Investigation of Femoropopliteal In Situ Valve Formation with the InterVene System

INFINITE-US

Version: CLN 004 Rev 06

Version Date: 23 Mar 2022

Sponsor

InterVene, Inc.

415 Grand Ave, Ste. 302

South San Francisco, CA 94080

USA

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INVESTIGATOR PROTOCOL SIGNATURE PAGE

Investigation of Femoropopliteal In Situ Valve Formation with the InterVene System (INFINITE-US)

Investigator Name (Print)

Investigational Site Name **Investigational Site Number**

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the device relating to past non-clinical and clinical experience, which were furnished to me by the Sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study.

I agree to keep records on all subject information (e.g., case report forms and informed consent statements), device shipments and return forms, and all other information collected during the study, in accordance with local and national regulations.

Investigator's Signature **Date**

ABBREVIATIONS

AC	Active Compression
ACT	Activated Clotting Time
AE	Adverse Event
AVF	Arteriovenous Fistula
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
CA	Competent Authority
CEAP	Clinical Etiological Anatomical Pathophysiological
CEC	Clinical Events Committee
CRO	Contract Research Organization
CRF	Case Report Form
CTV	Computed tomographic venography
CVI	Chronic Venous Insufficiency
DOAC	Direct Oral Anti-Coagulant
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
DVR	Deep Vein Reflux
DVT	Deep Venous Thrombosis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFS	Early Feasibility Study
FDA	Food & Drug Administration
FIH	First In Human
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form

IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IPC	Intermittent Pneumatic Compression
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVUS	Intravascular Ultrasound
MEC	Medical Ethics Committee
MRI	Magnetic Resonance Imaging
MRV	Magnetic Resonance Venography
NYHA	New York Heart Association
OVPT	Occlusive Valve Pocket Thrombus
PE	Pulmonary Embolism
rVCSS	revised Venous Clinical Severity Score
RT	Reflux Time
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOC	Standard of Care
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analogue Scale
VPT	Valve Pocket Thrombus

CLINICAL STUDY SYNOPSIS

Protocol Number	CLN 004 Rev 06
Investigational Device	BlueLeaf® Endovenous Valve Formation System (BlueLeaf System)
Study Title	Investigation of Femoropopliteal In Situ Valve Formation with the InterVene System (INFINITE-US)
Sponsor	InterVene, Inc. 415 Grand Ave, Ste. 302 South San Francisco, CA 94080 USA
Study Purpose	To evaluate the safety and technical feasibility of the BlueLeaf System for the restoration of deep venous competence for the treatment of symptomatic chronic venous insufficiency (CVI)
Study Population	Subjects with symptomatic CVI and a Clinical Etiological Anatomical Pathophysiological (CEAP) classification of C5 to C6
Subjects	Up to 25 treated subjects
Investigational Sites	Up to 5 investigational sites in the United States
Study Design	Prospective, non-randomized, multicenter pre-market early feasibility study (EFS) to evaluate subjects treated with the BlueLeaf System for the treatment of symptomatic CVI of the lower extremity
Primary Endpoint	Primary Safety Endpoint is a composite endpoint consisting of the following major adverse events occurring through the 30-day follow-up window, as adjudicated by the CEC: • Symptomatic pulmonary embolism (e.g. chest pain, hemoptysis, dyspnea, hypoxia, etc.) confirmed via computer tomographic pulmonary angiography • DVT anywhere in the deep venous system of the treatment limb • Occlusive valve pocket thrombus (OVPT) • Non-occlusive stenosis in the target vessel (including due to scarring, inflammation, VPT, etc.) confirmed via DUS and not present prior to the BlueLeaf procedure, leading to persistent worsening of symptoms attributable to venous flow obstruction, or requiring post-procedural surgical or endovascular re-intervention • Device or procedure-related venous or arterial injury in the treated limb (such as Arteriovenous Fistula (AVF's), bleeding, pseudo aneurysm) leading to worsening of symptoms that require post-procedural surgical or endovascular re-intervention or requiring transfusion of more than 2 units of blood. (NOTE: Peri-procedural stiches placed to assist with

	closure of the access site will not be characterized as a primary safety failure.) • Device or procedure-related death <u>Primary Efficacy Endpoint</u>: Is the change in Venous Clinical Severity Score (rVCSS).
Inclusion Criteria	Subjects must meet the following criteria to be included in the study: 1. 18 years of age or older 2. Willing and able to sign the approved informed consent form (ICF) 3. Willing to comply with follow-up evaluations and protocols 4. Symptomatic CVI subjects, Clinical Etiological Anatomical Pathophysiological (CEAP) classification of C5 to C6 5. Failed at least 6 months of conservative therapy at some point during the course of their CVI management (symptoms not adequately resolved or patient non-compliant/unable to tolerate) 6. Deep system venous reflux characterized by >1 second reflux time in two vein segments (vein segments defined as: proximal femoral, distal femoral, and popliteal), as assessed by duplex ultrasound (DUS) with patient in the standing position 7. Presence of at least two potential target sites within a target vessel as assessed preliminarily by DUS, and presence of at least one potential target site within a target vessel as assessed with IVUS peri-procedurally, with a target site being defined as a segment within the femoral or popliteal vein that is: a. 7mm to 12mm in luminal diameter, and b. at least 3cm long (two target sites in a row must be spaced at least 1 cm apart), and c. absent features that, in the Investigator's opinion, would preclude formation of a monocuspid or bicuspid valve (at any orientation). These features may include thrombus, synechiae, natural valves, major tributaries (valves can be formed opposite tributaries) or severe heterogenous changes of the vessel wall (homogenous thickening allowed) with all assessments completed while vein is under physiologically appropriate hemodynamic pressure. 8. In the Investigator's opinion, the subject is a good candidate for treatment with the BlueLeaf System based on their symptoms, quality of life, anatomy, and the likelihood of benefit from continued conservative therapy

Exclusion Criteria	Subjects with any of the following criteria are ineligible for inclusion in the study: 1. Untreated significant superficial venous incompetence which, in the opinion of the Investigator, may be the primary source of existing symptoms 2. Anatomy that does not support proper device access of the treatment vein through the ipsilateral common femoral or femoral vein 3. Acute deep venous thrombosis (DVT) within 1 year of consent (subjects with prior DVT with no apparent cause should undergo a hypercoagulability work-up prior to study entry to confirm eligibility vis-à-vis exclusion criteria #10) 4. Deep venous intervention (includes stenting) in the target limb or outflow vessels within 3 months of consent 5. Flow-limiting venous outflow obstruction central to the intended target sites, defined by a common femoral vein duplex exam found to have a continuous waveform without respiratory variation, or a ≥ 50% reduction in luminal cross–sectional area as determined by computed tomography venography (CTV), magnetic resonance venography (MRV) or IVUS 6. Inadequate flow into or through the target vessel (Investigator's opinion) 7. Luminal diameter, in any vein segment through which the device is likely to be inserted, that is < 6mm, or between 6mm and 7mm for a section of vein > 1cm in length, as assessed by IVUS while the vein is under physiologically appropriate hemodynamic pressure 8. A competent vein valve in any vein segment through which the device is likely to be inserted, as assessed by DUS (≤ 1 second reflux time) or with contrast venography (Investigator's opinion) 9. Contraindications to all protocol specified anticoagulation options 10. Known and uncontrolled hypercoagulopathy (i.e. hypercoagulopathy that cannot be adequately managed/controlled with medication) 11. Women on long-term oral contraceptives 12. Non-ambulatory patients 13. Significant peripheral arterial disease with an ankle-brachial index of < 0.70 or with incompressible vessels 14. NYHA Class III or IV heart failure 15. Patients with a history of right heart failure occurring as a consequence of, for example, biventricular failure, intrinsic pulmonary disease, chronic thromboembolic pulmonary

	hypertension, and other etiologies that result in elevated right-sided pressures. 16. Active systemic infection 17. Invasive surgical procedure within the last 3 months that in the Investigator's opinion would interfere with the study procedure or results 18. Chronic renal insufficiency with creatinine level of ≥ 2 g/dL 19. Hemoglobin level < 9.0 g/dL 20. Platelet count < 50,000 or > 1,000,000/mm^3 21. Total white blood cell count < 3,000/mm^3 22. Pregnant or lactating female; positive pregnancy test, women of childbearing potential must be tested within 7 days of planned procedure 23. Subject is enrolled in another clinical study that, in the opinion of the Investigator, may conflict with this study or compromise study results 24. Comorbidity risks or other concerns which, in the opinion of the Investigator, either limits longevity or likelihood of complying with the protocol and its prescribed follow up (e.g. recent cancer or stroke); or precludes patient from being transitioned to open surgery if complication requiring surgical intervention occurs during the procedure (such as severe vein laceration).
Follow-Up Schedule	Subjects will be followed through 1 year with annual visits through 5 years. See Table 2, Schedule of Assessments.
Core Laboratory	Assessment of duplex ultrasound and wound imaging will be performed by an independent Core Laboratory.

1 INTRODUCTION AND BACKGROUND

Chronic Venous Insufficiency (CVI) is a disease characterized by venous hypertension in the lower extremity, and a progressive spectrum of signs and symptoms. The classification system commonly used to describe the disease is CEAP (Clinical Etiological Anatomical Pathophysiological), where the Clinical (C) component is the physical description of the disease state.[1] Symptoms include pain and discomfort of the legs, often described as aching, heaviness, itching, burning and swelling. Signs of CVI include varicose veins (C2), venous edema (C3), skin changes (C4) and in the most severe patients, venous stasis ulceration (C5/6) (**Figure 1**)[2]. These symptoms are the source of significant patient discomfort, lost productivity and economic costs to society at large.[3,4,5]

Figure 1: Stages of progression from varicose veins to active ulceration in patients with chronic venous insufficiency

CVI is extremely common. Numerous reports looking at populations across Europe, Latin America, the Middle East and the Far East show that C2-C6 CVI disease is present in over 30% of the adult population.[6] Extrapolating results to the US population, it is estimated that over 40 million Americans suffer from C3 disease or worse, 8.5M Americans suffer from C4 disease or worse, and 1.6 - 2.2 million Americans suffer from a new venous ulcer every year.[7,8] A recent study based on private and public health insurance claims, estimates that venous ulcers cost the US healthcare system $14.9B, which equates to about 0.5% of all US healthcare spending. These numbers are expected to rise as the population ages, as CVI severity has been shown to correlate positively with increasing age.[6,8]

1.1 Pathophysiology of Chronic Venous Insufficiency

There are three main systems of veins in the lower leg: the superficial system, the perforators, and the deep system. The deep venous system is the main axial return pathway from the lower leg to the heart, with superficial veins connecting into deep veins via the perforating veins (**Figure 2, left**). Healthy venous return is typically characterized by an active calf pump, working one-way vein valves to prevent blood from flowing retrograde (backwards toward the feet), and an unobstructed path to the heart.

The most frequent causes of CVI are from primary abnormalities of the venous wall and vein valves, leading to vein valve failure, which causes reflux (blood is permitted to flow retrograde toward the feet), or secondary changes resulting from previous venous thrombosis that lead to

reflux, obstruction or both.[10] When vein valves fail, blood is permitted to flow retrograde toward the feet (reflux), leading to elevated venous pressures (**Figure 2, right)**, which triggers an inflammatory cascade that leads to the edema, skin changes and ulceration previously described.[16] Venous obstruction also leads to hypertension and similar symptoms.

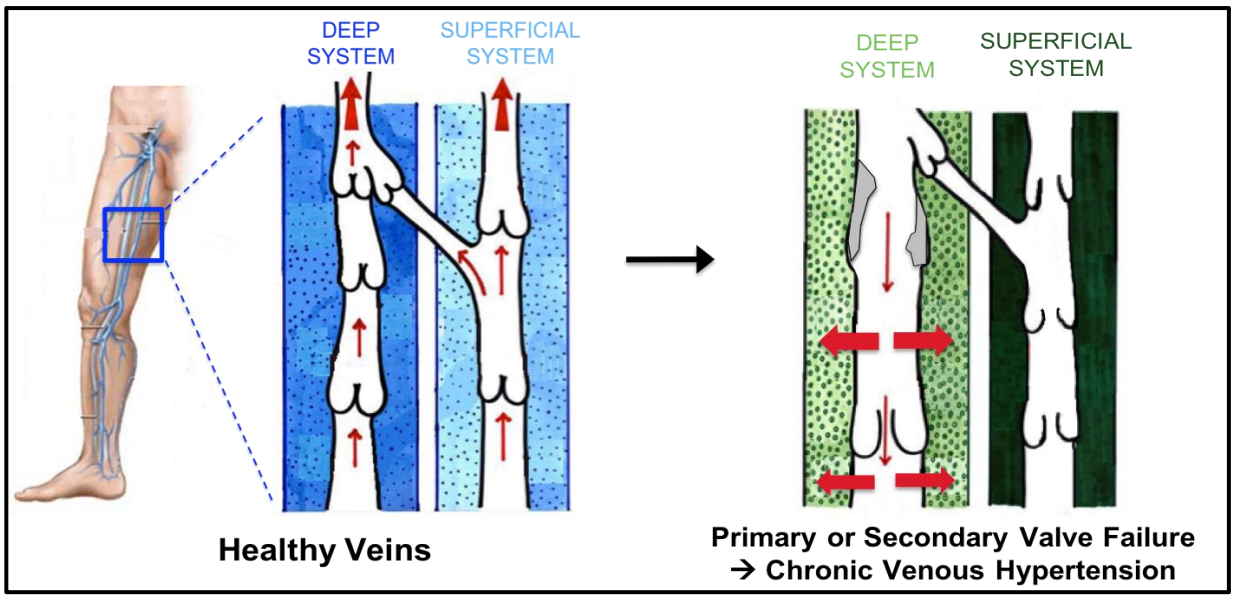


Figure 2. Healthy and diseased veins in the human lower extremity with reversal of flow in the superficial and deep venous systems.

1.2 Clinical Need

CVI patients may have one or more of the following underlying functional etiologies: deep vein reflux (DVR), superficial vein reflux, or venous obstruction. Endovenous treatments for superficial reflux and outflow obstruction (in the pelvic veins) exist and are widely used by vascular interventionalists, but patients with DVR have few therapeutic options. Some open, vein valve reconstruction surgeries exist, but they are rarely performed, and are reserved only for the most severe patients due to their morbidity and technical difficulty. The standard of care for DVR is palliative, and includes compression therapy, leg elevation and regular wound care as needed. Unfortunately, multiple studies have shown that compression therapy suffers from poor compliance - with one study reporting that 63% of patients either don't use their compression stockings at all or abandon them after a trial period.[9,10,11] Furthermore, even when patients are compliant, compression still fails to address symptoms in about 37% of patients.[9] I. As a result of a lack of therapeutic options, patients with DVR often suffer from a lifetime of severe symptoms. To illustrate this point graphically (**Figure 3**), the Bonn Vein Study revealed that patients with the most severe symptoms, and thus with the greatest clinical need, are the most likely patients to have DVR:

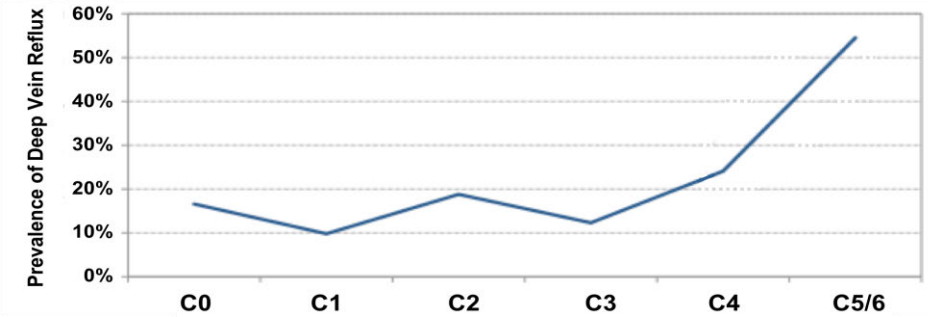


Figure 3: Correlation of Deep Vein Reflux with increasing disease severity (data to construct graph taken directly from table V. of the Bonn Vein Study)[7]

Millions of Americans suffer from untreated DVR and moderate to severe CVI. Extrapolating the German Bonn Vein study data to Americans, , it is estimated that about 6.5 million Americans have DVR and C3 disease or worse, and about 2.5 million Americans have DVR and C4 disease or worse.[7] Studies have shown that patients with chronic venous ulcers suffer a reduced quality of life similar to that of patients with malignancies, diabetes and congestive heart failure.[4]

These ongoing symptoms are not only burdensome for patients, but are costly to the US healthcare system, especially in the case of venous ulceration. The median direct cost of venous ulceration over a 1-year period has been estimated to be $6,719[8] - $15,732[12]. About 20% of venous ulcers take longer than a year to heal and impart a median cost of $33,907[12]. Based on the results shown above from the Bonn Vein Study and other reports, it is reasonable to assume that many of these 'difficult-to-heal' ulcer patients have untreated DVR. A less invasive, and easy to perform deep vein valve intervention is sorely needed for this painful condition and costly patient population.

1.3 Treatment strategies for Deep Vein Reflux

Open surgical and, more recently, minimally invasive techniques have been used to restore valve competence in the deep veins (13,14). Minimally invasive techniques have historically focused on valve implantation with a foreign body, but no clinically viable implant technologies have been proven out to date.[13,14] Open surgical procedures do exist that aim to restore vein valve competency without the need for a significant implant, but these techniques are invasive and technically challenging. For these reasons, deep vein valve reconstruction surgeries are performed in only a handful of highly specialized centers and are reserved only for the most severely symptomatic patients. While these techniques are not widely available, certain surgical variations – most notably, 'Neovalve' formation, pioneered by Dr. Oscar Maleti - do support the hypothesis that restoration of normal vein valve function in only one or two locations, without a significant foreign body implant, can relieve the symptoms of CVI without the significant safety concerns of valve implantation.[15] This observation is the basis of InterVene's approach. The BlueLeaf System is designed to mirror the goals of open surgical valve formation, but with a less invasive, easier to perform, endovenous procedure. Refer to the Investigator's Brochure (IB) for additional background information.

1.4 Manufacturer

The BlueLeaf System is manufactured for InterVene, Inc., located at 415 Grand Ave. Ste. 310, South San Francisco, CA 94080, USA.

1.5 Intended Use of the System

The BlueLeaf System is designed to treat patients with symptomatic CVI with evidence of deep vein reflux in the femoropopliteal veins. The device is intended to form autogenous valves from the inner layer of the venous wall, without the use of a permanent implant.

An autogenous valve will henceforth be defined as a non-native, newly formed valve that is monocuspid (one autogenous leaflet / pocket) or bicuspid (two autogenous leaflets / pockets).

1.6 Device Description

The BlueLeaf System is a single-use, disposable device designed to modify the vein wall to form one or more functional autogenous valves to improve the hemodynamics of the deep venous system treated (**Figure 4**). The device is supplied as a single, integrated system, but can be conceptually divided into four sub-components (**Figure 5**). The system is single use and provided in sterile form.

The BlueLeaf System is intended to be inserted through an access sheath in the groin area, and advanced into the femoropopliteal treatment vein. A physician operator will then advance the working end of the catheter to a treatment site, which is determined by physician interpretation of both fluoroscopic and intravascular ultrasound (IVUS) imaging modalities. The device is then used to form a monocuspid or bicuspid autogenous valve. Using venography and IVUS, the operator can then perform hemodynamic assessments of the valve, and then reposition the catheter at a different treatment site for formation of an additional valve. Once the operator is confident that the goals of the procedure have been accomplished, or if no additional valves can be formed, the device is withdrawn and the point of entry sealed.

The BlueLeaf System will be used only by qualified operators. For complete instructions, refer to the manufacturer's Instructions for Use (IFU) and the Procedure Training Guidelines. For additional device design and testing information, refer to the IB.

Device information including device description, required accessory components and preparation and usage steps are provided in the Instructions for Use (IFU) included in every device. A more detailed description of the procedural steps including patient screening, target site selection, and use of IVUS and fluoroscopy to accomplish the procedural steps, as well as the collection of procedural study endpoints, is included in the Procedure Training Guidelines.

1.7 Device Accountability

It is expected that an average of approximately 1.5 BlueLeaf Systems per subject will be used.

1.7.1 Accountability of Investigational Devices

Each batch of devices will be assigned, at a minimum, a lot number and serial number which will be used for tracking purposes. Device inventory will be managed using the Device Accountability Log which will include details concerning device receipt and disposition.

Access to device inventory will be controlled and devices will be housed in a secure location. Records will be maintained to document the physical location of inventory from shipment/removal from InterVene's manufacturing facility through use and/or return or disposal.

The investigational sites will be responsible for keeping records of receipt, use, return and disposal of the investigation device which shall include, at a minimum, date of receipt, device lot and serial number, expiration date, date of use, subject identification code, and date of disposition. A Device Accountability Log is provided for this purpose.

If the device is associated with a possible device-related adverse event or device deficiency, the device should be returned to InterVene, Inc. for evaluation. The InterVene representative present at the procedure will assist the investigational site with device return instructions.

All unused devices must be returned to InterVene, Inc.

1.7.2 Other Accessories and Equipment

In addition to the investigational device, a table mount interface system will be provided by InterVene (Top Mount Single Arm with QC Fitting and Rail Clamp, Model 73000-TM from Mediflex or similar).

The following accessories are also required and are the responsibility of the investigative site. See the IFU for specific recommendations for each item.

- Introducer Sheath
- Intravascular Imaging Catheter and Corresponding Imaging Capital Equipment
- Inflation Device
- 0.035 guidewire (260cm length minimum)
- Syringes, stopcocks, RHV, extension lines and other standard interventional accessories (optional: the BlueLeaf Accessory Kit (Merit Medical Part Number K12-11604)

These items are available commercially for the indications for which they are proposed in this study and will not be tracked as part of device accountability.

The commercially available accessories used with the BlueLeaf System will be disposed of as per standard institutional practice.

2 JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN

2.1 Measuring Outcomes of Symptomatic CVI in the Lower Extremity

The study will capture information on the anatomic and physiologic characteristics of the femoral and popliteal vein before and after formation of autogenous valves, with respect to imaging and hemodynamic data from venography, IVUS and duplex ultrasound. This data will be used to determine the appropriate imaging and physiologic measures for subsequent investigations. In addition, the study will assess changes in general and venous quality of life indices including a general patient reported outcome survey such as SF-36, revised venous clinical severity score (rVCSS) and Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptoms questionnaires (VEINS-QOL/Sym) as they relate to the study procedure. Finally, the study will also capture the gross physical status of the treatment limb, such as wound management methods and ulcer status when present.

2.2 Pre-Clinical Testing

The BlueLeaf System has undergone design verification and validation testing to demonstrate device functionality per the product specification, and successful mitigation of safety risk to justify use in a clinical trial. A brief summary of the in- and ex- vivo testing is outlined the below sections. This testing demonstrated that the BlueLeaf device is in compliance with the InterVene quality system. Further details are available in the Investigator's Brochure.

2.2.1 In Vivo Animal Testing

Design validation was performed on the BlueLeaf System to verify that the design meets the clinical requirements and user needs of the device. Design validation was performed in an animal model per the In Vivo testing section in the Investigator Brochure, however, due to limitations of the animal model to simulate the human vein wall in terms of mechanical properties and thickness, or to simulate worst case tortuosity of clinical anatomy, additional, ex vivo and simulated use bench tests are performed simulating these specific situations.

2.2.2 Ex Vivo Tissue Testing

The BlueLeaf System was evaluated in an ex vivo tissue model (cadaveric femoral veins in the size range indicated for use by the BlueLeaf System). The test verified the ability of the device to access the vein wall and to form monocuspid autogenous valves. The test also verified that the device could be used with fluoroscopic and IVUS imaging.

Valve functionality was also tested as part of the simulated use testing via measuring flow rate. Flow rate through the vein was measured in what would clinically be the retrograde direction prior to the simulated BlueLeaf procedure (baseline) and after the simulated procedure. A reduction in flow rate demonstrates that the valves are functioning as intended, namely limiting the amount of blood refluxing in the retrograde direction. The valve flow rate is presented below as Table 1.

Table 1: Ex Vivo Tissue Testing Valve Flow Rate

Procedure / vein ID	Baseline Flow	Flow after Valve 1	Flow after Valve 2	Valve Width Valve 1	Valve Width, Valve 2	Is Flow statistically reduced from baseline flow?
	mL/sec (% Baseline)			(% of circumference)		
#1 / 01	59.3	50.5 (85%)	**9.4 (16%)**	25.8%	46.4%	Yes
#2 / 05	56.1	18.0 (32%)	**7.6 (13%)**	42.3%	47.2%	Yes
#3 / 04	56.9	22.3 (39%)	**9.4 (16%)**	43.1%	46.8%	Yes
#4 / 06	56.9	30.6 (54%)	**29.7 (52%)**	46.1%	32.1%	Yes

The amount of flow reduction required for a clinically significant benefit to a patient is not currently known given the early stage of device development. Data will be gathered in this early feasibility clinical study to address that question.

2.3 Prior Clinical Investigations

The first generation InterVene device, the ReLeaf Catheter System, was evaluated in two patients in New Zealand in a First-in-Human experience (ClinicalTrials.gov NCT02462096), and is described in the IB. The first-generation device was a larger-bore system (20Fr), and utilized a distinct approach for valve formation, with separate tools for valve pocket formation and intimal incision.

The second generation InterVene device, the BlueLeaf System, is being evaluated for safety and effectiveness as part of an ongoing feasibility study being conducted outside the US, referred to as the INFINITE-OUS Study (ClinicalTrials.gov NCT03216005), and is described in the IB.

The INFINITE-OUS and the INFINITE-US studies are being performed to allow the Sponsor to collect additional safety and effectiveness data on the BlueLeaf System in preparation for a larger Feasibility and/or Pivotal study.

3 STUDY OBJECTIVES

3.1 Study Purpose

The purpose of this early feasibility study is to provide information on the BlueLeaf System for the formation of one or more autogenous vein valves constructed from the vein wall of the femoral and/or popliteal vein, in subjects with CVI and who meet the specified eligibility criteria. In particular, the safety and technical feasibility of the procedure will be validated in patients in the United States, including the procedural steps, operator technique, and subject characteristics. The study will assess the safety and effectiveness of the study device acutely and through 5 years.

3.2 Scope and Duration of the Study

The study is expected to commence enrollment in the first half of the 2019 calendar year. The enrollment and treatment period is expected to conclude 3 years later and subjects will be followed for 5 years after treatment.

Up to 5 investigational sites within the United States will treat up to 25 subjects.

The study will provide initial insights into the following aspects of the study device and procedure:

- whether the device can be successfully delivered to the intended locations in the target vessel and form at least one autogenous valve;
- human factors related to the device and comprehension of the procedural steps;
- clinical safety of the device-specific aspects of the autogenous valve formation procedure;
- whether the device performs its intended purpose of forming functional autogenous valves that are durable over early (30-day) and long-term (1-, 2-, 3-, 4- and 5-year) follow-up;
- characterization of any device failures and analysis of their causes;
- anatomic and other patient-related characteristics that may impact device performance;
- therapeutic parameters that may impact device use, including sizes and actuation scheme of the device components.

3.3 Iterative Evaluation Process for Device, Procedure, Protocol Modifications

The study will have periodic subject outcome assessments and analyses by the Data Safety Monitoring Board (DSMB) in addition to a review by the Sponsor.

Reporting Sponsor will provide a report to the FDA for each subject after the 7-day follow-up evaluation, for the first 5 subjects treated under the IDE. These reports will also include updates regarding safety and effectiveness information from previously treated subjects (e.g. 30-day follow-up data) and any device deficiency findings. After the first 5 subjects treated, the Sponsor will provide a report to the FDA for each additional set of 5 subjects treated.

4 CLINICAL STUDY DESIGN

This Study of the BlueLeaf System (INFINITE-US) is an interventional, non-randomized, multicenter, pre-market, single-arm prospective early feasibility clinical trial. The analyses are descriptive in nature, with no planned statistical comparisons. The study is not hypothesis-driven and no formal hypotheses will be tested. For this reason, there is no sample size calculation but the total sample size is pre-specified at 25 treated subjects with data analyzed in an iterative fashion.

Note that throughout this document, use of the word “should” implies a recommendation and nonconformance is not considered to be a protocol deviation. By contrast, use of the words “must,” “will” or “shall” imply a mandatory procedure or assessment and nonconformance will constitute a protocol deviation.

4.1 Study Population

The study population will include up to 25 male and female subjects who are candidates for lower extremity endovascular venous intervention enrolled with symptomatic CVI and deep vein reflux.

For the initial device use at an investigational site, non-sequential enrollment will be considered. This means that the first device use at each site should target subjects with more favorable anatomical characteristics as compared to the population otherwise eligible for the study. Treatment preference should be given to subjects who meet study eligibility requirements but do not have anatomic features that may increase the difficulty of device use (e.g. severe vein curvature or duplicated segments).

4.2 Inclusion Criteria

Subjects must meet the following criteria to be included in the study:

1. 18 years of age or older
2. Willing and able to sign the approved informed consent form (ICF)
3. Willing to comply with follow-up evaluations and protocols
4. Symptomatic CVI subjects, Clinical Etiological Anatomical Pathophysiological (CEAP) classification of C5 to C6
5. Failed at least 6 months of conservative therapy at some point during the course of their CVI management (symptoms not adequately resolved or patient non-compliant/unable to tolerate)

6. Deep system venous reflux characterized by >1 second reflux time in two vein segments (vein segments defined as: proximal femoral, distal femoral, and popliteal), as assessed by duplex ultrasound (DUS) with patient in the standing position
7. Presence of at least two potential target sites within a target vessel as assessed preliminarily by DUS, and presence of at least one potential target site within a target vessel as assessed with IVUS peri-procedurally, with a target site being defined as a segment within the femoral or popliteal vein that is:
    a. 7mm to 12mm in luminal diameter, and
    b. at least 3cm long (two target sites in a row must be spaced at least 1 cm apart), and
    c. absent features that, in the Investigator's opinion, would preclude formation of a monocuspid or bicuspid valve (at any orientation). These features may include thrombus, synechiae, natural valves, major tributaries (valves can be formed opposite tributaries) or severe heterogenous changes of the vessel wall (homogenous thickening allowed)

    with all assessments completed while vein is under physiologically appropriate hemodynamic pressure.
8. In the Investigator's opinion, the subject is a good candidate for treatment with the BlueLeaf System based on their symptoms, quality of life, anatomy, and the likelihood of benefit from continued conservative therapy

4.3 Exclusion Criteria

Subjects with any of the following criteria are ineligible for inclusion in the study:

1. Untreated significant superficial venous incompetence which, in the opinion of the Investigator, may be the primary source of existing symptoms
2. Anatomy that does not support proper device access of the treatment vein through the ipsilateral common femoral or femoral vein
3. Acute deep venous thrombosis (DVT) within 1 year of consent (subjects with prior DVT with no apparent cause should undergo a hypercoagulability work-up prior to study entry to confirm eligibility vis-à-vis exclusion criteria #10)
4. Deep venous intervention (includes stenting) in the target limb or outflow vessels within 3 months of consent
5. Flow-limiting venous outflow obstruction central to the intended target sites, defined by a common femoral vein duplex exam found to have a continuous waveform without respiratory variation, or a ≥ 50% reduction in luminal cross–sectional area as determined by computed tomography venography (CTV), magnetic resonance venography (MRV) or IVUS
6. Inadequate flow into or through the target vessel (Investigator's opinion)
7. Luminal diameter, in any vein segment through which the device is likely to be inserted, that is < 6mm, or between 6mm and 7mm for a section of vein > 1cm in length, as

assessed by IVUS while the vein is under physiologically appropriate hemodynamic pressure

8. A competent vein valve in any vein segment through which the device is likely to be inserted, as assessed by DUS (≤ 1 second reflux time) or with contrast venography (Investigator's opinion)
9. Contraindications to all protocol specified anticoagulation options
10. Known and uncontrolled hypercoagulopathy (i.e. hypercoagulopathy that cannot be adequately managed/controlled with medication)
11. Women on long-term oral contraceptives
12. Non-ambulatory patients
13. Significant peripheral arterial disease with an ankle-brachial index of < 0.70 or with incompressible vessels
14. NYHA Class III or IV heart failure
15. Patients with a history of right heart failure occurring as a consequence of, for example, biventricular failure, intrinsic pulmonary disease, chronic thromboembolic pulmonary hypertension, and other etiologies that result in elevated right-sided pressures.
16. Active systemic infection
17. Invasive surgical procedure within the last 3 months that in the Investigator's opinion would interfere with the study procedure or results
18. Chronic renal insufficiency with creatinine level of ≥ 2 g/dL
19. Hemoglobin level < 9.0 g/dL
20. Platelet count < 50,000 or > 1,000,000/mm^3
21. Total white blood cell count < 3,000/mm^3
22. Pregnant or lactating female; positive pregnancy test, women of childbearing potential must be tested within 7 days of planned procedure
23. Subject is enrolled in another clinical study that, in the opinion of the Investigator, may conflict with this study or compromise study results
24. Comorbidity risks or other concerns which, in the opinion of the Investigator, either limits longevity or likelihood of complying with the protocol and its prescribed follow up (e.g. recent cancer or stroke); or precludes patient from being transitioned to open surgery if complication requiring surgical intervention occurs during the procedure (such as severe vein laceration).

4.4 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint consisting the following major adverse events occurring through the 30-day follow-up window, as adjudicated by the CEC:

- Symptomatic pulmonary embolism (e.g. chest pain, hemoptysis, dyspnea, hypoxia, etc.) confirmed via computer tomographic pulmonary angiography
- DVT anywhere in the deep venous system of the treatment limb
- Occlusive valve pocket thrombus (VPT)
- Non-occlusive stenosis in the target vessel (including due to scarring, inflammation, VPT, etc.) confirmed via DUS and not present prior to the BlueLeaf procedure, leading to

persistent worsening of symptoms attributable to venous flow obstruction, or requiring post-procedural surgical or endovascular re-intervention
- Device or procedure-related venous or arterial injury in the treated limb (such as Arteriovenous Fistula (AVF's), bleeding, pseudo aneurysm) leading to worsening of symptoms that require post-procedural surgical or endovascular re-intervention or requiring transfusion of more than 2 units of blood. (Note: Peri-procedural stiches placed to assist with closure of the access site will not be characterized as a primary safety failure.)
- Device or procedure-related death

4.5 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in Venous Clinical Severity Score (rVCSS).

4.6 Additional Outcome Measures

The following will be additional outcome measures:

- Acute Device Success;
- All-cause mortality;
- Deep venous thrombosis (DVT) as defined above beyond 30-day follow-up;
- Pulmonary embolus as defined above beyond 30-day follow-up;
- Major bleeding, defined as Type 3a or greater bleeding using the Bleeding Academic Research Consortium (BARC) criteria;
- Valve Pocket Thrombus (VPT) not qualifying as a target vessel DVT;
- Asymptomatic non-occlusive stenosis of the target vessel;
- For CEAP 6 subjects, venous ulcer changes
- Post-procedural reflux times (RT) and volumetric flow rates within a target vessel;
- Disease-specific Quality of life indices, VEINES-QOL/Sym;
- General patient reported outcome survey such as the SF-36 and EQ-5D-5L
- CVI symptom evaluation, including VAS pain score and calf swelling
- Air plethysmography (APG) metrics as detailed in the Manual of Operations.

4.7 Study Assessments

The following study procedures and assessments will be required as noted in Table 2.

A more complete description of the imaging assessments is included in the Imaging Manual of Operations. In case of any discrepancies between this protocol and the Imaging Manual of Operations, the Imaging Manual of Operations will be followed.

4.7.1 Compression Therapy Use:

Baseline and study duration compression therapy use information will be collected for all subjects at each follow up visit. The type (i.e. 20-30 mm HG below-knee compression hose) and frequency of use (i.e. daily use) should be documented.

Recommended post-procedural compression use is described in section 5.6.

4.7.2 Wound Care Regimen:

Baseline and study duration wound care regimen information (frequency of visits to a wound clinic and note of type of treatments received) will be collected for subjects presenting with leg wounds upon enrollment. Wound care regimen information will continue to be collected for these subjects for the duration of their study follow up. If a leg wound develops during the study for any subject, this same wound care regimen information will be collected upon first presentation of the wound and for the duration study participation.

Recommended post-procedural wound care is described in section 5.6.

4.7.3 Ulcer Photography:

Subjects with leg ulcers upon enrollment must have photography of the ulcers at each visit where at least one ulcer is present (excluding pre-discharge). If an ulcer is completely healed during the course of follow-up, photography will be completed at the first visit following ulcer healing, but not in subsequent visits, unless an ulcer recurrence occurs. Refer to the Wound Imaging Guidelines for additional photography instruction and information.

4.7.4 Revised Venous Clinical Severity Score:

The rVCSS (see Appendix B) will be determined for each subject by assigning a score (0, 1, 2, or 3) to each of the ten attributes of venous disease, per the specific guidelines for each attribute.

A trained and independent physician or other qualified evaluator (not participating in the BlueLeaf procedure) will be responsible for determining the subjects rVCSS at each required timepoint. Every attempt should be made to blind the independent evaluator to the outcome of the BlueLeaf procedure to minimize the introduction of potential bias to the evaluation. Additionally, as much as is possible, the same independent evaluator should be used to evaluate a subject through all visits.

The rVCSS evaluation and CEAP classification must be completed within 14 days of the index procedure.

4.7.5 Patient Reported Outcome Surveys:

Short form surveys SF-36, EQ-5D-5L or similar, will be completed to capture general patient reported health outcomes.

Pain VAS Score: A pain VAS (visual analogue scale) is a unidimensional measure of pain intensity. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the “no pain” anchor and the subject’s mark, providing a range of scores from 0–100, where a higher score indicates greater pain intensity.

4.7.6 VEINES-QOL/Sym Questionnaire:

The VEINES-QOL/Sym is a patient-based questionnaire that is designed for self-completion. The questionnaire measures the impact of CVI-related symptoms and quality of life from the patient’s

perspective. Questions cover symptoms, limitations in daily activities, time of day of greatest intensity, changes over time, and psychological impact.

4.7.7 Duplex Ultrasound (DUS):

In the screening phase, DUS will be obtained to document target vessel patency, reflux, lumen diameters and other relevant subject screening information, with subject in the supine and standing positions, per specific guidelines outlined in the Imaging Manual of Operations. Waveform analysis of the common femoral vein will be used to rule out subjects with obvious outflow obstructions. Baseline reflux time and volumetric flow measurements will be made in the femoral and popliteal veins.

In the follow-up visits, the autogenous valve(s) will be assessed and quantitative and qualitative data will be taken. Qualitative assessments, such as leaflet visibility and mobility, will be taken for each treatment site. Reflux measurements and volumetric flow will be obtained at least two specified positions in the target vessel (for comparison to baseline).

Specific parameters for DUS procedures, such as use of an automated calf cuff and subject positioning will be provided in the Imaging Manual of Operations, and must be adhered to, in order to insure consistency between subjects and between visits.

4.7.8 Air Plethysmography (APG) (Optional)

Air Plethysmography (APG) is an optional assessment. When APG is performed at the baseline, the assessment must be conducted at 7-day, 30-day, 12-week, 210 and 365-day follow-up visits per the APG Instructions provided in the study Manual Of Operations (MOPs) and will be considered per protocol.

Sites collecting APG data will record the APG tracing and submit to the Sponsor.

4.7.9 Venography:

Contrast venography will be performed prior to commencement of the index procedure. The access site may be chosen at the Investigator's discretion. Access will be achieved percutaneously using ultrasound guidance or through an open surgical venous exposure. The venogram will be performed with a radiographic ruler present in the field of view.

Pre-procedurally, a controlled bolus descending contrast venography should be performed as specified in the Imaging Manual of Operations. Additionally, the extent of flow limiting post-thrombotic changes in the target vessel, as well as target vessel characteristics relevant for target site selection will be assessed using contrast venography as specified in the Imaging Manual of Operations.

Presence of any competent vein valves between the access site and the most proximal potential treatment site must be identified for subject exclusion.

Contrast venography will be performed following completion of each autogenous vein valve formed, assessing the amount of residual reflux and the extent of any vessel damage visualized, and the degree of vessel stenosis at the site of the target sites. A final contrast venogram will be performed after the final autogenous valve has been formed, which should be initiated from the

same location as the baseline contrast venography performed before the procedure, with the same controlled bolus, as specified in the Imaging Manual of Operations.

4.7.10 Intravascular Ultrasound (IVUS):

IVUS will be performed using machines and probes at the Investigation's discretion, but with appropriate MHz frequency to adequately visualize the target vessel. IVUS will be used to identify the locations of target sites within the target vessel, including but not limited to measurements of vein diameters (in multiple planes), characteristics of the vein wall and disease morphology, and presence of any intraluminal changes such as webs, spurs or synechiae. IVUS may also be used in vessels superior to the target vessel. Reference diameters will be measured prior to any treatment in the proximal femoral, distal femoral and popliteal veins.

During the valve creation procedure, after the formation of each new autogenous leaflet, IVUS will be utilized to assess certain parameters, such as leaflet and pocket mobility, pocket filling and other physical characteristics of the autogenous valve site.

4.7.11 Outflow Obstruction Assessment:

Outflow obstruction will be initially assessed by DUS. Subjects with a negative result for obstruction via DUS (e.g. normal respiratory variation observed in the common femoral vein) will also have a secondary imaging modality of CTV, MRV, IVUS or venography performed to confirm the absence of outflow obstruction prior to insertion of the BlueLeaf Catheter into the subject's venous system. Historical CTV, MRV, IVUS or venography may be used as the confirmatory imaging if it was performed within 6 months of study consent. The imaging hierarchy for outflow obstruction assessment is detailed in the Imaging Manual of Operations.

Table 2: Schedule of Assessments

Assessment	Screening		Post-Procedure Follow-up							
	Pre-Procedure	Intra-Procedure	Pre-Discharge	7-day Visit	30-day Visit	12 week Visit	210-day (7 Month) Visit [C]	365-day (1 Year) Visit	Year 2-5 Annual Visits	Heightened Observation Program [G]
Assessment Window	- 60 d	0d	NA	± 3d	± 14d	- 21d	± 30d	± 60d	± 60d	
Medical History	X									
Blood Tests	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Pregnancy Test (females of reproductive potential)	X [A]									
Physical Examination	X			X	X	X	X	X	X	X
Compression Therapy Usage	X			X	X	X	X	X	X	
Wound Care Regimen	X			X	X	X	X	X	X	
Ulcer Photography (CEAP 6 subjects only)	X	X [E]		X	X	X	X	X	X	
rVCSS [F] (revised Venous Clinical Severity Score)	X [H]				X	X	X	X	X	
Patient Reported Outcomes Surveys	X				X	X	X	X	X	
VEINES-QOL/Sym	X				X	X	X	X	X	
Duplex Ultrasound	X		X [B]	X	X	X	X	X	X	X
Plethysmography (APG) (Optional)	X			X	X	X	X	X		
Venography	X [D]	X								
Intravascular Ultrasound (IVUS)	X [D]	X								
Adverse Event Reporting		X	X	X	X	X	X	X	X	X

[A] For females of reproductive potential, pregnancy test must be done within 7 days of planned procedure date.

[B] If the discharge date falls within the 7-day visit schedule window (4-10 days post-procedure), a pre-discharge DUS is not required, only the one for 7day. Note, the pre-discharge DUS is less extensive than other follow up DUS assessments, and only entails a safety check for DVT or other obvious safety related changes.

[C] The 210-day visit is scheduled to collect data at least 4 weeks after discontinuation of anticoagulant therapy in subjects not requiring anticoagulation therapy for more than 168 days.

[D] An additional venography or IVUS may be performed prior to the day of the index procedure to assess outflow obstruction. CTV or MRV may be performed in lieu of those assessments.

[E] Peri-procedural ulcer photography may be performed any time during the index procedure visit, preferably before the index procedure.

[F] rVCSS evaluation should be completed by the same independent physician or other qualified evaluator at each visit.

[G] Subjects experiencing an asymptomatic DUS imaging finding in the target vessel will be followed per Section 6.6 Heightened Observation Program.

[H] The rVCSS evaluation and CEAP classification must be completed within 14 days of the Index Procedure.

5 INVESTIGATIONAL PROCEDURE AND POST-PROCEDURAL CARE

5.1 Investigational Device Use Training

The BlueLeaf System will be utilized by physicians experienced in endovascular procedures including the management of CVI patients. Investigators will be trained using appropriate training materials and methods.

At minimum, two investigators at each investigational site will be required to be trained on how to use the BlueLeaf System to perform the procedure through didactic and hands on training. At least one investigator should be skilled in the use of IVUS. The training session will be conducted in person by Sponsor personnel or designee prior to the first study procedure. Best efforts will be made to conduct the training of both users in the same session.

The two main user roles for the BlueLeaf procedure the investigators will be trained to are:

- Primary User - Investigator who is responsible for the implementation of the patient's treatment plan (e.g. confirming anatomical location is a suitable autogenous valve site) and for operating the controls of the BlueLeaf System (e.g. balloon inflation, valve pocket dissection)
- Second User - Investigator who is responsible for assisting with the physical securement and movement of the BlueLeaf System in relation to the table top clamp and sheath. The second user may also assist with certain ancillary devices (IVUS catheter, guidewire, hydrodissection infusion).

The didactic portion will be conducted first and will utilize the instructions for use (IFU) and detailed Procedure Training Guidelines. The goal is to instruct the users on the basic principles of the procedure, how to perform the individual procedural steps, procedural imaging interpretation, and how the two user roles interact during the procedure.

The hands-on instruction will be conducted after the didactic training. The hands-on training model set-up consists of a synthetic "vein" in a water tank and a functional BlueLeaf System, which will allow the users to perform the critical steps of valve formation (device positioning, sizing and pocket creation) while in a fluid environment. The hands-on portion also allows the two users to interact while in their designated procedure roles.

In addition, as necessary, in-service training will be provided to the surgical site staff.

A Sponsor representative(s) will also be present at each procedure to provide device/procedure support.

5.2 Preparation of the Subject for the Procedure

The subject will undergo a comprehensive screening process, as detailed below in section 6.2, to establish initial study eligibility prior to exposing the subject to the investigational procedure, at which time final study eligibility will be assessed as outlined in section 5.4 below.

The subject will be prepared for the planned index procedure according to standard hospital procedures. The planned access site, either the ipsilateral common femoral or femoral vein, will be prepared and draped in a sterile manner. Local, regional or general anesthesia will be used at the operator's discretion. Venous access to the target vessel will be obtained in a retrograde

direction from the ipsilateral common femoral or femoral vein. Access may be obtained with an open surgical exposure or percutaneously. Venous access must be performed under ultrasound guidance if done percutaneously.

5.3 Medications

The peri-, intra-, and post-procedure anticoagulation/antithrombotic regimen is detailed below and summarized in **Table 3**.

5.3.1 Periprocedural Medications

Subjects will be treated with antiplatelet agents beginning on the day of the procedure and continued for at least 12 weeks thereafter. Aspirin is required (recommended dose of 81-100 mg/day) and use of Clopidogrel or Prasugrel is optional per Investigator discretion. Subjects currently taking:

- Aspirin - May remain on their currently prescribed dosage per the local Standard of Care (SOC), or as directed by Investigator.
- Clopidogrel/Prasugrel - Additional antiplatelets should be continued per local SOC, unless otherwise directed by Investigator.
- Anticoagulant - May be either continued or temporarily withheld prior to and during procedure per local SOC, or as directed by Investigator; taking into consideration if the patient has high bleeding risk factor (e.g. >65 years old).

5.3.2 Intraprocedural Medications

Once venous access has been safely obtained, the subject will be anticoagulated with unfractionated heparin to achieve an Activated Clotting Time (ACT) of at least 250 seconds, unless a lower level is warranted per the local SOC or the Investigator's discretion. Heparinization should be continued with repeated boluses or a continuous intravenous infusion, at the operator's discretion, to maintain an adequate ACT throughout the interventional procedure. Unfractionated heparin anticoagulation will be discontinued at the conclusion of the procedure unless the Investigator chooses to maintain lower doses of unfractionated heparin up until discharge. The use of protamine sulfate is discouraged.

5.3.3 Post-Procedure Medications

Investigators have two options for anticoagulation:

Option 1:

Enoxaparin (e.g. Lovenox or Clexane) is begun within 2 hours of index procedure, using a weight-based twice daily administration (1mg/kg q 12h). If dose rounding is required due to medication packaging, rounding up is recommended if it is clinically reasonable to do so. If the investigator feels it is more appropriate to round down, it is not a protocol deviation, but it should be noted in the study records. Subjects are to be provided with training on the administration of Enoxaparin injections by healthcare personnel. The Sponsor will provide funds for additional assistance (e.g. home-care nurse) if necessary. Enoxaparin is continued for 30 days at this dosage, or longer if Warfarin bridge has not yet achieved an INR ≥ 2.5.

Warfarin is begun prior to discontinuation of Enoxaparin with an appropriate overlap period as determined by Investigator to achieve INR ≥ 2.5 (prior to discontinuation of Enoxaparin), and

administered at a therapeutic dose as typical for acute DVT per local SOC. Warfarin is continued at least until the subject is 168 days post-index procedure, unless bleeding complications occur.

Option 2:
Enoxaparin (e.g. Lovenox or Clexane) is begun within 2 hours of index procedure, using a weight-based twice daily administration (1mg/kg q 12h). If dose rounding is required due to medication packaging, rounding up is recommended if it is clinically reasonable to do so. If the investigator feels it is more appropriate to round down, it is not a protocol deviation, but it should be noted in the study records. Subjects are to be provided with training on the administration of Enoxaparin injections by healthcare personnel. The Sponsor will provide funds for additional assistance (e.g. home-care nurse) if necessary. Enoxaparin is continued for 30 days at this dosage.

Direct Oral Anticoagulant (DOAC) such as Apixaban, Dabigatran or Rivaroxaban is begun within 10 hours of the discontinuation of enoxaparin at a therapeutic dose as typical for acute DVT per local Standard of Care (SOC) and is continued at least until the subject is 168 days post-index procedure, unless bleeding complications occur. Choice of approved DOAC is of the discretion of the investigator, but must be compatible with a twice daily dosing schedule.

The below guidance statements should be taken into consideration when determining if the DOAC option should be used for a given patient:

- Apixaban is recommended.
- Rivaroxaban is not recommended, especially in younger, more robust individuals, particularly robust young males.
- Recommend the appropriate standard dosing of the DOAC in patient with a BMI ≤ 40 kg/m^2 and weight ≤ 120 kg (265 lb).
- Suggest that the DOAC option not be used in patients with a BMI of > 40 kg/m^2 or a weight of >120 kg (265 lb) because there are concerns about underdosing in the population at the extreme of weight[16]; thus, the Warfarin option should be considered instead.

Table 3: Anticoagulation and Antithrombotic Regimens

Agent		Start	Stop	Notes
Antiplatelet (Clopidogrel or Prasugrel are optional as stated above):				
Aspirin		On day of and prior to index procedure	At least 12 weeks post-index procedure	Recommended dosage: 81-100mg daily (unless currently taking a different dose)
Procedural Anticoagulation:				
Unfractionated heparin		After access achieved	After intervention (or may be continued at lower doses until discharge)	At the time of procedure, bolus to achieve an ACT >250 (or level corresponding to the local standard of care) prior to the insertion of the BlueLeaf System. Bolus intermittently during the procedure to maintain target ACT. Record final ACT at the end of the procedure (i.e. sheath removal).
Post-Procedural Anticoagulation (Option 1 or Option 2 below):				
Option 1	Enoxaparin	Within 2 hours of index procedure	30 days post-index procedure, but not until INR ≥2.5	Required dosage: 1mg/kg q 12h
	Warfarin	Prior to discontinuation of Enoxaparin, on or after day of index procedure, with appropriate overlap period to achieve INR ≥ 2.5	At least 168 days post-index procedure unless bleeding complication occurs	Therapeutic dosage for acute DVT per local SOC
Option 2	Enoxaparin	Within 2 hours of index procedure	30 days post-index procedure	Required dosage: 1mg/kg q 12h
	DOAC (Apixaban, Dabigatran, Rivaroxaban)	Within 10 hours after discontinuation of Enoxaparin	At least 168 days post-index procedure, unless bleeding complication occurs	Therapeutic dosage for acute DVT per local SOC (loading dose not required)

ACT, Activated clotting time; INR, International normalized ratio; SOC, Standard of care.

5.4 Imaging

Venography and IVUS will be utilized to assess subject eligibility prior to the insertion of the BlueLeaf System and then during the procedure steps and assessments as specified in sections 4.7.8 and 4.7.10 above, and as detailed in the Imaging Manual of Operations.

If the initial venography and/or IVUS imaging determine the subject's anatomy to be ineligible for study treatment, the subject will be a screen failure and the imaging catheters will be removed and the incision closed. Providing that the patient did not experience any adverse events during this final screening assessment period, the subject is to be followed per the institution's standard of care for undergoing the given imaging procedure. If the subject did experience an adverse event related to undergoing the image screening (e.g. anesthesia related, access site related), the subject will be monitored until the event is either resolved or is clinically stable.

5.5 Sheath/Guide Removal

It is important to refrain from occluding the femoral vein outflow when applying manual pressure after sheath/guide removal. Ultrasound may be used to assure continued flow through the femoral vein at this time, at the discretion of the operator.

5.6 Post-Procedural Care Regimen

Following the procedure, and after the investigator has assured access site hemostasis, the subject should ambulate as often as feasible.

An Active Compression (AC) device (e.g. intermittent pneumatic compression (IPC) or other compression therapy device), if available, is strongly recommended the night of the procedure. Additionally, AC should be used for the 7 days after the procedure if the subject remains in hospital. The subject is encouraged to use the AC device whenever they are non-mobile. Subjects unable to tolerate AC devices or who do not have access to such devices should be instructed in foot dorsiflexion exercises and instructed to perform when supine at night and during extended stationary times for at least 7 days after the procedure.

The subject should wear medium-level (e.g. 20-30 mm Hg) below-knee level compression hose when out of bed, up to the 30-day follow-up visit. After the 30-day follow-up visit, the subject should return to his or her pre-procedure compression level both in type and frequency. For example, if the subject is regularly using 10-20 mm HG below-knee compression hose prior to the study procedure, the subject should continue on regular use of 10-20 mm HG compression hose after the 30-day follow-up visit is completed. If the subject is not using any compression hose prior to the study procedure (but is still included in the study due to prior history of failed conservative therapy), the subject should discontinue compression after the 30-day follow-up visit is completed, unless otherwise specified by investigator.

The failure or inability to comply with the aforementioned compression hose and AC device regimen will not be considered a protocol deviation but the reason for non-compliance is to be recorded. Compression therapy usage will be tracked at each study follow-up visit.

Strict compliance with the post-procedural anticoagulation/antithrombotic regimens described in

Table 3 is required. Extended travel (i.e. > 4 hours) after the procedure but before the 7-day follow-up visit, including but not limited to air travel, is strongly discouraged, and the Sponsor is willing to offer reasonable accommodations local to the investigational site to accommodate non-local subjects between discharge and the 7-day follow-up visit.

Reasonable measures may be undertaken to promote compliance with anticoagulation/antithrombotic regimens, compression therapy, and mobility. A log of enoxaparin injection times and dates for all post-procedural days up to and including the day of the 30-day follow-up visit must be maintained and logged into the appropriate CRF. The log also includes information on subject compliance with compression and mobility. The exact mechanisms for promoting compliance will vary from site to site, but some examples of reasonable measures include but are not limited to:

- at-home (or in-hotel) nursing services;
- third party nursing or research coordinator phone calls, or other communication efforts to track and promote compliance;
- outpatient administration of enoxaparin shots by clinical site staff.

The type and frequency of wound care for subjects with active venous ulcers is not explicitly defined, and should be per local standard of care. It is recommended that the subject receive the same type and frequency of wound care pre and post procedure, as long as that falls within the local standard of care. Subjects with active ulcers, not receiving sufficient wound care prior to study enrollment, should be further evaluated for ability to resolve symptoms with conservative measures prior to study enrollment, per inclusion criteria #8.

6 ASSESSMENTS AND FOLLOW-UP SCHEDULE

Subjects will undergo the assessments depicted in the Schedule of Assessments (**Table 2**)**.**

6.1 Point of Enrollment

Subjects will be consented prior to study participation, at a point where the anatomic eligibility criteria may be unknown to the Investigator. Diagnostic imaging will be utilized to confirm anatomic eligibility criteria, which may be carried out on the same day as the index procedure but prior to device insertion into the vasculature, or at a prior date within 2 months of the index procedure. A subject is considered enrolled in the study at the point of insertion of the study device into the vasculature, when the device enters the portion of the sheath/guide that resides within the subject's vascular tree.

Subjects who have provided written informed consent but were not enrolled in the study as defined above will also be tracked for final reporting.

6.2 Screening/Baseline Assessment

An initial evaluation should be completed to determine if a subject may be considered for enrollment. This evaluation may include an assessment of diagnostic testing that would have been done as part of a subject's routine care. If the initial assessment shows that the subject may be

potential study candidate, the subject may be approached for study participation and informed of the risks and benefits of the study. If the subject provides written informed consent, then all inclusion/exclusion criteria are to be evaluated. The final disposition (e.g., enrollment, ineligibility, or decision by the subject or physician not to enroll) must be noted.

The data captured for the Screening Visit may be gathered over the course of more than one office visit; however, the data must have been obtained within 60 days of the scheduled procedure date. The following procedures will be performed at the Screening visit prior to the procedure and all data must be recorded in the subject's CRF:

- Demographic information
- Medical history including risk factors
- Physical examination with ankle-brachial index
- Compression therapy utilization (last 3 months)
- Ulcer and wound care history (i.e. onset date of longest current active ulcer and recent utilization of wound care)
- Ulcer photography (if applicable)
- Screening laboratory values to include hemoglobin, platelet count, total white blood cell count, and serum creatinine.
    - Clinical laboratory tests are expected to be performed at this visit to establish baseline levels. It is recognized that specific panels may vary between institutions. Laboratory data will not be specially analyzed but will be used only to support adverse event evaluations.
- Duplex ultrasound
    - **IMPORTANT:** The DUS imaging must be submitted to independent medical reviewer to confirm anatomical eligibility prior to performing the procedure.
    - The Investigator and independent medical reviewer assessments will be used to determine DUS-related eligibility criteria; whereas the duplex imaging core lab assessments will be used for DUS-related data analysis.
- Quality of life indices, general and disease-specific and pain VAS score
- Serum or urine pregnancy test for females of childbearing potential.
    - The test must be negative at baseline (within 7 days of the planned procedure date) and subject must be using a medically acceptable method of birth control. Acceptable methods of birth control include: barrier method with spermicide, steroidal contraceptive, contraceptives in conjunction with a barrier method, intrauterine device, or abstinence. No pregnancy test is required for post-menopausal women or women who are surgically sterile.

The procedure will be scheduled to allow InterVene personnel attendance.

6.3 Treatment

The procedure will be conducted in accordance with the IFU and the Procedure Training Guidelines, where up to two (2) monocuspid and/or bicuspid valve formation(s) may be attempted per subject.

Anticoagulation therapy to ensure an ACT of at least 250 seconds is recommended. Investigator discretion is advised regarding antiplatelet therapy and blood pressure adjustment.

Subjects who are deemed eligible for treatment; however, who do not have an autogenous valve formation attempted (i.e. Tissue Access without Autogenous Valve Attempt) are not required per protocol to undergo the post-procedural care regimen, such as the initiation of the anticoagulation medication (section 5.6) but may at the discretion of the treating physician. However, these subjects regardless post-procedural care regimen will be followed through the 5-year follow-up period.

Subjects who require conversion to open surgery due to treatment failure with the device will be followed through the 5-year follow-up period.

The following data are to be recorded on the subject's Procedure CRF.

- Venous access site
- Number and location of created valves[a]
- Planned additional and/or adjunctive procedures
- Number and location of attempted and unsuccessful valve creations
- Blood loss and replacement fluids (blood products) administered
- Required unplanned additional/adjunctive procedures
- Adverse events and device deficiencies that occur during the index procedure
- Procedure time (access stick to last sheath/guide removed)
- Device time (introduction of study device to removal of study device)

6.4 Follow-Up Assessments

Each follow-up assessment will include a duplex ultrasound study to evaluate target vessel patency and valvular function and assessments as listed in Table 2 and detailed in section 4.7. Additionally, subjects with suspected pulmonary embolism due to signs or symptoms, will be assessed for potential pulmonary embolism at each scheduled follow-up visit, as well as any unscheduled follow-up visits as recommended by Konstantinides et al[17]. Subjects reporting one or more of the following symptoms including sudden onset dyspnea, chest pain, fainting (or syncope), and hemoptysis that cannot be explained by another diagnosis will be further evaluated with objective testing. When suspected, objective testing to establish the presence or absence of pulmonary embolism will typically be performed as summarized in Figure 6 or per the clinician's standard of care.

[a]Location as reported at time of index procedure in centimeters above the patella measured in skin along medial aspect of thigh.

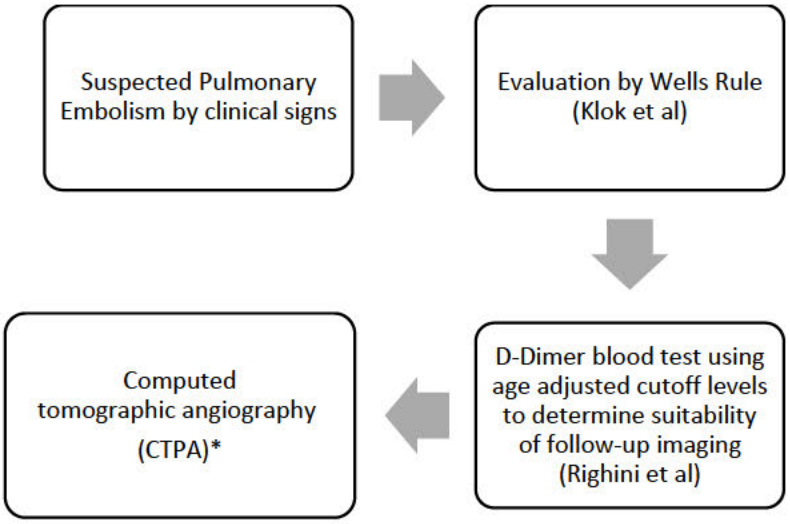


Figure 6 - Suspected Pulmonary Embolism Objective Testing Scheme[18,19]
***or ventilation/perfusion (V/Q SPECT) scan if CTPA is contraindicated**

6.5 Follow-up Visit Windows

Follow-up visits will be scheduled as calculated in **Table 4** below.

Table 4: Follow-up Visit Windows (Days from Procedure)

Follow-up Visit	Visit Window	Minimum Date	Target Date (Days)	Maximum Date
Procedure			0	
7 Day	± 3 days	4	7	10
30 Day	± 14 days	16	30	44
12 weeks	- 21 days	63	84	84
210 Day (7 Months)	± 30 days	180	210	240
365 Day (1 Year)	± 60 days	305	365	425
2 Year	± 60 days	670	730	790
3 Year	± 60 days	1035	1095	1155
4 Year	± 60 days	1400	1460	1520
5 Year	± 60 days	1795	1825	1855

6.6 Heightened Observation Program

If a treated subject experiences an asymptomatic DUS imaging finding in the target vessel, determined by the Investigator to be abnormal and not present prior to the BlueLeaf procedure (including but not limited to VPT, inflammation or scarring in a vein lumen), they will be followed per the heightened observation protocol with the 'observation visits' as detailed below.

6.6.1 Observation visits

An identified subject will be asked to return for a follow up DUS scan within 2 weeks[b] (+ 3 days) of the initial identification of the abnormal finding. The DUS scan should include an evaluation the status of the previously identified abnormality, as well as, evaluate for evidence of DVT elsewhere in the deep venous system of the treatment limb.

1. If the abnormal DUS finding has resolved, the subject will return to normal study follow-up visits.

2. If the abnormal DUS finding persists, as determined by the investigator, the subject will remain in the heightened observation protocol and will be seen at 2-week intervals until the abnormal finding is resolved. If the abnormal finding is still present but determined by the Investigator to be stable and no longer posing additional risk, the subject may return to normal study visit follow-up only.

NOTE: If an Observation Visit occurs outside a regular follow-up window, the visit is completed in addition to all follow-up visits outlined in the clinical protocol and documented using the Unscheduled Visit eCRF.

If an Observation Visit occurs within a regular follow-up window, the DUS scan will be completed as described above, in addition to all other clinical protocol specified measurements and assessments, and the visit can be utilized as a regular follow-up visit in addition to meeting the requirements for an “observation visit”.

Subjects who are clinically asymptomatic, but experience a limitation during the completion of the DUS imaging, such as:

- subject discomfort (e.g. discomfort during evaluation of venous access site);
- inability to ambulate;
- physical limitations (e.g. access site wound dressing)

will not routinely be considered for the Heightened Observation Program solely on sub-optimal imaging. To avoid ambiguity, patients who are missing images, are not automatically included in the Program due solely to that reason in the absence of any clinical symptoms.

6.7 Unscheduled Follow-up Visits

If a subject returns to the investigator for clinical follow-up visits or undergoes imaging studies not protocol-specified but for matters related to the study procedure, such visits will be considered unscheduled visits. The assessments completed at such visits will be performed at the discretion of the Investigator. CRF pages are provided for unscheduled visits and contain the same

[b] Every effort should be made to have the subject return ***within*** 2 weeks of the initial abnormal DUS finding and at regular 2 week intervals until the finding is resolved or deemed stable (not a safety risk) by the Investigator.

information as all the follow-up visits, in addition to the reason for the visit. See also details regarding assessment of potential PE as summarized in section 6.4.

6.8 Study Exit, Withdrawal and Lost to Follow-Up

Participation is completely voluntary, and each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw the subject from the study in the event of illness, adverse events or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw for any reason, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal must be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

Subjects will be exited from the study by completing a Study Exit CRF at the time of study completion provided the subject has not experienced an adverse event that is ongoing and unexplained, or, in the opinion of the Investigator, requires continued monitoring. Following study exit, the subject will undergo standard medical care for their condition as determined necessary and appropriate by their physician.

Subjects may be prematurely terminated or withdrawn from the study if, in the Investigator's opinion, it is not in the best interest of the subject to continue study participation.

For subjects who are more than one month out of a study visit window and three documented attempts to contact the subject are unsuccessful, the subject will be considered lost to follow-up. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up. A missed visit will be considered a protocol deviation and the deviation will be documented and reported as required.

All subjects treated with the study device, including those withdrawn or lost to follow-up, shall be accounted for and documented. The reason for and date of withdrawal must be recorded on the subject's Study Exit CRF. If the reason for the withdrawal is a device-related or procedure related adverse event (AE), the event must be reported to the Sponsor and recorded in the CRF. If a subject is exited from the study before the last day of any window, any required visits or imaging studies within that window that were not performed will not be considered missed for the purposes of protocol compliance.

7 STATISTICAL CONSIDERATIONS

7.1 Statistical Methodology

This is a descriptive study and, as such no performance goals have been defined for the primary safety or procedural success endpoints.

The primary safety endpoint of the study is a composite endpoint consisting of a hierarchical (includes only the most serious event for each patient) tabulation of the following adverse events within the 30-day follow-up window, as adjudicated by the CEC:

- Symptomatic pulmonary embolism (e.g. chest pain, hemoptysis, dyspnea, hypoxia, etc.) confirmed via computer tomographic pulmonary angiography

- DVT anywhere in the deep venous system of the treatment limb
- Occlusive valve pocket thrombus (OVPT)
- Non-occlusive stenosis in the target vessel (including due to scarring, inflammation, VPT, etc.) confirmed via DUS and not present prior to the BlueLeaf procedure, leading to persistent worsening of symptoms attributable to venous flow obstruction, or requiring post-procedural surgical or endovascular re-intervention
- Device or procedure-related venous or arterial injury in the treated limb (such as Arteriovenous Fistula (AVF's), bleeding, pseudo aneurysm) leading to worsening of symptoms that require post-procedural surgical or endovascular re-intervention or requiring transfusion of more than 2 units of blood. (NOTE: Peri-procedural stiches placed to assist with closure of the access site will not be characterized as a primary safety failure.)
- Device or procedure-related death

7.2 Sample Size Calculation

There is no formal sample size calculation in this descriptive, non-hypothesis generating clinical study. The treatment of up to 25 subjects is consistent with the number of subjects typical for early feasibility studies in the FDA Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies guidance document (section *7.1 Risk analysis and mitigation*, page 21).

7.3 Study Visit Window

The follow-up visit windows that will be used for analysis are specified in **Table 2** and **Table 4.**

7.4 Missing Data

Best efforts will be made to minimize the amount of missing data. Imputation of missing data will not be performed.

7.5 Demographics and Baseline Characteristics

The baseline demographics and anatomic characteristics of the treated subjects will be presented with descriptive statistics.

7.6 Data Analysis

Descriptive statistics will be calculated for all study observations.

7.7 Subgroup and Other Analyses

Outcomes will be reported for the following subject subgroups:

- BMI
  - ≤ 35
  - > 35

- Post-Thrombotic Syndrome
  - Yes
  - No

- CEAP: “Clinical” classification
  - C5
  - C6

- Number of autogenous valves formed
  - 1 valve
  - 2 valves
  - Monocusp vs bicusp

8 DATA HANDLING AND RECORD KEEPING

8.1 General

The investigators shall ensure the accuracy, completeness, legibility and timeliness of the data reported in the Case Report Forms (CRFs) and in all required documentation. Data reported on the CRF shall be consistent with the source documents, with any discrepancies being explained. Any corrections made to documents will be handled according to ISO 14155 guidelines. Failure to meet the documentation requirements may lead to the disqualification of an investigator.

The clinical investigator(s) will permit trial-related monitoring, audits, ethics committee review and regulatory inspection(s), providing direct access to the trial site and to source data/documents on request.

8.2 Monitoring

This clinical trial sponsored by InterVene, Inc. may be conducted under the Standard Operating Procedures of a qualified clinical research organization hired by the Sponsor. The Sponsor’s staff and/or representatives will closely monitor the conduct of the clinical investigation so that any questions and problems that may arise can be promptly resolved. Such monitoring will also ensure that the clinical investigation is conducted in accordance with this clinical investigation plan, including all amendments, applicable regulations and GCP guidelines. Monitoring will involve frequent visits by the Sponsor's representative to the investigation center to verify good management of subjects and the clinical investigation devices, to observe procedures and to audit the clinical investigation for quality control purposes (e.g., to check device accountability and supplies, presence of required documents, informed consent and to compare case report forms with source data). There may also be frequent telephone contact and written communication between monitor and clinical investigator.

During the periodic visits to the center, the monitor reviews the source documents used in the preparation of the case report forms to verify the accuracy and completeness of the information contained in those forms. All data generated during this study, and the source documents from which they originated, are subject to inspection by the Sponsor and its designees or other regulatory authorities. On-site audits may take place independent of, and separate from, routine monitoring or quality control functions. They may take place at various stages during the trial. The clinical investigator(s) will be informed in a timely manner in writing and/or by telephone that a quality control audit is to take place and about the items for which the audit will be performed. Whenever possible, the auditor will be accompanied by the responsible monitor. The auditor may stay at the trial site as long as deemed necessary for the audit. The conduct of such an audit will be confirmed by certification.

Source data verification will be performed on the data that entered onto the case report forms. Regulations require that all data for the clinical investigation are captured as part of the subject's medical records (i.e. source documentation). The questionnaires completed by the subjects are considered primary source documents. All source documentation must be made available for inspection by the monitor, Sponsor's staff or other authorized personnel.

8.3 Case Report Form

An electronic data capture (EDC) system with eCRFs (electronic Case Report Forms) will be used for this study. Subjects are uniquely identified by a study subject number. All eCRFs are completed in English and the investigator, or investigator's qualified designee, must review, electronically sign and date each completed eCRF where requested. The investigator must electronically sign and date the study Exit CRF.

8.4 Record Retention

An investigator or sponsor shall maintain required records during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Required records to be retained per 21 CFR 812.140, includes but is not limited to: all correspondence, documentation of device receipt and disposition, each subject's case history and record of exposure to the device, the protocol and amendments, and dates and reasons for any protocol deviations.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

8.5 Other Aspects of Clinical Quality Assurance

The Sponsor, or the Sponsor's representative, may conduct audits at the investigation sites. Audits may include, but are not limited to, device receipt and disposition, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

9 RISK ANALYSIS

9.1 Risks to the Subjects

Treatment with the BlueLeaf System is a procedure that poses significant risks to the subject, although these risks are not expected to be greater than with other endovascular treatment or open surgery. A summary of some of the known risks are provided below; however, there may be risks that are not known or are unforeseen at this time. The risks related to the device and to the procedure including those commonly related to general anesthesia and concomitant medications used peri-procedurally and during follow-up are listed below.

9.1.1 General Venous Intervention Risks

Anticipated risks that are associated with general venous interventions, and thus may be encountered in this study but are not considered unique to the BlueLeaf device include but are not limited to:

- Air or thrombotic emboli (venous or arterial)
- Hypotension
- Vascular injury
- Access site complications
    - Bruising
    - Bleeding, hemorrhage
    - Pain
    - Hematoma
    - Infection
    - Wound dehiscence
    - Serous wound drainage
    - Lymphorrhea
    - Ecchymosis
- False aneurysm due to inadvertent arterial puncture
- Local
    - Leg edema
    - Leg pain
    - Back pain
- Sepsis
- Phlebitis
- Retained foreign body
- Recurrent or worsened venous disease, related to clinical symptoms or pathophysiology
- Radiation exposure related complication
- Reaction to contrast solution
- Complication resulting in death

9.1.2 BlueLeaf Device and Procedure Risks

Potential risks of the BlueLeaf device and procedure are presented below as event categories, with specific events sub-listed when appropriate. Note that a sub-listed event may fit multiple categories. For example, a “venous perforation” may be a vascular injury during device introduction or positioning or a clinically significant vascular injury due to valve formation steps, depending on which action was being conducted at the time of its occurrence.

- Vascular injury during device introduction or positioning, such as:
    - Venous perforation
    - Arterial perforation
    - Vascular dissection
    - Bruising

  - Hematoma
- Clinically significant vascular injury due to valve formation steps, such as:
  - False venous aneurysm formation
  - False aneurysm formation
  - Vascular occlusion
  - Arteriovenous fistula
- Deep Vein Thrombosis
- Valve Pocket Thrombus
- Embolism (thrombus or air), such as:
  - Pulmonary embolism
  - Paradoxical embolization
  - Superficial thrombophlebitis
  - Distal embolization
- Device embolization
- Allergic or adverse reaction to ingredient or agent of concomitant medications used peri-procedurally and during follow-up, contrast or anesthetic
- Allergic or adverse reaction to device materials
- Unusually prolonged clinical procedure, resulting in complications of extended general anesthesia
- Device cannot be removed safely using standard techniques, resulting in unanticipated surgical maneuvers to remove device
- Unsuccessful formation of functional (i.e. hemodynamically active) valves
- Valves are not durable over time and heal in non-functional position

9.1.3 General Anesthesia Risks

Secondary effects of surgery and sedation that are expected as a result of this type of procedure are reflected in the list below.

- Anxiety
- Chipped teeth
- Bowel function impairment
- Depression
- Fever
- Headache
- Hemoptysis, self-limiting – blood visible in sputum
- Hoarseness, difficulty in speaking
- Lethargy and disorientation
- Nausea or vomiting/dyspepsia
- Pain
- Sore throat, difficulty in swallowing
- Breathing difficulties
- Stroke

- Imbalance

9.1.4 Concomitant Medications Risks

Potential side effects of the protocol required concomitant medications are reflected in the below lists.

9.1.5 Aspirin

- Black, bloody, or tarry stools
- Coughing up blood
- Severe nausea, vomiting, stomach pain
- Extended fever
- Swelling, or extended pain
- Hearing problems, ringing in ears

9.1.6 Enoxaparin

- Hemorrhage, bleeding
- Anemia
- Thrombocytopenia
- Elevation of serum aminotransferase
- Diarrhea
- Nausea

9.1.7 Warfarin

- Tissue necrosis
- Calciphylaxis
- Systemic atheroemboli and cholesterol microemboli

9.1.8 Direct Oral AntiCoagulant (Apixaban, Dabigatran, Rivaroxaban)

- Uncontrolled bleeding

Further details of risks associated with a specific anesthesia and anticoagulation regimen should be detailed in a separate institution-specific pre-operative consent and/or may be cited from public domain information (e.g. drug manufacturer's labeling). Externally referenced risks for the anesthesia and concomitant medications will be tracked as adverse events but not categorized as unanticipated.

9.2 Risk Mitigation

The Sponsor designed the BlueLeaf System to minimize risks to study participants and the risk management for the system was completed in accordance with ISO 14971.

The clinical investigational protocol, which includes the study eligibility criteria, was also designed to minimize risks to study participants. The eligibility criteria were formulated to limit use of the study device to subjects and venous pathology that fit the device specifications. Subjects will be seen more regularly by study personnel than standard practice for CVI patients which allows more thorough oversight and clinical care. Evaluation of safety data by an independent Medical Monitor

and DSMB and assessment of imaging studies by an external core laboratory will provide an ongoing assessment of safety-related events, both individually and in aggregate.

9.3 Benefit to Subjects

It is hoped that the BlueLeaf System will provide an additional treatment alternative for patients with CVI and incompetent deep venous valves. Currently there exist few definitive options for such patients. Conservative measures such as compression stockings and leg elevation treat the symptoms but do not address the underlying venous incompetence. Open surgical interventions including venous valve transposition, valvuloplasty, and other surgical methods are invasive and have been associated with suboptimal outcomes. A minimally invasive modality such as endovascular valve construction, if durable, would hold the potential to alleviate the pain, edema, ulceration and other aspects of chronic venous incompetence; an entity that, in its severe form, afflicts up to 10% of the general population [2, 5, 20, 21].

10 DEVICE DEFICIENCIES

10.1 Defining Device Deficiency

A **device deficiency** is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

10.2 Reporting of Device Deficiency

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the Sponsor. Device deficiencies will be reported to the FDA as detailed in section 0.

11 SAFETY ASSESSMENTS AND ADVERSE EVENT REPORTING

11.1 Adverse Events and Adverse Device Effects

Adverse Event: any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

- Note 1: This definition includes events related to the investigational device
- 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 the investigational medical device.

Adverse Device Effect: adverse event related to the use of an investigational medical device.

- Note 1: This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the investigational device.
- Note 2: This definition includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

11.2 Serious Adverse Events and Serious Adverse Device Effects

Serious adverse event (SAE): an adverse event that

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

NOTE: This includes device deficiencies that might have led to a serious adverse event 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.

In addition, SAEs for hospitalization or surgery to treat pre-existing conditions, without a serious deterioration in health, will also not be reported as SAEs.

Serious adverse device effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated adverse device effect (UADE): any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.3 Severity

The severity of an adverse event is a qualitative judgment of the degree of intensity, as determined by the Investigator or as reported by the Subject, according to the following scale:

- **Mild:** Transient, requires no special treatment or intervention, does not generally interfere with usual daily activities
- **Moderate:** Alleviated with non-invasive therapeutic treatment or intervention, impacts usual daily activities.
- **Severe:** Requires invasive therapeutic treatment or intervention, interrupts usual daily activities.

The assessment of severity should be made independent of the relationship to the investigational device and therapy or the seriousness of the event.

11.4 Relatedness

The relationship of the adverse event to the device and procedure should be evaluated as detailed below but Investigators should also consider a general assessment as to whether the device or procedure may have contributed to the event. In all cases, as much information as possible should be provided in the CRFs for any AE. Though there is very limited clinical experience with

the use of the investigational device, an attempt will be made to classify the relationship with the device as best as possible using the following definitions:

- Not Related: The adverse event is clearly not related to the investigational device: the event has no temporal or other relationship to the administration of the investigational device, follows no known or suspected pattern of response, and an alternative cause is present.

- Unlikely: The adverse event is unlikely related to the investigational device: the event does not follow a clear temporal relationship to the investigational device or does not follow a known pattern of response, or is otherwise likely to be due to the subject's clinical state or other modes of therapy.

- Possible: The relationship with the use of investigational device is weak but cannot be ruled out completely. Alternative causes are also possible. Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

- Probable: The adverse event is likely related to the investigational device: the event has a temporal relationship to the investigational device, follows a known or suspected pattern of response, or is otherwise logically related to the investigational device, but an alternative cause may be present.

- Causal: The adverse event is clearly related to the investigational device: the event has a temporal relationship to the investigational device, follows a known pattern of response, or is otherwise logically related to the investigational device, and no alternative cause is present.

Though there is very limited clinical experience with this procedure, an attempt will be made to classify the relationship to the procedure (such as an endovascular catheter based procedure) as best as possible using the following definitions:

- Not Related: The adverse event is clearly not related to the procedure: the event has no temporal or other relationship to the procedure, follows no known or suspected pattern of response to an endovenous catheter based procedure, and an alternative cause is present.

- Unlikely: The adverse event is unlikely related to the procedure: the event does not follow a clear temporal relationship to the procedure or does not follow a known pattern of response to an endovenous catheter based procedure, or is otherwise likely to be due to the subject's clinical state or other modes of therapy.

- Possible: The relationship with the procedure is weak but cannot be ruled out completely. Alternative causes are also possible.

- Probable: The adverse event is likely related to the procedure: the event has a temporal relationship to the procedure, follows a known or suspected pattern of response to an

endovenous catheter based procedure, or is otherwise logically related to the procedure but an alternative cause may be present.

- Definite: The adverse event is clearly related to the procedure: the event has a temporal relationship to the procedure, follows a known pattern of response to an endovenous catheter based procedure, or is otherwise logically related to the procedure, and no alternative cause is present.

Every effort should be made to determine the cause of each adverse event, because a judgment should be made as to the relationship to the device or procedure. If an investigator or the medical monitor cannot assign a causality category the event will be considered possibly related to the investigational device for reporting and analysis.

11.5 Reporting of Adverse Events

Adverse event reporting, including SAEs, will start at the initiation of the study procedure (i.e. active preparation of the subject, such as initiating hospital's anesthesia protocol). Adverse events/SAEs and concomitant medication that occur between the signing of the informed consent and the initiation of the study procedure thus will not be reported on the AE CRFs.

All reportable adverse events must be captured on the Adverse Event CRF. The report should include, wherever possible, severity, duration, outcome, and the Investigator's written medical judgment as to the relationship of the adverse event to the study device, procedure, or underlying disease.

All SAEs must be reported to the Sponsor or designee immediately, but no later than 3 calendar days of the Investigator's knowledge of the event. All UADEs must be reported to the Sponsor or designee immediately, but no later than 10 working days of the Investigator's knowledge of the event. The SAE or UADE are reported via the electronic data capture system. IRB, MEC, CA and/or FDA notification of the adverse event may also be required, depending on the conditions of approval or requirements of the respective committee.

Non-serious adverse events are to be submitted via the electronic data capture system in a timely fashion. Certain reportable events may require adjudication; therefore, supporting documentation may be requested to be sent to the Sponsor or designee.

11.6 Medical Monitor

A medical monitor who is an independent physician not participating as an investigator in the clinical trial will provide general safety oversight for the investigation. Responsibilities of the medical monitor may include but are not limited to:

- Provide medical and scientific input to review clinical data, subject medical safety data and laboratory values;
- Maintain ongoing assessment of the safety profile of the investigational device during the investigation;
- Provide medical surveillance and evaluation of Serious Adverse Events (SAEs)
- Perform review of all adverse events .

11.7 Clinical Events Committee (CEC)

An independent multidisciplinary CEC will be periodically convened during the conduct of the study and will be responsible for adjudicating the following:

- Potential study endpoint related adverse events
- Potential device related adverse events
- Any other clinical event at the request of the sponsor

The CEC will be composed of at least 3 physicians with relevant clinical experience and specialty. Meetings will be scheduled and conducted per the CEC charter.

11.8 Data Safety Monitoring Board (DSMB)

The DSMB will have access to all data relevant to patient safety (including potential measures of efficacy) to ensure that it is ethical to continue the study, based on the absence of unacceptable risks to the subject. There will be no formal interim analysis of the primary endpoints.

The DSMB will meet after 7-day follow-up data is complete on the first five subjects prior to continued treatments. Subsequent DSMB assessments will occur if/when there are substantial changes to the device or procedure which could impact subject safety. Additionally, the DSMB will be convened for each subsequent group of 5 subjects enrolled.

The DSMB will operate in accordance with the study's DSMB Charter.

12 STUDY ADMINISTRATION

12.1 Site Initiation

A Site Initiation Visit (SIV) will be conducted by the Sponsor or other appropriate designee (e.g., a CRO) to ensure that all study supplies are present, to ensure proper training of the Investigator and study staff members in study-specific procedures, to ensure regulatory requirements are fulfilled prior to enrollment of the first study subject at a site, and to verify the site facilities and equipment are appropriate for conduct of the study.

The following items will be reviewed at the SIV. All training will be documented and must contain signatures of participants.

a) Introduction and overview of agenda
b) Obligations of the Investigator, including his/her responsibilities to ensure only appropriately qualified staff participate in the study conduct, and notification to the Sponsor or its CRO of any change in staff listed on the Delegation of Authority (refer to the site's Regulatory Binder) during the course of the study
c) Protocol (overall review including, but not limited to, inclusion/exclusion criteria, recruitment/withdrawal of subjects, study restrictions);
d) Completion and maintenance of the Delegation of Authority
e) Adverse event reporting and UADE reporting
f) CRFs (procedures, corrections, timely completion, retention)
g) Source document preparation and retention
h) Role of the IRB/MEC
i) Informed Consent Process

j) Study file documents and document retention (ensure all pertinent regulatory documents are collected prior to the site starting the study)
k) Clinical supplies and device management (storage and accountability; device dispensing, labeling, and packaging)
l) Core laboratory processes
m) Requirements for reporting any clinical data back to the Sponsor. (e.g., annual and final reports)
n) Monitoring schedule/plan
o) Other items that may be discussed: background and purpose of the study, previous studies/data, regulatory requirements, policy for publishing trial results, special equipment (if necessary).

12.2 Confidentiality Regarding Study Subjects

The Investigator must ensure that best efforts will be made to hold the privacy of all subjects, including their personal identity and all personal medical information. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an individual identification code.

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

12.3 Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with endovascular techniques, access to required facilities and equipment, sufficient and adequately trained personnel, and availability of potential subjects.

12.4 Responsibilities

Investigator responsibilities include, but are not limited to, the following:

a) Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study subjects
b) Informing all subjects that the device being utilized is for investigational purposes only, and ensuring that the requirements relating to obtaining informed consent and IRB/MEC approvals are met
c) Ensuring that informed consent is obtained for each study subject in accordance with applicable regulations (e.g. CFR 50, ISO 14155)
d) Ensuring that IRB/MEC approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation
e) Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
f) Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
g) Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required)
h) Controlling of all investigational devices under investigation.

13 INFORMED CONSENT PROCESS

The investigator is responsible for assuring that informed consent is obtained and appropriately documented from each subject prior to participation in the clinical investigation.

The informed consent form will be prepared in accordance with this protocol, 21 CFR 50, ISO 14155 and IRB/MEC requirements. Subjects will be consented using IRB/MEC approved versions of the informed consent.

While an investigator, or delegated personnel, may discuss availability of the investigation with a prospective subject without first obtaining consent, informed consent must be obtained from a subject prior to initiation of any clinical assessments or procedures dictated by the protocol that are performed solely for the purpose of determining eligibility to participate in the clinical investigation.

Subjects must be fully counseled and informed of their options, risks and benefits, and have an opportunity to ask questions about participation in the investigation. This process includes a thorough explanation of the informed consent document that the subject will be asked to personally sign and date acknowledging that they understand and desire to participate in the investigation. The subject will receive a copy of the informed consent form.

If new information regarding the investigational device becomes available and/or the protocol changes and this information can significantly affect a subject's future health and medical care, subjects will be informed of the information and may be asked to sign a revised informed consent form.

13.1 Vulnerable Population

The subject population of this clinical investigation does not meet the criteria for a vulnerable population as defined in ISO 14155, Section 3.44. If a subject loses ability to consent during the course of the study this will lead to study exit. Such subjects will be followed on safety parameters for the course of the study, but their data will not be used for data analysis.

14 PROTOCOL MODIFICATIONS

No changes from the final approved (signed) protocol will be initiated without appropriate regulatory oversight of the FDA, CA and IRB/MEC review and approval, as appropriate, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator will acknowledge the amendment by signing the protocol signature page.

15 PROTOCOL DEVIATIONS

A protocol deviation is the non-adherence to or divergence from the protocol-specific study procedures or assessments. For example, divergence from the specified inclusion and exclusion criteria, deviations from the schedule of required follow-up assessments, improper or lack of consent, and lack of IRB/MEC approval, would all be considered protocol deviations. A protocol deviation undertaken to protect the life or physical well-being of the subject in an emergency is a special circumstance that must be reported to the Sponsor within 5 working days and the reviewing

IRB/MEC per local requirement. No other type of prospective protocol deviation is permitted without prior approval. A record of all protocol deviations will be maintained and reviewed throughout the conduct of the study. The Sponsor will address deviations and take appropriate corresponding action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

16 SUSPENSION OR PREMATURE TERMINATION

16.1 Investigator Termination Criteria

The Sponsor reserves the right to terminate an investigator/investigational site for any of the following reasons:

- Failure to secure subject informed consent including protection of personal data prior to enrollment
- Failure to report serious adverse events within 24 hours of discovery or UADEs within 10 working days to the Sponsor or its designee and to the IRB/MEC within its required reporting time after learning of the event
- Repeated investigational plan deviations
- Repeated failure to appropriately complete case report forms and/or complete in a timely manner (> 5 business days)
- Failure to enroll an adequate number of subjects
- Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)
- Loss of or unaccounted for investigational product inventory.

16.2 Investigation Premature Termination Criteria

The Sponsor may choose to suspend or prematurely terminate the investigation at any time. Situations that could warrant study termination include, but are not limited to:

- Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard
- Device deficiency or malfunction
- Administrative decision

In the event of termination, the Sponsor will promptly notify the investigators, IRB/MEC, FDA and CA as required.

16.3 Requirements for Subject Follow-up

Should the investigation be prematurely terminated, efforts will be made to contact all participating subjects to inform them of the study termination. Any ongoing medical needs will be assessed at that time.

17 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in compliance with the principles that have their origin in the Declaration of Helsinki, this clinical investigation plan, ISO 14155 (Good Clinical Practice), requirements of the approving IRB/MEC, 21 CFR Parts 11, 50, 54, 56, 812 and local law.

This clinical investigation will not be initiated until approval has been obtained from the IRB/MEC, FDA and/or CA. Any additional requirements imposed by the IRB/MEC, CA or FDA will be followed. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and IRB/MEC except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the IRB/MEC as soon as possible.

Clinical trial insurance will be secured prior to initiation of this clinical investigation.

18 PUBLICATION POLICY

18.1 Publication by Sponsor

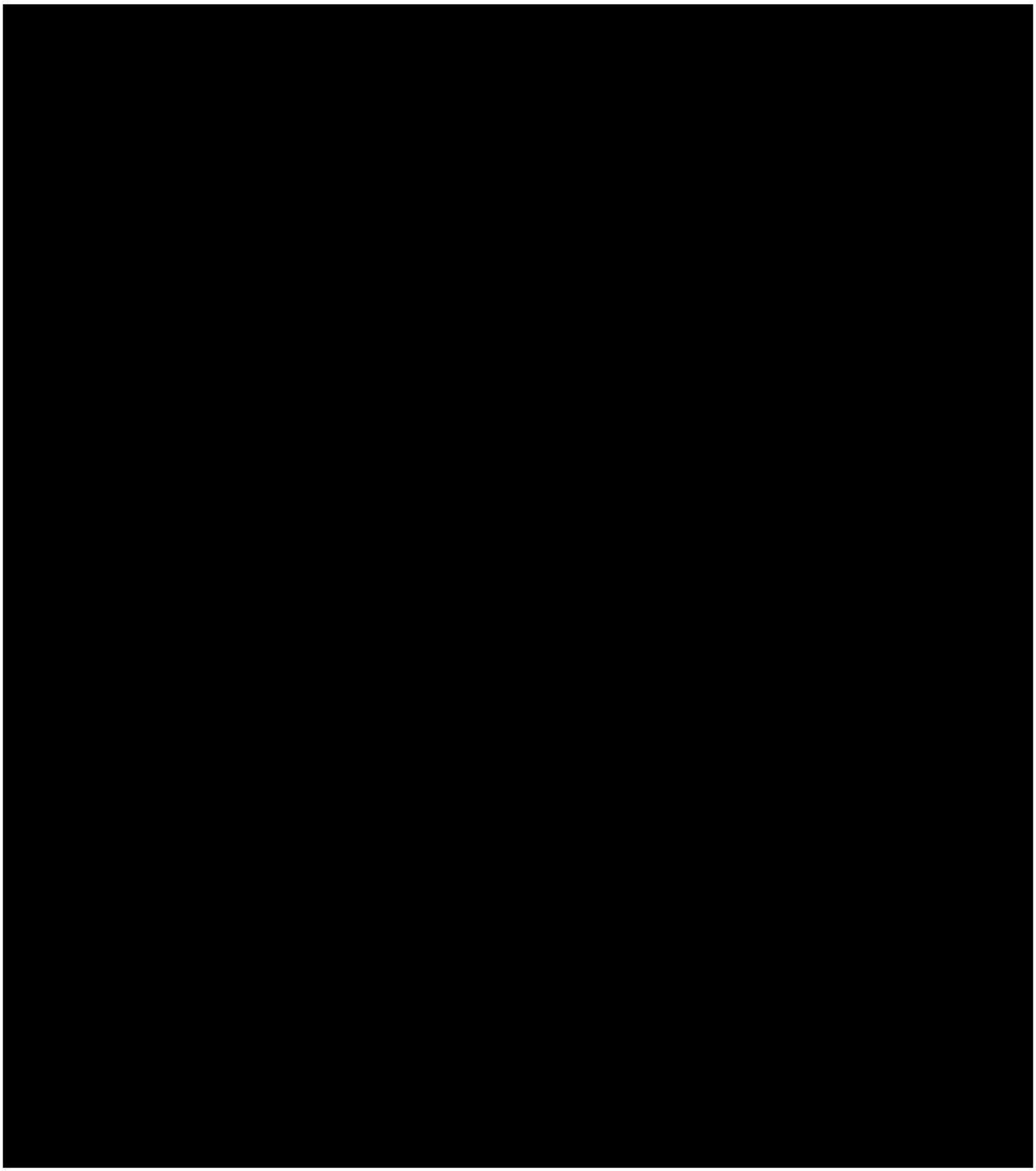
After study closure, the results of this study will be summarized in a Final Report, which will be submitted to the IRB/MEC, CA and FDA per local requirements.

The Sponsor may publish the results of and information pertaining to the investigational subjects. The publications will comply with regulatory requirements pertaining to subject protected health information.

18.2 Publication by the Investigation sites

The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement.

19 REVISION HISTORY



APPENDIX A – STUDY DEFINITIONS

Acute Device Success: Is defined as the BlueLeaf System was delivered to the intended Target Site, Valve Formation Attempt was completed, and the device was retrieved / removed from venous system. If a procedure is aborted (e.g. patient does not have a suitable Target Site as determined by IVUS, other extenuating circumstance, etc.) before the BlueLeaf System enters the venous system, it is not considered a device failure. Aborted procedures will not be included in Success rate calculations.

Autogenous Leaflet: Is defined as the layer of tissue dissected away from the vein wall, comprising a portion of an Autogenous Valve.

Autogenous Pocket: Is defined as the space between an Autogenous Leaflet and the remaining portion of the vein wall, comprising a portion of an Autogenous Valve.

Bicuspid Autogenous Valve: Is defined as a structure with two Autogenous Leaflets and two Autogenous Pockets.

Bleeding Academic Research Consortium (BARC) definition for Bleeding:

Type 0:

- No bleeding

Type 1:

- Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.

Type 2:

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

Type 3:

Type 3a:

- Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed),
- Cardiac tamponade,
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),
- Subcategories confirmed by autopsy or imaging or lumbar puncture,
- Intraocular bleed compromising vision.

Type 4:

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

Type 5:

- Fatal bleeding

Type 5a:

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

Type 5b:

- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Bicuspid Autogenous Valve: Is defined as a structure with two Autogenous Leaflets and two Autogenous Pockets at the same Level (or partially overlapping).

Classification of the Clinical Extent of Venous Disease - CEAP: Is defined as:

C (Clinical Manifestations), E (Etiology), A (Anatomic Distribution), P(Pathophysiology)

Stage	Changes
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C2r	Recurrent varicose veins
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to chronic venous disease
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C4c	Corona phlebectatica
C5	Healed venous ulcers
C6	Active venous ulcers
C6r	Recurrent active venous ulcer

Competent Vein Valve: Is defined a native valve with a ≤ 1 second reflux time as assessed by DUS or imaged with contrast venography (Investigator's opinion)

Deep Vein Thrombosis (DVT): The presence of thrombus within the lumen of a deep vein as confirmed by DUS, accompanied by at least two of the following:

- non-compressibility of the vein at site of thrombus;
- absence of spontaneous flow at site of thrombus;
- presence of symptoms attributable to DVT.

Deep Venous System of the Treatment Limb: A connected system of veins within the treated lower limb consisting of the three paired peripheral calf veins (anterior tibial, posterior tibial and peroneal veins) converging into the popliteal vein extending centrally into the femoral, common femoral, external and common iliac veins. The profunda femoris will also be included in this definition. For the purpose of clarity, the perforating veins, and the veins of the foot are NOT considered part of the deep venous system.

Dissector Actuation: Is defined as the opening and closing of the dissector arms.

> **Full Dissector Actuation:** Is defined as a Dissector Actuation in which the dissector is opened to an expanded geometry deemed adequate for successful Valve Formation at a particular Target Site

Partial Dissector Actuation: Is defined as a Dissector Actuation in which the dissector is opened less than a Full Dissector Actuation (for example, during initial dissector sizing and on the first actuation for a given position)

Dissection Pass: Is defined as a series of Dissector Actuations and Translations spanning the length of one Autogenous Valve following Tissue Access.

Dissector Translation: Is defined as moving the dissector in a longitudinal direction.

Flow-limiting venous outflow obstruction central to the intended target sites: Is defined as

- by a common femoral vein duplex exam found to have a continuous waveform without respiratory variation, or
- a ≥ 50% reduction in luminal cross–sectional area as determined by computed tomography venography (CTV), magnetic resonance venography (MRV) or IVUS

Level: Is defined as an axial position along a vein.

Monocuspid Autogenous Valve: Is defined as a structure with one Autogenous Leaflet and one Autogenous Pocket.

Mouth Cut: Is defined as Dissector Translation following a Dissection Pass while the Dissector Assembly remains in the open configuration.

New York Heart Association (NYHA) Functional Classification:

Class I: No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).

Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).

Class III: Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).

Class IV: Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).

Non-Occlusive Stenosis of the Target Vessel: Includes both symptomatic and asymptomatic post-procedural scarring or inflammation that may lead to changes in hemodynamics or luminal thrombogenicity that could lead to stasis and potentially thrombosis at the site of stenosis or at an alternate location.

Symptomatic is defined as a non-occlusive stenosis within the target vessel, not present prior to the BlueLeaf procedure[c], regardless of etiology (scarring, inflammation, etc.), that leads to persistent worsening of symptoms attributable to venous flow obstruction. Subjects experiencing symptomatic non-occlusive stenosis will be included in the composite primary safety endpoint.

Asymptomatic, is defined as a non-occlusive stenosis within the target vessel, not present prior to the BlueLeaf procedure, regardless of etiology (scarring, inflammation, etc.) which may be visualized with DUS but clinically asymptomatic. Subjects experiencing asymptomatic non-occlusive stenosis will be followed under the Heightened Observation Program and will not be included in the composite primary safety endpoint.

Occlusive Valve Pocket Thrombus: The presence of thrombus confined to the pocket of the autogenous valve as confirmed by DUS imaging, accompanied by the absence of spontaneous flow.

Puncture Site: Is defined as the planned or actual location where the Needle Assembly enters the vein wall.

Serious adverse event (SAE): Is defined as an adverse event that:

a) Led to death,

b) Led to serious deterioration in the health of the subject, that either:

   1. resulted in a life-threatening illness or injury, or

   2. resulted in a permanent impairment of a body structure or a body function, or

   3. required in-patient hospitalization or prolonged hospitalization, or

   4. resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: This includes device deficiencies that might have led to a serious adverse event 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.

In addition, SAEs for hospitalization or surgery to treat pre-existing conditions, without a serious deterioration in health, will also not be reported as SAEs.

[c] i.e. not seen on pre-procedure DUS, or IVUS and venography prior to BlueLeaf device insertion.

Subject Enrollment: A subject is considered enrolled in the study at the point of insertion of the study device into the vasculature, when the device enters the portion of the sheath/guide that resides within the subject's vascular tree.

Symptomatic Chronic Venous Insufficiency (CVI): Is defined as a patient with Clinical Etiological Anatomical Pathophysiological (CEAP) classification of C5 to C6.

Target Site: Is defined as a 3 cm long, 180° radial section of vein wall suitable for Valve Formation.

Target Vessel: Is defined as the common femoral, proximal femoral, distal femoral and popliteal vein segments, in continuity (including duplications), of the treatment limb.

Tissue Access: Is defined as the puncture of a vein wall and advancement into a vein wall layer by the Needle Assembly and the Dissector Assembly.

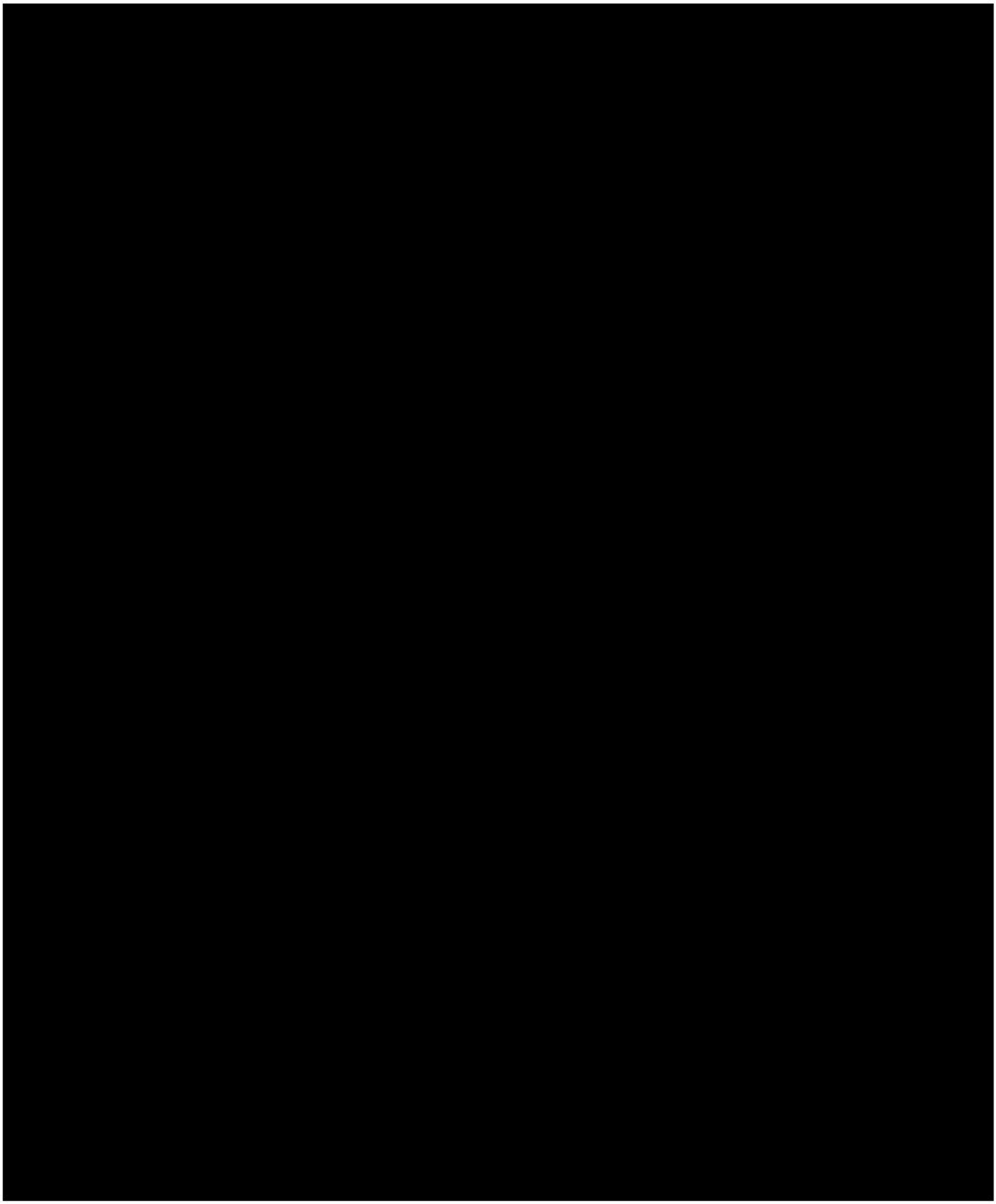
Valve Formation Attempt: Is defined as Tissue Access followed by at least one Dissector Actuation at a single Target Site**.**

Valve Formation: Is defined as Tissue Access followed by at least one Dissection Pass and Mouth Cut at any one Level within a vein.

Valve Pocket Thrombus: The presence of thrombus confined to the pocket of the autogenous valve as confirmed by DUS imaging.

Venous Access Site: Is defined as the site where the sheath and BlueLeaf System are inserted into the patient's venous system.

APPENDIX B - rVCSS



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