject, they can discontinue the participation of the subject at any time. When withdrawing the participation of a subject for any reason, the Site Investigator or Sub-Investigator records the date of discontinuation, the reason for discontinuation, and the subject's condition at the time of discontinuation in the Subjects medical record and on the appropriate electronic case report form. If the discontinuation is caused by the development or worsening of AEs, information on the AEs should also be recorded in the subject's medical record and on the appropriate electronic case report form. All data generated prior to subject withdrawal will be maintained, and study data will be used as appropriate.

If the subject declines the six month angiographic follow-up, he/she will be asked to undergo clinical follow-up at six months and continue to be followed through the duration of the study. Subjects who have not voluntarily withdrawn from the study but fail to return for follow-up visits will be considered 'lost to follow-up' only after every effort has been made to encourage them to comply with protocol. Before a subject is considered "lost to follow-up", the subject's primary physician will be contacted to obtain clinical follow-up. Efforts to ensure that every enrolled subject completes every follow-up visit will be documented.

It is important that the investigator encourage subjects to return for all required follow-up visits. The clinical study objectives may not be met if a significant number of subjects miss scheduled follow-up visits or are lost to follow-up.

5.10. Subject Lost to Follow-Up

A subject will be considered lost to follow-up and withdrawn from the study once they have missed two consecutive follow-up visits and three documented attempts have been made by the Investigator or designee to contact the subject or next of kin. One of the three documented attempts should include a certified letter or comparable communication.

5.11. Subject Study Completion

A subject has completed the study when:

- The subject completes the 24-month follow-up visit
- Surgical bypass of the Target lesion
- Death
- Voluntary withdrawal
- Investigator withdrawal

Subjects will not be provided with any medical care under this protocol by the Sponsor after study completion or withdrawal. It is expected that subjects will be treated according to hospital standard of care once they have completed the study or are withdrawn from the study.

5.12. Device Deficiencies

Device deficiencies are defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.[15] A device deficiency may be attributable to a number of causes, including design, manufacturing, import, distribution, use, etc.

Device Deficiency Reporting: All device deficiencies – even those that could have led to a SAE should be reported to the Sponsor immediately. The following information on each reported deficiency will be collected:

- Description of deficiency
- Date of occurrence
- Batch code and lot number of the affected device
- Related subject AE information (if applicable)

6. Study Administration

6.1. Training

All investigators performing an intervention with the GORE® DCB Catheter must be trained on the Protocol, study device IFU and receive didactic training on the GORE® DCB Catheter from a Sponsor associate or designees prior to use of the study device.

6.2. Monitoring

Site monitoring for this study will be provided by InnoRa GmbH (Berlin, Germany). Monitoring oversight will be provided by the Sponsor.

The Site monitors are qualified by training and experience to oversee the progress of the study at the Site and will verify that the Investigators and their staff understand and adhere to both the applicable regulatory requirements and the study Protocol. In addition, they may assist in resolution of any problems that may arise during the study.

Site initiation will be performed to verify that each Investigator and his / her staff understands the Protocol, applicable regulations, and the Investigator's obligations (including protecting the rights, safety, and welfare of subjects under the Investigator's care). This visit will confirm that required documentation with the appropriate approval is in place prior to subject enrollment.

Site monitoring will occur to verify continuing adequacy of facilities and adherence to the study Protocol, the GCPs, and applicable regulations and laws that pertain to the conduct of the study. These activities will also include the review of the CRFs and source documentation, the timely submission of accurate records to the Sponsor, and the maintenance of proper records. A report will be written following each Site visit and a follow-up letter will be provided to the Site with a summary of findings. Details of the site monitoring will be covered in a Clinical Monitoring Plan and will outline the frequency of visits based on the number of subjects enrolled per site and site performance. It is expected that each site will be visited a minimum of one time per year and more often based on enrollment at the site. Each Site will also be visited at close-out to confirm that all documentation is complete and that Site personnel understand any ongoing responsibilities pertaining to the study.

6.3. Device Accountability, Storage and Return

A variety of sizes (diameter and lengths) of the GORE® DCB Catheters will be provided free of charge to the Investigators. GORE® DCB Catheter sizing information is provided in Table 5. The longest study device available is 150mm in length. The longest lesion to be treated is 150mm in length. Due to overlap requirements this longest lesion length should be treated with a minimum of two study devices. Depending on the variety of sizes on hand at each site, it is estimated that the number of study devices to be used during this study will range from 52 (one per subject) to 104 (two per subject for longest length lesion). This number will be higher should more than two devices be required to successfully treat the target lesion.

These devices may only be used under the supervision of the Investigator and in strict accordance with this Protocol and applicable laws and regulations. The device may only be used in subjects who sign the ICF, meet the inclusion / exclusion criteria set forth in this Protocol and the device may be used only as described in this Protocol. The Investigator will maintain accurate, detailed records of all devices received from the Sponsor, or the Sponsors designee, and the disposition of each device. Information collected on the Device Accountability Log include: date of receipt, catalog number and batch code (Lot # / Serial #), expiry date, date of use, subject identification, the date of return of used and unused devices. The Investigator will record each device used on the corresponding CRF and Device Accountability Log. The Investigator will notify the Sponsor immediately if any devices are damaged or unaccounted for. At each study site, the GORE® DCB Catheter will be kept at room temperature in locked storage to which only authorized study personnel have access. All other devices and medications required for patient treatment in this study will be provided by the hospital and treating Investigator / study personnel according to institutional practice.

The study monitor will periodically check the supply of study devices held by the Investigator or his designee to verify accountability of all study devices.

All used and unused GORE® DCB Catheters will be returned to the Sponsor or to the Sponsor designee after use or at the end of the trial or whenever the Sponsor requests the Investigators to return the devices, regardless of the reason. A specimen shipping kit will be made available to the Site for such return. The specimen shipping kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

The Sponsor will have the used GORE® DCB Catheter analyzed for the remaining drug on the balloon. Because of this, the used GORE® DCB Catheter should be prepared for return per the directions in the specimen shipping kit.

In the event that a GORE® DCB Catheters is opened but not used, return such device as explained in the specimen shipping kit.

Upon completion or termination of the study or the Investigator's participation in the study, or at the Sponsor's request, the Investigator will return any remaining supply of the device to the Sponsor or dispose of the devices as directed by the Sponsor.

6.4. Core Lab

All ultrasound and angiographic images collected during the study will be analyzed by a core laboratory. The core lab services for this study will be provided by coreLab Black Forest GmbH, Medical Quality Analysis Center (Bad Krozingen, Germany).

All Images will be collected in accordance with the imaging guidelines provided by the core lab and either sent via CD/DVD or uploaded thru an image transfer service provided by the core lab or other image transfer vendor. Sponsor may also request copies of images sent directly to the Sponsor.

6.5. Protocol Deviations

A Protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. The Investigator is responsible for promptly recording and reporting Protocol Deviations to the Sponsor and the reviewing EC per EC policy, if applicable. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the study and subject safety and determine if additional reports or actions are required. Additional action may include Site retraining, removal of devices from the Site, and / or Site termination.

The Investigator must follow the protocol, except in the event of an immediate hazard(s) to a subject. The Investigator must report those deviations immediately to the sponsor. The Investigator will report the Protocol Deviation in accordance with the applicable regulations.

6.6. Protocol Amendments

The Sponsor will obtain EC approval and depending on national regulations, competent authority approval, and approval of other authorities (as applicable), on all amendments prior to implementation, in a timely manner. The Sponsor will assure and document proper training of Investigator and Site staff on all protocol amendments.

6.7. Presence of Sponsor Representatives

Subject to the Site's approved ICF, Sponsor representatives may be present during study procedures to observe and provide technical assistance to the Investigator in the use of the device. The activities of these Sponsor representatives will be supervised by the Investigator.

6.8. Access to Source Data/Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the Clinical Investigation.

The Investigator will keep all study records, source data and investigational devices available for inspection by the Sponsor, Sponsor's monitors, EC, and regulatory authorities.

6.9. Study Records Retention

The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Records will be maintained during the study and for a minimum of 15 years after study completion. Documents required for the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz – BfS) must be maintained for 10 years. In any event, study records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but not be limited to: All correspondence with another investigator, an EC, the Sponsor, a monitor, or Regulatory Authority, including required reports:

- Records of receipt, use or disposition of a device that relate to:
    - The type and quantity of device(s) received, the date(s) of its receipt, and lot or batch number or code mark and expiry date.
    - The names of all persons who received, used, or disposed of each device.
- Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records, including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
    - Documents evidencing informed consent. For any use of a device without informed consent, a written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain the informed consent is required. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
    - All relevant observations, including records concerning adverse device effects (anticipated and unanticipated), the information and date and condition of each subject upon entering the study, and information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, any amendments, and documentation of any deviations from the protocol, including the dates and the reasons for such deviations.
- Any other records that Regulatory Authority requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- A signed Investigator Agreement.
- Any other records as required by the Regulatory Authority, the EC and the Sponsor.

The Investigator will prepare and submit the following reports:

- Withdrawal of EC approval: The Sponsor should receive information of the withdrawal of EC approval prior to the Investigator notice from the EC. The Investigator will confirm any withdrawal of approval within 5 working days after the Investigator has been notified of the withdrawal.
- Progress reports: Progress reports documenting the procedure, AEs and follow-up data concerning individual subjects will be submitted to the Sponsor on standardized CRFs. The Investigator may also be required to submit progress reports and final reports to the EC and to the Sponsor summarizing the Investigator's experience during the study.
- (S)AEs and UADE Reports: (S)AEs and UADEs shall be reported as described in Section 9.
- Device deficiencies: Device deficiencies shall be reported as described in Section 5.12. Device deficiencies that could have led to a SAE must be reported as described in Section 9.1.4.
- Protocol Deviations shall be reported as described in Section 6.
- Other: Any other reports as reasonably requested by the Sponsor or required by Regulatory Authority.

6.10. Publication Plan

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. The Sponsor will register the study and post results as required by this policy and applicable any other local laws and regulations.

It is the intent that the multicenter results of this study will be submitted for publication (in a peer reviewed journal). A publications committee will be established to review the multicenter results and develop publications. The publications committee is anticipated to consist of the Lead (National) PI (first author) and other enrolling physicians in the study, along with Sponsor representation. The timing of the multicenter publication may be dependent on regulatory submissions and approvals but is anticipated to occur within 12 -24 months after receiving CE Mark approval to commercially market the GORE® DCB Catheter. Individual Sites should coordinate requests for publication through the Sponsor or a publications committee.

7. Data Collection and Submission

The validated Clinical Data Management System (CDMS) for this study will be provided by Medrio, 345 California Street, Suite 325, San Francisco, CA 94104. The Sponsor will keep a separate Clinical Data Management Plan describing the procedures for verification, validation and security of the CDMS. The Clinical Data Management Plan will describe and document procedures regarding data management processes for this investigation.

7.1. Data Collection Methods

This study will report clinical data using the Medrio eClinical application. The CDMS will be the database of record for the protocol and subject to regulatory inspections and quality assurance review. All users will be trained to use the CDMS and will comply with study specific guidelines / instructions as well as applicable regulatory requirements.

Subject data will be collected using protocol-specific case report forms (CRF). Site staff will enter data directly into the CRF for transmission to the Sponsor. The Sites will be notified of any significant amendments to the CRFs.

7.2. Data Clarification and Correction

Once entered, data will be evaluated to confirm that it is complete, consistent and logically sound. If changes to the data in the CDMS are required, all changes, reasons for changes, and persons making the changes will be captured in the CDMS's audit trail. Sponsor will perform periodic data reviews throughout the entire study. Procedures and documentation for regular and ongoing data review are described in the Clinical Data Management Plan.

7.3. CRF Completion Schedule

CRFs will be completed and updated as soon as reasonably possible during or after each subject visit and monitoring visit.

8. Risk Assessment

8.1. Potential Risks

The risks associated with the GORE® DCB Catheter for the treatment of PAD are expected to be similar to the risks associated with devices used for peripheral dilation catheterization procedures.

Such risks associated with the peripheral dilation catheterization procedure using these devices include, but are not limited to:

- Abnormal heart rhythms
- Abrupt vessel closure
- Allergic reaction
- Aneurysm or rupture of the artery
- AV fistula
- Bleeding
- Death
- Dissection
- Embolization
- Femoral nerve compression with associated neuropathy
- Groin area bruising and discomfort
- Hematoma
- Infection
- Kidney failure
- Low blood pressure
- Perforation

- Pseudoaneurysm
- Respiratory Failure
- Restenosis
- Stroke
- Total occlusion or thrombosis
- Vessel trauma that may require re-intervention or surgical repair

Such risks associated with these devices, including the GORE® DCB Catheter, which might be associated with the addition of paclitaxel to a PTA balloon catheter include, but are not limited to:

- 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
- Peripheral neuropathy

The adverse events (clinical harms) and adverse event rates reported at 1 and 2 years in both the Medtronic SFA I&II and the Bard LEVANT 2 trials were reviewed and can be found in Appendix 1 of the GORE® DCB Catheter IB. It is expected that the adverse events and adverse event rates in the GORE® DCB Catheter trial will be similar to those observed in the Medtronic SFA I&II and LEVANT 2 trials. This is expected because the GORE® DCB Catheter has shown similar safety and performance in animal studies to the DCBs studied in these trials and the patient populations are similar.

The adverse events with occurrence rates greater than 5% from the above clinical studies are: Femoral artery stenosis, intermittent claudication, restenosis of the non-study vessel, peripheral artery occlusive disease, congestive cardiac failure, and coronary artery disease. These adverse events are typical for patients with PAD due to concomitant underlying disease and disease progress. No paclitaxel-related events were reported.

Other known risks:

- The additional radiation exposure of the 6 month angiography (pelvis-leg arteriography) is equivalent to a dose of approximately 10 mSv.
- The potential risk of loss of data confidentiality. Sponsor has taken necessary precautions in the data collection systems and by training the site personnel.

There may be unexpected risks that are not identified here or the occurrence and severity of risks can be different in a clinical study compared to routine clinical practice. Other than those listed in Section 8.1, Sponsor does not anticipate or expect any additional risks to study subjects.

8.2. Minimization of Risks

Potential risks associated with the use of the GORE® DCB Catheter may be minimized by the following activities:

- The sponsor has conducted risk management activities for the GORE® DCB Catheter according to ISO14971:2012. Risks remaining after the risk control measures have been implemented are acceptable and the effectiveness of these measures have been verified. The combined impact of the individual risks has been assessed and found to be acceptable. The benefit of the product has been assessed against the overall residual risk and determined that the medical benefit of the product outweighs the risk. The overall residual risk for this product is comparable to similar products. Therefore, overall residual risk has been evaluated for the GORE® DCB Catheter and has been deemed acceptable. All appropriate methods are in place to collect clinical information during the trial for the GORE® DCB Catheter. All risks related to the design, manufacturing and usability of the medical device have been reduced as far as possible.
- The Sponsor has performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production. Investigators will be selected who are knowledgeable and experienced in PAD procedures.
- Comprehensive Site Investigator and staff training will be conducted to share information regarding design and proper use of the GORE® DCB Catheter.
- The Site Investigator, Sub-Investigators, Study Coordinator(s) or designee at each Site will be trained to the protocol and subject follow-up requirements.
- Protocol inclusion/exclusion criteria and follow-up schedules are designed to select appropriate subjects and identify potential complications early. Subjects will be assessed post-procedure and subsequently on a regular basis to collect information on the subject's status and any reportable Adverse Events.
- Data completed by the Sites will be monitored to evaluate protocol compliance and for accuracy and subject safety.
- Safety and efficacy findings during the study will be shared with the Site Investigators to aid understanding of the device and potential complications associated with its use.
- An independent CEC / DSMB will meet regularly to review safety events occurring in the study. Once a combined CEC / DSMB is established, a charter will be created to include study stopping rules to protect the safety of study subjects, and describe the meeting schedule to review AEs. Termination or modification of the study may be recommended by the CEC / DSMB for any perceived safety concern based on clinical judgment, including, but not limited to, a higher than anticipated rate for any component of the safety endpoint, device failures resulting in AEs or unexpected SAEs. Study discontinuation or suspension will be in accordance with Section 11.8.

- Possible interactions with concomitant medical treatments is not expected as such treatment will be consistent with best medical practices and institutional standards. No interactions with antiplatelet therapy or paclitaxel have been reported in other drug coated balloon trials.

8.2.1. Early Safety Monitoring

As a means to monitor subject safety during the early clinical experience, the following process will be followed:

- The first 10 consecutive subjects will be enrolled at a single center by the Coordinating Investigator.
- Pharmacokinetic testing for plasma paclitaxel level will be performed at the following periods: pre-procedure, immediately post procedure, 1 hour post procedure, 3 hours post procedure and at 24 hours or at discharge whichever is sooner. The paclitaxel concentration data will be used to construct pharmacokinetic curves, calculate elimination half-life, calculate area under the curve and measure maximum concentration of paclitaxel in the blood stream.
- Site will complete a 14 day follow-up telephone call with these first 10 subjects to assess their adverse event status. The Site will make every attempt to complete this telephone call shortly after the end of the 14 day period. The telephone call with be documented in the subjects medical record and data will be entered into the EDC on the adverse event form (if appropriate).
- Once all 10 early safety monitoring subjects have reached 14 days post-treatment or have discontinued (whichever is sooner) and a telephone interview has occurred, Sponsor will request that the site enter all known data into the EDC, the data will be verified by the Sponsor's Clinical Research Monitor, and the EDC will be signed by the Coordinating Investigator. Sponsor will then export the AE / SAE data and provide it to the independent CEC / DSMB who will meet and provide a formal written recommendation to continue, modify, or stop the study. This recommendation will be provided to the German competent authority prior to continuation of further enrollment in the study.
- As stated in Section 8.2, the independent CEC / DSMB is responsible for developing stopping rules and evaluating the safety outcomes of all subjects relative to these rules.
- Once the Sponsor receives a positive response or approval from the German competent authority to continue enrollment in the study, enrollment will be opened to all Investigators and will continue until a total of 52 subjects are enrolled. If the recommendation is to modify the study, further enrollment will be stopped until such time as the modifications are approved by the German competent authority. If the recommendation is made to stop the study, the Sponsor will halt further enrollment.

- As stated in 8.2, the CEC / DSMB will continue to monitor subject safety for the duration of the study and retains the ability to make recommendations to terminate or modify the study.
- This formal CEC / DSMB recommendation will be communicated to the Sponsor, German competent authority, and ethics committee(s).

8.3. Summary of Expected Benefits

The benefits of the GORE® DCB Catheter have not been determined because the device has not yet been evaluated in humans. However, because the GORE® DCB Catheter has demonstrated similar pharmacokinetics and safety in animal studies (see IB) as other commercially available DCBs, the clinical benefit is expected to be similar. Those benefits include, but are not limited to, reduced late lumen loss, restenosis rate, and target lesion revascularization and increased patency.

8.4. Risk-to-Benefit Rationale

Paclitaxel has been used safely in humans for over 20 years at doses much higher than the dose applied to the GORE® DCB Catheter. In addition, paclitaxel-coated balloons have been used safely in humans since 2004 with similar doses of paclitaxel as the GORE® DCB Catheter. Pre-clinical animal studies of the GORE® DCB Catheter were conducted to demonstrate safety and evaluate device performance (See IB for detailed descriptions and results of these studies). All devices performed as expected in the porcine models; no additional procedural risks were identified. Post mortem examination of the treated arteries demonstrated freedom from injury associated with the device. No potential clinical harms resulting from treatment with the GORE® DCB Catheter were identified from the animal studies. These pre-clinical animal studies support the expectation that the benefits of the GORE® DCB Catheter described in section 8.3 outweigh the potential risks described in section 8.1.

In addition, the sponsor has conducted risk management activities for the GORE® DCB Catheter according to ISO14971:2012. Risks remaining after the risk control measures have been implemented are acceptable and the effectiveness of these measures have been verified. The combined impact of the individual risks has been assessed and found to be acceptable. The benefit of the product has been assessed against the overall residual risk and determined that the medical benefit of the product outweighs the risk. The overall residual risk for this product is comparable to similar products. Therefore, overall residual risk has been evaluated for the GORE® DCB Catheter and has been deemed acceptable. All appropriate methods are in place to collect clinical information during the trial for the GORE® DCB Catheter. All risks related to the design, manufacturing and usability of the medical device have been reduced as far as possible.

9. Adverse Events and Safety Monitoring

Adverse Events (AEs) are defined per ISO 14155:2011[15], as any untoward medical occurrences, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject, user or other persons from the beginning of the Index procedure until the final follow-up visit, whether device-related or not.

[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 For users or other persons, this definition is restricted to events related to investigational medical devices.]

9.1. Anticipated Adverse Events

Anticipated AEs are complications that are known to be associated with PAD patients undergoing endovascular PTA procedures. See Section 8, Risk Assessment.

9.1.1. Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device, procedure, or disease. The CEC / DSMB will review this information and provide a final adjudicated relationship.

Only one primary relationship will be assigned to each reported AE.

Study Device-related

The functioning or characteristics of the device caused or contributed to the Adverse Event. This includes adverse device effect (ADE), defined as an adverse event related to the use of an investigational medical device.

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Study Procedure-related

The Index procedure (and not the device) caused or significantly contributed to the Adverse Event.

Disease-related

The underlying PAD disease progression caused or contributed to the Adverse Event, and not the device or procedure.

Not-related

An Adverse Event which cannot be attributed to the device, procedure, or PAD disease.

Unknown relationship

The relationship of the Adverse Event to the device, procedure, or disease cannot be determined.

9.1.2. Adverse Event Classification

Each AE, regardless of the causal relationship with the investigational device, will be assessed by the Investigator to determine if it is Serious or Non-serious, as defined below. The CEC / DSMB will review this information and provide a final adjudicated classification.

Serious Adverse Event (ISO 14155:2011 Definition[15])

A Serious Adverse Event is an Adverse Event that

- led to death
- led to serious deterioration in the health of the subject that either resulted in
  - a life threatening illness or injury, or
  - a permanent impairment of a body structure or body function, or
  - inpatient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note 1: In the EU, 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: For the purposes of this study, inpatient hospitalization includes any hospitalization lasting 24 hours or more. Hospitalization without the onset of a new adverse event or aggravation of a pre-procedure complication, such as hospitalization listed below, will not be handled as serious adverse events and do not have to be reported to the sponsor.

- Hospitalization planned prior to enrollment in the study
- Administrative hospitalization (e.g. hospitalization for a regular medical checkup, examination or training)
- Hospitalization at a rehabilitation facility

Note 3: In Germany, this includes the Serious Adverse Event (SAE) definition according to §2 No. 5 MPSV - A serious adverse event is any undesirable event that occurred in the course of a clinical trial or perfomance evaluation requiring approval which, directly or indirectly, has led, might lead or might have led to death or to a serious deterioration in the state of health of a subject, or user or other person whether or not the event was caused by the investigational medical device.

Serious Adverse Device Effect (SADE)
A serious adverse device effect is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Non-serious Adverse Event
Any AE not meeting the above definition of serious.

9.1.3. Adverse Event Reporting and Coding

AEs will be reported on the appropriate case report form (CRF) and documented in the subject's medical record. The Investigator at each Site is ultimately responsible for reporting AEs to the Sponsor.

The following information on each reported Adverse Event will be collected:

- AE description
- AE onset date
- Date AE was reported to the Sponsor
- Timing of the event (during or after the Index procedure)
- Relationship
- Seriousness
- Treatment
- Outcome
- Resolution Date

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

AE submission guidelines:

- AE reporting begins once the patient is enrolled in the study. All AEs should be reported from enrollment through study completion / discontinuation.
- Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. AE should be reported using the full name without abbreviations or narratives.
- AEs with an outcome status of “Ongoing” should be assessed at each follow-up evaluation to determine if the event has resolved. AE ongoing at study completion / discontinuation should be left as “Ongoing” on the AE case report form.

9.1.4. Serious AE reporting

The following AEs must be reported immediately (without unjustified delay) to the Sponsor:

- Serious AE (including MAE): all AEs which the Investigator classifies as serious and all MAE without regard to the cause or relationship to the device.
- Device deficiencies that could have led to a serious adverse device effect.
- Study drop-out due to AE: all AEs which lead to the drop-out of a subject from continued study participation.

The site Principal Investigator or designee must immediately report all such AEs to the Sponsor by phone, fax or e-mail, as soon as possible, and within 24 hours of onset, observation, or first reporting of the occurrence. The initial report should include all available information on the event, including a written narrative detailing the clinical course of the AE. The information and causal evaluations in the narrative must be consistent with the information recorded on the AE CRF.

Updated AE CRFs and subject narratives must be forwarded when further information becomes available. The Investigator must provide a final AE CRF and the subject narrative after final assessment of the AE. Source documents must be submitted upon request (e.g., histopathology findings, catheter lab reports, etc.). All source documents must be blinded using only the subject's unique study identifier and forwarded to the Sponsor.

Additional reporting of adverse advents, serious adverse events, and device deficiencies should be conducted according to the local EC and national regulations.

In Germany, serious adverse events (regardless of causality) including device deficiencies that led or could have led to a serious adverse device effect must be reported by the Investigator to the Sponsor. The Sponsor must report all SAEs to the German regulatory authority (BfArM). If the relationship of the SAE to the study device or the study procedures performed as part of the clinical trial cannot be excluded reporting must be done immediately (without unjustified delay) by completing the "Report form for reporting of serious adverse events (SAE) in clinical trials". If the relationship of the SAE to the study device or study procedures performed as part of the clinical trial can be excluded, reporting must be done quarterly by completing the MEDDEV 2.7/3 Report table.

In addition, a quarterly summary evaluation of all SAEs must be submitted to the BfArM by completing the forms provided on the BfArM website. Details of this quarterly summary evaluation and the general requirements for SAE reporting to the BfArM including the forms to be completed may be found on the BfArM website.

9.1.5. Subject Death

In this study, death is not considered an AE, but rather the outcome of an AE. An AE reported as having an outcome of death should match the cause of death on the subject's death certificate. An ongoing AE at the time of death or study withdrawal will remain categorized as ongoing.

Attempts will be made by the Site to obtain death certificate and autopsy reports, when possible.

9.1.6. Subject Withdrawal or Discontinuation

Any ongoing or unresolved AEs at the time of withdrawal or discontinuation will be indicated as "ongoing" on the CRF.

9.2. Unanticipated Adverse Device Effects (UADE)

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, degree of incidence or outcome in the IB, investigational plan or protocol.

UADEs will be handled in accordance with Sections 9.1.1 thru 9.1.6.

9.3. Clinical Events Committee/Data Safety Monitoring Board

A combined Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) will be established to review and adjudicate all accumulating safety events (including but not limited to: relatedness of event, seriousness of event, and endpoint evaluation) and primary endpoints on a regular basis and will advise the Sponsor regarding the continuing safety of study subjects as well as the continuing validity and scientific merit of the study.

This committee will operate under pre-specified procedures as outlined in the CEC / DSMB Charter in accordance with the FDA's Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees. The CEC / DSMB will be responsible for conducting periodic reviews of aggregate data on a prescribed basis. The frequency of data review and other roles and responsibilities of the CEC / DSMB will be specified in the CEC / DSMB Charter. The CEC / DSMB will also establish stopping rules to protect the safety of the study subjects.

Based on the review of safety data, the CEC / DSMB will make recommendations to the Sponsor. Recommendations may include study termination, study continuation with or without major or minor modifications, temporary suspension of enrollment and / or study intervention until some uncertainty is resolved. All final decisions regarding study modifications rest with the Sponsor.

Termination or modification may be recommended for any perceived safety concern based on clinical judgment, including, but not limited to, a higher than anticipated rate for any component of the primary safety endpoint, device failures resulting in AEs, or unexpected Serious Adverse Events (SAEs). Section 11.8 provides additional detail regarding suspension or termination of the study.

The DCB 15-02 CEC / DSMB will consist of members not participating in the study and who are independent from the study Sponsor and experienced in peripheral interventions. The team shall include a biostatistician. The members will be compensated for their involvement in the CEC / DSMB, including reimbursement for reasonable travel expenses to attend meetings.

10. Statistical Analysis

10.1. Study Hypotheses

The study is designed to show that the performance of the GORE® DCB Catheter is superior to a performance goal derived from literature reports of uncoated PTA balloons, measured six months after intervention.[23-29]

The statistical hypothesis is specified as:

$$H_0: \mu_T \geq PG$$
$$H_A: \mu_T < PG$$

Where:

H_0: The study's Null Hypothesis states that the Mean LLL from the GORE® DCB Catheter is equal to or greater than the performance goal

H_A: The study's Alternate Hypothesis states that the Mean LLL from the GORE® DCB Catheter is less than the performance goal

μ_T is the mean LLL for the test group(GORE® DCB).

PG is the performance goal.

The performance goal considered for the GORE® DCB Catheter is 0.9 mm. The upper limit of the 95% confidence interval for the mean LLL at six months below 0.9 mm in the study would meet the requirement of the superiority of the GORE® DCB Catheter to the uncoated PTA.

10.2. Sample Size Assumptions

Previous DCB studies that were intended to supply clinical data to support CE mark approval have used uncoated PTA as a comparator for the test DCB. Given the prominent role that uncoated PTA balloons continue to play in the endovascular management of PAD lesions, peer-reviewed published data from uncoated PTA balloons were used as the starting point for calculation of a performance goal. [23-29] The clinical studies that supplied data for performance goal calculation demonstrate considerable homogeneity and bear many similarities to the proposed GORE® DCB Catheter European CE mark pivotal clinical investigation.

A random effects meta-analysis was performed for these data. This provided a value of 1.2 mm as an estimate of the mean LLL of uncoated PTA with a standard error of 0.15 mm. The resulting 95% confidence interval on the mean was [0.9 mm, 1.5 mm].

The lower limit of the 95% confidence interval of the mean LLL at six months i.e., 0.9 mm is considered the performance goal for the GORE® DCB Catheter European CE mark pivotal clinical investigation. This performance goal ensures that the GORE® DCB Catheter LLL will be superior to the uncoated PTA LLL results from the literature.

10.3. Sample Size Determination

The following assumptions were used to calculate sample size:

- Performance Goal = 0.9 mm
- One-sided Level of significance = 0.025
- Power = 90%
- LLL SD = 0.9 mm (average SD for DCBs across the published DCB studies)
- 20% loss to follow-up (average loss to follow-up across the published DCB studies)
- Expected GORE® DCB Catheter six month LLL = 0.44 mm (median DCB LLL from the published DCB studies)

Using these assumptions, the calculated sample size is 52 subjects.

10.4. Data Analysis

10.4.1. Timing of Analyses

One formal statistical analysis is planned for the European CE mark approval when all enrolled subjects would have either completed six month follow-up and the data are available or would have completed the study as defined in this protocol. Other informal analyses may be performed throughout the course of the study. The final analysis will be performed once all subjects will have completed the study.

10.4.2. Analysis Populations

All subjects enrolled into the study will be part of the ITT population dataset. In addition a Per-protocol population dataset will be created and will consist of all subjects enrolled into the study who meet all inclusion and exclusion criteria and receive treatment as per protocol.

10.4.3. Pooling of Data

All the sites in the study will follow the same protocol, receive the same training and will be monitored for adherence to the study plan and regulations, the data collection and handling procedures and guidelines will also be same for all sites. Therefore the data from all sites will be pooled and analyzed.

10.4.4. Statistical Analysis of Primary Endpoint(s)

The 95% confidence interval for the estimated mean LLL at six months will be constructed using a normal distribution. The upper limit of the confidence interval below the performance goal of 0.9 mm will lead to reject the null hypothesis. The one sided p-Value will be obtained using the test for the equality of mean to the performance goal and will provide consistent decision if the p-Value is less than 0.025.

No formal performance goal is specified for the Safety Endpoint. The presentation will include frequency and the percentage of the composite MAEs along with its components i.e., Death, CD-TVR and Major Amputation occurring within 30 days of the initial procedure.

Any deviation(s) occurring from the original statistical plan during the course of this study will be documented in the Sponsors Statistical Analysis Plan.

10.4.5. Statistical Analysis of Secondary Endpoint(s)

No formal performance goals are specified for the secondary endpoints. The numeric endpoints will be analyzed using mean and standard deviations whereas qualitative or categorical endpoints will be presented using frequencies and percentages with confidence intervals as appropriate. Kaplan Meier estimates will be calculated for the endpoints involving time to event.

10.4.6. Subgroup Analysis

In addition to the overall analysis, the LLL will also be presented by Age and Gender. Subject numbers are insufficient to test clinically meaningful variation in performance among sub-groups. Therefore, no hypothesis is specified for such analysis.

11. Ethical and Regulatory Considerations

11.1. Statement of Compliance

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) – as applicable, ISO 14155:2011, and other applicable regulatory requirements.

The following are applicable to this study:

21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 50	Protection of Human Subjects

21 CFR Part 54	Financial Disclosure By Clinical Investigators
21 CFR Part 56	Institutional Review Boards
21 CFR Part 812	Investigational Device Exemptions
ICH-GCP E6	International Conference on Harmonization Regulations Guideline For Good Clinical Practice
Amendment to the MDD (2007/47/EC) Article 15 Annex X	Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007
ISO 14155:2011 (E)	Clinical investigation of medical devices for human subjects – Good clinical practice
MPG	The Act on Medical Devices (Medizinproduktegesetz – MPG) in its currently effective version
MPKV	Ordinance on Clinical Investigations with Medical Devices (Verordnung über klinische Prüfungen von Medizinprodukten (MPKPV) in its currently effective version
MPSV	Ordinance on the Central Collection, Analysis and Prevention of Risks Arising from the Use of Medical Devices / Safety Plan for Medical Devices (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten) in its currently effective version

11.2. Compliance Responsibilities

The Sponsor will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing EC and German competent authority. Any additional requirements imposed by the EC or regulatory authority shall be followed. The Sponsor will be responsible for documenting that Investigators have the necessary skills, training and information to properly conduct the study. The Sponsor will confirm proper monitoring of the study and is responsible for obtaining EC and BfArM approval prior to enrollment. The clinical investigation shall not begin until the Sponsor has confirmed the required approval / favorable opinion from the EC or regulatory authority have been obtained. The Sponsor will provide information to the Investigators, the reviewing EC and German competent authority concerning the progress of and any new material information about the study.

The Investigator will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing EC and German competent authority. Any additional requirements imposed by the EC or regulatory authority shall be followed. The Investigator will verify EC approval is obtained prior to enrollment, maintained throughout the course of the study, and that all EC reporting requirements are met, if required per national regulations. The Investigator is responsible for protecting the rights, safety, and welfare of subjects under the Investigator's care and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is properly obtained.

The Sponsor will obtain clinical trials insurance as required by the laws of each country in which the study is conducted.

The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

11.3. Informed Consent

The Investigator shall verify that all potential subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.

The formal consent of a subject, using the EC-approved consent form, must be obtained by the Investigator before that subject undergoes any study-related procedure. The consent form will be signed and personally dated by the subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the subject records. A copy of the informed consent document will be given to the subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a subject's willingness to continue to take part in the study will be provided to the subject.

The Investigator shall verify that documentation of the acquisition of informed consent is recorded in each subject's records in accordance with applicable regulations.

Emergency contact details for reporting serious adverse events and serious adverse device effects will be listed in the EC-approved Informed Consent Form.

11.4. Independent Ethical Review

The Investigator shall not enroll any subjects prior to obtaining approval for the study from a properly constituted independent EC.

The Sponsor will submit the protocol, protocol amendments, informed consent forms, other information to be provided to subjects such as survey instruments or questionnaires, and any proposed advertising / recruitment materials, to the EC for written approval.

11.5. Conflict of Interest

All Investigators will follow applicable laws and regulations as well as the conflict of interest policies of their Site and the reviewing EC.

11.6. Emergency / Compassionate Use

No emergency or compassionate use of GORE® DCB Catheter will be allowed.

11.7. Confidentiality

All subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

The Investigator will inform the subjects that their records will be reviewed.

De-identified data generated by this study may also be reviewed by the Site's EC and other regulatory bodies, [e.g., FDA, BfArM, MPA Sweden, BSI, PMDA].

11.8. Study Discontinuation or Suspension

The entire study may be suspended or prematurely terminated by the Sponsor in the following cases:

- Serious adverse events as defined in section 9.1.2 attributable to the investigation.
- If new data become available which raises concern about the safety of the GORE® DCB Catheter, so that continuation of the study might cause unacceptable risks to the subjects.
- If suspicion of an unacceptable risk to subjects arises during the clinical investigation, the Sponsor may suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed.
- National regulatory authority withdrawal of study approval.
- On recommendation by the CEC / DSMB for any perceived safety concern based on clinical judgment, including, but not limited to, a higher than anticipated rate for any component of the safety endpoint, device failures resulting in AEs or unexpected SAEs.

Study participation of an individual study site or an individual member of a study site may be suspended or prematurely terminated by the Sponsor in the following cases:

- If a principal investigator, EC or regulatory authority responsible for the study has withdrawn approval for any reason.
- If Sponsor monitoring or auditing identifies serious or repeated deviations on the part of the study site or an individual study investigator.

Procedures for suspension or premature termination of this study are:

- If the Sponsor, EC or regulatory authority suspends or prematurely terminates the study, all enrolled subjects shall continue to be followed and treated as per standard of care at each site. The Sponsor may request that subjects are contacted or complete an office visit prior to study termination.

- The Investigator or each site or authorized designee shall promptly inform the enrolled subjects.
- If the Sponsor received notice that the EC and / or regulatory authority approval has been withdrawn for any reason, the Sponsor shall notify the Investigator as soon as possible and preferably within 24 hours. Study enrollment must immediately cease until such approval is reinstated.
- If the Investigator receives notice that the EC and / or regulatory authority approval has been withdrawn for any reason, the Investigator shall notify the Sponsor as soon as possible and preferable within 24 hours. Study enrollment must immediately cease until such approval is reinstated.
- If the Sponsor suspends or prematurely discontinues the study the Sponsor shall inform the investigators, the ECs and the authority of the rational and provide them with the relevant data supporting this decision.
- If the study (or a study site) is prematurely terminated a routine close out visit as described in Section 6.2 will be performed.

The procedures of premature study termination of an individual patient (voluntary withdrawal or withdrawal of the patient by the investigator) are detailed in section 5.9 and 5.11 of the study protocol.

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 shall obtain concurrence from the ECs and, where appropriate, the regulatory authority by providing the rational and relevant data supporting this decision before the clinical investigation resumes.
- When concurrence from ECs and, where appropriate, other regulatory authorities is obtained, the Sponsor shall inform the investigators to resume the clinical investigation.
- If subjects have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.

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