VICARES

CLINICAL STUDY PROTOCOL - CL-001

Study Name:	VICARES
Study Title:	A Prospective, Randomized, Controlled, Multi-Center, Double Blind Study of ClariVein RES for Treatment of Venous Insufficiency Associated with Incompetent Saphenous Veins due to Superficial Venous Reflux
Study Phase:	Phase 2/Pilot
Study Product Name:	ClariVein RES
IND Reference Number:	128303
Sponsor:	Vascular Insights, LLC 1 Pine Hill Drive Two Batterymarch Park Suite 100 Quincy, MA 02169 Telephone**:** 203-446-4953
Protocol Version:	1.1
Amendment Version:	0.0
Release Date:	11 July 2017

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. This trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States federal regulations and International Council for Harmonisation (ICH) guidelines.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by the Sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this study.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated. I agree that regulatory authorities (FDA, EMA, and other local and country-related agencies) can audit and review source documents.

I further agree not to originate or use the name of Vascular Insights, LLC or any of its employees, in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to his protocol, to any amendment hereto, or to the performance hereunder, without the prior written consent of Vascular Insights, LLC.

_____ _____

Investigator's Signature Date

_____

Name of Investigator (Typed or Printed)

_____

Institution Name

_____

Institution Address

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PROTOCOL SYNOPSIS

Names of Sponsor/Company: Vascular Insights, LLC	
Name of Investigational Product: ClariVein® RES (Sodium Tetradecyl Sulfate 1% and 3% Injection delivered via the ClariVein infusion catheter system)	
Name of Active Ingredient: Sodium tetradecyl sulfate (STS) **Name of the Delivery System**: ClariVein®	
Study Title: A Prospective, Randomized, Controlled, Multi-Center, Double Blind Study of ClariVein RES for Treatment of Venous Insufficiency Associated with Incompetent Saphenous Veins due to Superficial Venous Reflux (VICARES)	
Number of Study Centers/Patients: Approximately 10 study centers/50 patients in the USA	
Study Period: Estimated date of first patient's consent: Q3 2017 Estimated date of last patient's last visit: Q1 2018	**Phase of Development:** Phase 2 (Pilot)
Study Purpose The purpose of the study is to utilize the ClariVein infusion catheter system specifically for delivery of the STS injection to treat venous insufficiency associated with incompetent saphenous veins.	
Primary Objective Improvement in patient reported symptoms using, HASTI symptoms (heaviness, aching, swelling, throbbing and itching) from the VEINES-QOL/Sym Questionnaire at post treatment Week 12 compared to Baseline.	
Secondary Objective Elimination of saphenous vein reflux post treatment as demonstrated by duplex ultrasound at Week 12 post treatment.	
Tertiary Objectives Assessment of patient improvement at Week 12 post treatment as compared to the Baseline using the following scales: • Clinical-Etiology-Anatomy-Pathophysiology (CEAP) Classification • European Quality of Life Scale (EQ-5D-5L) • Revised Venous Clinical Severity Score (rVCSS) • Wong Baker Visual Analog Pain Scale (VAS scale)	
Study Design: This Phase 2 clinical study is designed as a prospective, randomized, controlled, multicenter, double-	

blind study of ClariVein RES for the treatment of venous insufficiency associated with incompetent saphenous veins due to superficial venous reflux.

Population:
The study will be conducted in adult patients with the diagnosis of incompetent saphenous veins.

Inclusion Criteria
An individual must meet **all** the following inclusion criteria to be eligible for this study:

1. Written informed consent
2. Age ≥18 years ≤ 80
3. Saphenous vein reflux > 500ms (0.5s), as measured by duplex ultrasound with patient in the standing position
4. Incompetent saphenous vein with vein diameter ≥ 4 mm and ≤ 12 mm, as measured by duplex ultrasound with patient in the standing position
5. Incompetent saphenous vein with treatable length ≥ 10 cm, as measured by duplex ultrasound with patient in the standing position
6. One or more of the HASTI symptoms related to the target vein: heaviness, achiness, swelling, throbbing and itching.
7. Candidate for endovenous procedure for the treatment of venous insufficiency or superficial venous reflux.
8. CEAP Score: C2 (symptomatic), C3, C4, C5
9. rVCSS ≥ 3

Exclusion Criteria

An individual will be ineligible for participation in this study if **any** of the follow criteria are met:

1. CEAP Score: C1, C2 (asymptomatic), C6
2. Second incompetent saphenous vein > 4 mm diameter in either leg
3. Arterial insufficiency demonstrated by a history of peripheral arterial disease (PAD) that would preclude the wearing of compression stockings
4. Absence of a palpable pulse at posterior tibial or dorsalis pedis and an Ankle-Brachial Index (ABI) ≤0.6
5. Multi-segmental axial deep venous reflux in at least two contiguous venous segments (e.g., femoral and popliteal) in the ipsilateral extremity
6. Previous surgical or endovenous procedure in the treatment section of the target vein (e.g., surgical, thermal ablation, chemical ablation, etc.)
7. Any major surgery, prolonged hospitalization, or pregnancy within 12 weeks prior to Screening (Visit 1)

8. Participation in an interventional clinical study with any investigational product (drug, biologic, device etc.) within 4 weeks prior to Screening (Visit 1)
9. Unable to:
10. walk unassisted, and
11. stand as needed for duplex ultrasound measurements of vein at scheduled visits
12. Previous superficial thrombophlebitis of the target saphenous vein with scarring in the treatment section
13. Female patients of childbearing potential with a positive result from a pregnancy test performed at Screening (Visit 1), Baseline (Visit 2), or Day of Treatment (Visit 3)
14. Known sensitivity or allergic response to:
15. sodium tetradecyl sulfate (STS) or any of its ingredients; and
16. other products if planned for use on the study patient and there is no available alternative, e.g., local anesthetic; latex stockings, or gloves
17. Known history of anaphylaxis or presence of multiple severe allergies
18. Known high risk of thrombosis, e.g., two or more risk factors including, current use of hormonal contraception, current use of hormone replacement therapy, extended periods of immobility, cancer, obesity, recent trauma
19. Known history of deep vein thrombus (DVT) or pulmonary embolism (PE), known history of acute superficial vein thrombus, known hypercoagulable condition, post thrombotic syndrome
20. Known history of drug or alcohol abuse within 2 years of Screening (Visit 1); and/or current chronic narcotic usage, including for pain (e.g., opioids)
21. Presence of tortuous target saphenous vein, which in the opinion of the Investigator will limit vascular access and/or require more than one access site to treat patient
22. Varicosities caused by known pelvic or abdominal pathology
23. Lymphedema
24. Fibromyalgia
25. Other medical conditions or comorbidities which, in the opinion of the Investigator, could interfere with study compliance, could affect the efficacy of treatment or could compromise patient care, or could interfere with data interpretation, including, but not restricted to any one of the following:
    a. severe illness
    b. edema not due to venous disease of the legs (e.g., latent cardiac insufficiency, renal insufficiency, etc.)
    c. documented human immunodeficiency virus (HIV)
    d. congestive heart failure, coronary artery disease, cerebral vascular disease
    e. active infection, tuberculosis, or sepsis
    f. active cancer or neoplasm (excluding non-melanoma skin cancer)
    g. uncontrolled systemic disease such as diabetes mellitus, toxic hyperthyroidism, blood dyscrasias, or acute respiratory (e.g., asthma), or skin diseases

26. Any patient that, in the Investigator's opinion, would be unlikely to receive clinical benefit from the study procedure

Efficacy Assessment (Primary, Secondary, Tertiary, Exploratory)

- European Quality of Life scale (EQ-5D-5L)
- VEINES-QOL/Sym
- VAS score
- CEAP
- rVCSS
- Ultrasound

Safety Assessment

Assessment of adverse events

Data Analysis

The study data will be analyzed and reported based on all patients' data from baseline up to the time when all patients have completed the Week 12 post-treatment follow-up visit or have discontinued from the study. If a patient has discontinued from the study, the Last Observation will be carried forward (LOCF) for analysis.

LIST OF ABBREVIATIONS AND TERMS

List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ASV	Accessory Saphenous Vein
CEAP	Clinical-Etiology-Anatomy-Pathophysiology Classification
DICOM	Digital Imaging and Communications in Medicine
DVT	Deep Venous Thrombosis
EO	Ethylene Oxide
EQ-5D-5L	European Quality of Life - 5 Dimensions
FDA	Food and Drug Administration (United States of America)
GCP	Good Clinical Practice
GSV	Great Saphenous Vein
HASTI	Heaviness, Achiness, Swelling, Throbbing, Itching
IC	Intravascular Coagulation
IRB	Institutional Review Board
MDU	Motor Drive Unit
PASTE	Post-Ablation Superficial Thrombus Extension
PE	Pulmonary Embolism
rVCSS	Revised Venous Clinical Severity Score
SAE	Serious Adverse Event
SFJ	Sapheno-Femoral Junction or Saphenofemoral Junction
SSV	Small Saphenous Vein
STS	Sodium Tetradecyl Sulfate
SVS	Saphenous Vein Segment
TS	Treatment Section
US	United States
VAS	Visual Analog Scale
VEINES-QOL/SYM	Venous Insufficiency Epidemiological and Economic Study-Quality of Life Questionnaire
VI	Vascular Insights, LLC

List of Terms and Definitions

Term	Definition
Adverse Event	An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a study product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that patient and is considered clinically significant.
Baseline	Establishment of patient eligibility for study treatment at least 7 days prior to Treatment visit (Visit 2)
CEAP Classification	The CEAP classification is a method for evaluating venous disease of the leg based on clinical, etiologic, anatomic, and pathophysiologic data.
CRO	Clinical Research Organization, which may be assigned responsibility to perform selected function of the study
Day-of-Treatment	The day on which the single-treatment procedure is performed– the treatment begins and ends on the same day (Visit 3)
End-of-Study for Patient	The end of study for a patient is when the patient has completed the required post-treatment study visits or has discontinued from the study.
Enrolled Patient	Individual who has signed the Informed Consent Form.
Elimination of Saphenous Vein Reflux	Vein closure and/or vein competence of the treatment section (TS) of the selected saphenous vein, as demonstrated by duplex ultrasound at Week 12 post treatment (Visit 6)
Follow-up Period	From the day following Day of Treatment (Visit 3) to completion of the Week 1, 6 and 12 (Visits 4, 5 and 6) post-treatment follow-up visits
HASTI	Heaviness, Achiness, Swelling, Throbbing, Itching symptom from VEINES-QOL/Sym questionnaire
Institutional Review Board (IRB)	A type of committee used in research in the United States that has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans
Regulatory Agency	USA Food and Drug Administration (FDA)
Saphenous Vein Segment	A segment of saphenous vein with no deep venous junction
Screening Period	After reviewing and signing the Informed Consent Form (ICF) for participation in the study, an individual will be screened for eligibility to participate in study during Screening (Visit 1), Baseline (Visit 2), Day of Treatment (Visit 3).
Sponsor	Vascular Insights, LLC

Term	Definition
Start-of-Study	Study starts when first patient signs the ICF (Visit 1).
Study Drug	Sodium Tetradecyl Sulfate (STS) 1% and 3%
Study Drug Delivery System	ClariVein infusion catheter system
Study Product	ClariVein RES (Sodium Tetradecyl Sulfate delivered via the ClariVein infusion catheter system)
VICARES Clinical Study Procedure Manual	A manual provided to the Investigational Sites that include instruction for device operation, study drug and delivery device preparation, and ultrasound assessments for the ClariVein RES.
Study Treatment	The study treatment, is the endovenous administration of either 1% or 3% STS delivered intravenously via the ClariVein, with a maximum STS volume of 10 mL per single treatment procedure.
Suspected Adverse Event	Any adverse event (AE) for which there is a reasonable possibility that the study product caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.
Treatment Section	The treatment section (TS) is the portion of the selected saphenous vein to be treated with ClariVein RES.
Treatment Section Length	The treatment section length (TSL) is the portion of the selected saphenous vein to be treated with ClariVein RES.
Treatment Section Diameter	The average diameter of the treatment section (TS).
Vein Closure	No discrete open section of vein >5 cm in length within the treatment section (TS) of the selected saphenous vein, as assessed by duplex ultrasound.
Vein Competence	Absence of retrograde flow >500ms (0.5s) within the treatment section (TS) of the selected saphenous vein, as assessed by duplex ultrasound.

1. BACKGROUND

Venous insufficiency, a serious health condition, is most commonly caused by incompetent valves in the affected veins which prevent blood from returning to the heart, causing blood to pool in the legs and, as a result, venous hypertension. Valve failure can be spontaneous in patients with congenitally weak valves; or congenitally normal valves can fail as a result of trauma, thrombosis, hormonal changes, or long-term environmental effects.

In the United States (US), varicose veins affect approximately 25% of the adult population (Criqui et al 2003). The prevalence and severity increase with age; however, the severity and extent of varicosities vary greatly among individuals and do not necessarily correspond to the severity of a patient's symptoms that result from venous hypertension. Venous hypertension may lead to progressive damage to the skin (e.g., edema, discoloration, hyperpigmentation, eczema, and ulceration), with symptoms that motivate patients to seek treatment; and in the US alone more than 400,000 patients are treated annually (Millennium Research Group 2009).

Over time this condition often develops into a progressive chronic disease. Chronic Venous Disease (CVD) is among the most frequently diagnosed diseases in Western populations that cause symptoms such as heaviness of the legs, pain, and swelling. While CVD encompasses the full spectrum of the disease (described by Clinical-Etiology-Anatomy-Pathophysiology [CEAP] classes C1 to C6), the term chronic venous insufficiency (CVI) is generally restricted to the more severe forms of the disease.

The ClariVein, a unique proprietary mechanical action infusion catheter, has been cleared by the FDA since 2008 as a Class 2 medical device *for the infusion of physician-specified agents in the peripheral vasculature* [510(k) K071468 and K153502]; and commercialized as the ClariVein IC. The ClariVein has been approved since 2010 in certain countries/regions outside the USA as the "ClariVein OC"; e.g., Europe (CE marked), Canada, Asia Pacific, Latin America and Middle East countries, with an additional specific indication *"for infusion of physician-specified agents in the peripheral vasculature, including for the occlusion of incompetent veins due to superficial venous reflux"*. The ClariVein IC and the ClariVein OC are physically identical products.

Globally, physicians have found great utility with the ClariVein® for the administration of sclerosing agents such as sodium tetradecyl sulfate and polidocanol for treatment of incompetent saphenous veins. More than 90,000 ClariVein devices have been distributed worldwide; and a significant body of clinical experience inclusive of published data, clinical studies and case reports, describes use of the ClariVein to mechanically deliver chemical scleorsant in over 1200 venous disease patients. Much of these data present ClariVein® administering sodium tetradecyl sulfate (STS) for the treatment of venous insufficiency attributed to incompetent saphenous veins due to superficial venous reflux.

The STS solution 1% and 3%, a chemical sclerosing agent, has been approved by the FDA since 1946 as a drug for the intravenous delivery and treatment of small uncomplicated varicose veins of the lower extremities that show simple dilation with competent valves. [NDA 05970, ANDA 40541].

Vascular Insights, LLC is investigating the ClariVein RES, i.e., the endovenous administration of STS (1% and 3%) mechanically delivered intravenously via the ClariVein infusion catheter

for the treatment of venous insufficiency associated with incompetent saphenous veins due to superficial venous reflux.

1.1. Rationale

CVI is a leading cause of chronic debilitating disease in the US (White 1993, Van den 1998); between 10% and 35% of the US adult population has some form of CVI (Criqui 2003, Simka 2003). In industrialized nations, 0.2% - 1% of people suffer from venous ulceration. This percentage increases to 4% in patients 65 years of age and older (White 1993; Reporting standards in venous disease 1988). Venous leg ulcers are extremely common in the United States and affect between 500,000 to 2 million people annually (Margolis 2002). Ineffective therapies and the progressive nature of the disease place a heavy burden on the US healthcare system. The population-based costs in the US for treatment of CVI and venous ulcer care have been estimated to exceed one billion dollars per year (Hume 1992; US Department of Health and Welfare 1935-1936) and as high as $14.9 billion (Rice 2014).

The high incidence and increasing cost of CVI care have garnered renewed interest in this disease process, which has led to interesting findings in the past decade. For example, the incidence of CVD correlates with a reduced quality of life, particularly in relation to pain, physical function, and mobility. It is also associated with depression and social isolation (Van Korlaar et al 2003). Impairment associated with CEAP classes C5 and C6 has been likened to that of impairment associated with congestive heart failure (Kistner et al 1996).

The majority (60–70%) of varicose vein patients have incompetent saphenofemoral junctions (SFJ) and GSV reflux (Labropoulos et al 1994). Typically, the first objective in the treatment of varicose veins is elimination of saphenous vein reflux by removing the offending vein from circulation. Thermal ablation in the form of radiofrequency (RF) and endovenous laser (EVL) techniques are currently the most common methods used for saphenous vein ablation to treat superficial venous reflux. However, use of either of these thermal technologies for saphenous vein treatment requires tumescent anesthesia, which is both time-consuming and painful for the patient. Furthermore, the edema, pain, and bruising that are secondary to thermal injury of surrounding structures are frequent post-operative patient complaints.

For many years, sclerotherapy was used clinically for telangiectasia and to close varicose veins. However, early studies using sclerotherapy for the treatment of saphenous vein reflux did not generate promising results. In recent years, another approach involving the creation of a “foam” from liquid sclerosant using the double-syringe “Tessari” method prior to injection has been used. This approach has led to the publication of multiple studies utilizing foam sclerotherapy to treat veins such as the GSV (Cavezzi et al 2002; Frullini 2003; Hamel-Desnos 2003). Results of foam sclerotherapy for treatment of the saphenous vein are inferior compared to thermal ablation (Rasmussen 2011).

The FDA has approved foam sclerosant for the treatment of incompetent veins; indicated for treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee (NDA 205098, Approval date November 25, 2013 for Varithena®, polidocanol foam). Other approved therapies for the treatment of venous insufficiency including incompetent veins include thermal technologies (i.e., laser and RF); and permanent implant devices (i.e., VenaSeal Closure System, PMA P140018, Approval date 15 Feb 2015).

Unlike the previously discussed therapies, ClariVein RES is not a foam, is not an implant, is not a thermal modality, and does not require tumescent anesthesia. ClariVein RES is the endovenous administration of liquid chemical sclerosant (STS) mechanically delivered intravenously via the ClariVein infusion catheter to the physician determined treatment section of the incompetent saphenous vein to effect engagement of the sclerosant to the vessel wall to achieve sclerosis to eliminate venous insufficiency.

2. STUDY DRUG AND DELIVERY SYSTEM

2.1. Study Product

The investigational study product, ClariVein RES, consists of two primary components: the study drug, STS (1% and 3%) and the study drug delivery system, ClariVein.

- **Study Drug**: The study drug (STS) has been commercially available outside of the USA since 1967 for treatment of venous insufficiency
- **Delivery System**: The delivery system (ClariVein) has been commercially available in the USA since 2008 marketed as the ClariVein IC for infusion of physician specified agents in the peripheral vasculature; and has been commercially available outside the USA since 2010 as the ClariVein OC for infusion of agents to treat saphenous veins with incompetent valves (superficial venous reflux).

STS, marketed in the USA under the brand name Sotradecol, was approved by the USA FDA in 1946 for treatment of small uncomplicated veins, such as spider veins, with competent valves.

2.1.1. Study Drug - Sodium Tetradecyl Sulfate (STS)

STS is provided as sterile 2 mL solution within a labeled glass ampule for single use; five 2 mL ampules are provided within a labeled shelf carton. Two concentrations will be evaluated:

- 1%, 20 mg/2 mL (10 mg/mL)
- 3%, 60 mg/2 mL (30 mg/mL)

Recommended storage for STS is 20° to 25°C (68° to 77°F) in a secure dry place. Do Not Freeze.

2.1.2. Delivery System - ClariVein®

The ClariVein is provided as a sterile disposable device for single patient use. The ClariVein is packaged in a tray within a sealed labeled pouch; five pouches are placed within a labeled shelf box, five (5) boxes are provided within a labeled shipping carton. The ClariVein is available in 3 models, 45, 65 and 85 cm lengths for physician selection based on patient anatomy. The disposable ClariVein consists of two primary components: a catheter assembly and integrated battery powered motor drive unit (MDU). All models of the ClariVein are physically identical except for the length of the catheter assembly.

3. STUDY OBJECTIVE

3.1. Objectives and Endpoints

Objectives and related endpoints are described in Table 1.

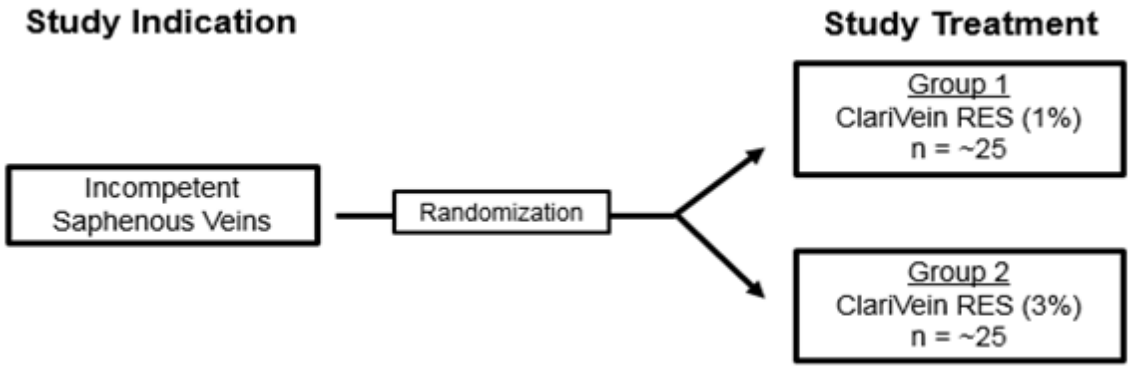
Table 1: Study Endpoints

Primary Endpoint	
Improvement in patient reported symptoms using, HASTI symptoms (heaviness, aching, swelling, throbbing and itching) from the VEINES-QOL/Sym Questionnaire at post treatment Week 12 compared to Baseline.	Section 11.3
Secondary Endpoint	
Elimination of saphenous vein reflux post treatment as demonstrated by duplex ultrasound at Week 12 post treatment.	Section 11.3.1
Tertiary Endpoints	
Assessment of patient improvement at Week 12 post treatment as compared to the Baseline using the following scales: • Clinical-Etiology-Anatomy-Pathophysiology (CEAP) Classification • European Quality of Life Scale (EQ-5D-5L) • Revised Venous Clinical Severity Score (rVCSS) • Wong Baker Visual Analog Pain Scale (VAS scale)	Section 11.4
Exploratory	
Assessment in patient reported symptoms **Week 1** VEINES-QOL-SYM (Questions 1 through 8) **Week 6** VEINES-QOL-SYM (Questions 1 through 8) **Week 12** VEINES-QOL/Sym (Question 1, excluding HASTI, through Question 8)	Section 11.5

4. STUDY DESIGN

This Phase 2 Investigational Study is designed as a prospective, randomized, controlled, multicenter, double-blind study of STS solution delivered by the ClariVein infusion catheter system in adult patients for the treatment of venous insufficiency associated with incompetent saphenous veins due to superficial venous reflux.

Figure 1: Study Design



4.1. Treatment Arms

During study treatment, patients will be randomized and enrolled in one of the following treatment arm groups:

- Group 1: 1.0% STS solution
- Group 2: 3.0% STS solution

Patients will be randomized in a 1:1 ratio to each treatment arm.

4.2. Study Periods

All patients enrolled should participate in the following study periods:

- Screening/Baseline period
- Treatment period
- Post treatment follow up period

Each study visit is described below and shown in Table 2. All patients are considered "on-study" until they complete the follow-up period, withdraw consent or are lost to follow up.

Table 2: Study Periods

Visit	Screening	Baseline	Study Treatment	Post Treatment Follow-up		
	1	2	3	4	5	6
Study Days	-30 to -7	-10 to -7	Day 1 Treatment (Procedure Day)	Week 1 - Day 7 - (±2 days)	Week 6 - Day 42 (±5 days)	Week 12 – Day 84 (±7 days)
Purpose	Study eligibility		Treatment	Safety/efficacy evaluation		

4.2.1. Screening/Baseline Period

The screening period begins once the patient has signed the study Informed Consent Form (ICF). Patients will be evaluated to ensure that they meet all of the inclusion and none of the exclusion criteria (Section 5.1, Section 5.2).

4.2.2. Treatment Day

The treatment period duration is one day. An enrolled and randomized patient will receive the single treatment procedure with ClariVein RES (approximately less than 30 minutes), unless the patient opts to discontinue or experiences unacceptable toxicity during the delivery of the study drug.

4.2.3. Post Treatment Follow-up (FU) Period

Patients will be followed for safety and efficacy evaluations post treatment at Week 1, Week 6 and Week 12. Details are provided in Table 3 and Section 7.6.

4.2.4. Definition of End of Study

The end of study will be when all patients have completed Treatment Day 1 and the Post treatment follow-up at Week 12 or have discontinued from the study

4.2.5. Study or Site Termination

The Sponsor reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual Investigator or Investigational Site for poor enrollment or protocol noncompliance.

If the Sponsor, Investigator, Medical Monitor, or regulatory agencies discover conditions during the study that indicate that the study or a site should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, and Medical Monitor.

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for GCP, *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Selection and Disposition of Patients.*

5. ELIGIBILITY CRITERIA

The study will be conducted in adult patients with venous insufficiency associated with incompetent saphenous veins due to superficial venous reflux. The Investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1. Inclusion Criteria

An individual must meet **all** the following inclusion criteria to be eligible for this study:

1. Written informed consent
2. Age ≥18 years ≤ 80
3. Saphenous vein reflux > 500ms (0.5s), as measured by duplex ultrasound with patient in the standing position
4. Incompetent saphenous vein with vein diameter ≥ 4 mm and ≤ 12 mm, as measured by duplex ultrasound with patient in the standing position
5. Incompetent saphenous vein with treatable length ≥ 10 cm, as measured by duplex ultrasound with patient in the standing position
6. One or more of the HASTI symptoms related to the target vein: heaviness, achiness, swelling, throbbing and itching.
7. Candidate for endovenous procedure for the treatment of venous insufficiency or superficial venous reflux.
8. CEAP Score: C2 (symptomatic), C3, C4, C5
9. rVCSS ≥ 3

5.2. Exclusion Criteria

An individual will be ineligible for participation in this study if **any** of the follow criteria are met:

1. CEAP Score: C1, C2 (asymptomatic), C6
2. Second incompetent saphenous vein > 4 mm diameter in either leg
3. Arterial insufficiency demonstrated by a history of peripheral arterial disease (PAD) that would preclude the wearing of compression stockings
4. Absence of a palpable pulse at posterior tibial or dorsalis pedis and an Ankle-Brachial Index (ABI) ≤0.6
5. Multi-segmental axial deep venous reflux in at least two contiguous venous segments (e.g., femoral and popliteal) in the ipsilateral extremity
6. Previous surgical or endovenous procedure in the treatment section of the target vein (e.g., surgical, thermal ablation, chemical ablation, etc.)

7. Any major surgery, prolonged hospitalization, or pregnancy within 12 weeks prior to Screening (Visit 1)
8. Participation in an interventional clinical study with any investigational product (drug, biologic, device etc.) within 4 weeks prior to Screening (Visit 1)
9. Unable to:
    a. walk unassisted; and
    b. stand as needed for duplex ultrasound measurements of vein at scheduled visits
10. Previous superficial thrombophlebitis of the target saphenous vein with scarring in the treatment section
11. Female patients of childbearing potential with a positive result from a pregnancy test at the Screening (Visit 1), Baseline (Visit 2), or at the Day of Treatment (Visit 3)
12. Known sensitivity or allergic response to:
    a. sodium tetradecyl sulfate (STS) or any of its ingredients; and
    b. other products if planned for use on the study patient and there is no available alternative, e.g., local anesthetic; latex stockings, or gloves
13. Known history of anaphylaxis or presence of multiple severe allergies
14. Known high risk of thrombosis, e.g., two or more risk factors including, current use of hormonal contraception, current use of hormone replacement therapy, extended periods of immobility, cancer, obesity, recent trauma
15. Known history of deep vein thrombus (DVT) or pulmonary embolism (PE), known history of acute superficial vein thrombus, known hypercoagulable condition, post thrombotic syndrome
16. Known history of drug or alcohol abuse within 2 years of Screening (Visit 1); and/or current chronic narcotic usage, including for pain (e.g., opioids)
17. Presence of tortuous target saphenous vein, which in the opinion of the Investigator will limit vascular access and/or require more than one access site to treat patient
18. Varicosities caused by known pelvic or abdominal pathology
19. Lymphedema
20. Fibromyalgia
21. Other medical conditions or comorbidities which, in the opinion of the Investigator, could interfere with study compliance, could compromise patient care, or could interfere with data interpretation, including, but not restricted to:
    a. severe illness
    b. edema not due to venous disease of the legs (e.g., latent cardiac insufficiency, renal insufficiency, etc.)
    c. documented human immunodeficiency virus (HIV)
    d. congestive heart failure, coronary artery disease, cerebral vascular disease
    e. active infection, tuberculosis, or sepsis
    f. active cancer or neoplasm (excluding non-melanoma skin cancer)

g. uncontrolled systemic disease such as diabetes mellitus, toxic hyperthyroidism, blood dyscrasias, or acute respiratory (e.g., asthma), or skin diseases

22. Any patient that, in the Investigator's opinion, would be unlikely to receive clinical benefit from the study procedure

6. TREATMENT OF PATIENTS

6.1. Study Treatment

ClariVein RES is the endovenous administration of STS injection (1% and 3%) mechanically delivered as intravenous infusion via the ClariVein for the treatment of venous insufficiency associated with incompetent saphenous vein due to superficial venous reflux.

This study is limited to the treatment of one incompetent saphenous vein per treatment procedure. Refer to Appendix C VICARES Clinical Study Procedure Manual for detailed on the treatment procedure including ultrasound measurements and calculation of the STS volume required for administration.

6.2. Study Duration

This study is limited to the treatment of one incompetent saphenous vein in one leg per treatment procedure. STS (1% or 3%) will be delivered as a single dose treatment. The ClariVein RES treatment procedure will be completed on each eligible patient on the Treatment Day (noted as Day 1), unless the patient experiences unacceptable toxicity and/or treatment is discontinued at the discretion of the Investigator or the patient.

Overall duration of the study from first patient enrolled to last patient completion of Week 12 follow-up is anticipated to be approximately 6 months. Study duration for individual study patients, including follow-up visits, is anticipated to be approximately 16 weeks (Visit 1 Screening, up to 30 days prior to treatment through Week 12 post-treatment.)

6.3. Potential Drug Interactions/Allergies

No well-controlled studies of the study drug (STS Injection 1% and 3%) have been performed on patients taking anti-ovulatory agents. The Investigator must use medical judgment and evaluate any patient taking anti-ovulatory drugs prior to initiating treatment with the study drug (STS) (Sotradecol Package Insert 2013).

Heparin should not be included in the same syringe as STS solution, since the two are labeled to be incompatible. (Sotradecol Package Insert 2013).

Patient should be observed for at least 30 minutes following treatment. The Investigator must be prepared to treat any allergic reaction to substances utilized during treatment procedure, including anaphylaxis reactions.

Emergency resuscitation equipment **must be immediately available** in the event of anaphylactic reactions.

6.4. Prior and Concomitant Treatment(s)/Therapy

All prior and concomitant medications taken within 30 days prior to the Screening (Visit 1) through completion of the last planned follow-up visit at Week 12 post-treatment (Visit 6) must be recorded in the eCRF.

At every visit, patients will be asked to confirm if there has been any change in medications taken since the last visit. Changes will be recorded on the concomitant medications eCRF and

coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) and further coded against Anatomical Therapeutic Chemical (ATC) classification.

All concomitant medications are to be documented and reviewed per the Study's Inclusion/Exclusion criteria (Section 5).

6.5. Prohibited Concomitant Procedures/Therapies/Medications

Any adjunctive procedures in either leg, including phlebectomy, will **not be allowed** prior to completion of the Week 12 post-treatment visit.

6.6. Patient Numbering, Treatment Assignment or Randomization

6.6.1. Subject Numbering

Each patient is identified in the study by a unique Subject Number (Subject No.), that is assigned when the patient is first enrolled for Screening.

The randomization assignment of a patient to treatment arm Group 1 or Group 2 will be performed at a 1:1 ratio.

6.6.2. Double Blind - Study Drug

The Sponsor, CRO, Investigational Site Staff, Investigators and patients will be blinded to the study drug and will use the product assigned via a validated randomization system. The study blind will be broken after the study database has been locked upon completion of the clinical study.

6.6.3. Emergency Breaking of the Study Blind

The study blind is not to be broken under ordinary circumstances. No change in standard emergency treatment is anticipated due to a difference in the strength of the study drug. However, unblinding should not necessarily be a reason for discontinuation of the study.

6.7. Preparation, Dispensing, and Storage of Clinical Supplies

Please refer to Appendix C VICARES Clinical Study Procedure Manual for information on the preparation, dispensing and storage of clinical supplies.

6.8. Study Drug and Device Accountability

The Investigational site is responsible for receipt, storage, and accountability of the Study Product, ClariVein RES (STS and ClariVein), supplied to the Investigational site specifically for use in this clinical study, in compliance with Good Clinical Practice.

7. VISIT SCHEDULE AND ASSESSMENTS

7.1. Study Visit Schedule and Assessments

A list of all study assessments is included in Table 3, which indicates with an "X" if the assessment performed at that visit.

The Screening (Visit 1) evaluation should be performed ≤ 30 days prior to Treatment (Visit 3). Additional screening will be performed at Baseline (Visit 2), not less than 7 days prior to Treatment (Visit 3).

Study visits, tests and/or procedures should occur on schedule per Table 3. Any exceptions will have to be approved by the sponsor.

Table 3: Visit Schedule and Assessments

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening Period		Treatment Period	Post-Treatment Follow-up Peirod		
	Screening	Baseline	Treatment	Week 1	Week 6	Week 12
Study Day(s)	-30 to -7	-10 to -7	Day 1	Day 7 (±2 days)	Day 42 (±5 days)	Day 84 (±7 days)
Informed Consent	X					
Inclusion/Exclusion criteria	X					
Medical History	X					
Diagnosis and Extent incompetent saphenous vein	X					
Demographics	X					
Physical Exam	X		X			
Pregnancy test (serum)		X				
Pregnancy test (urine)	X		X			
Height	X					
Weight	X					
Vital signs	X	X	X	X	X	X
Hematological Assessment[a,]		X		X	X	X
Intravascular Coagulation Assessment[b, c]		X	X	X	X	X
Adverse events	X	Continuous				
Concomitant medications and Non-Drug procedures	X	Continuous				
Ultrasound	X	X	X	X	X	X
CEAP Classification	X					X
rVCSS	X					X
HASTI symptoms – 7-day assessment			X	X	X	X
European Quality of Life scale (EQ-5D-5L)		X	X	X	X	X
VEINES-QOL-SYM		X	X	X	X	X
VAS score		X	X (Procedure only)	X	X	X
ClariVein RES procedure			X			

[a] Hematological Assessments include: Hemolysis, hematocrit, reticulocyte count, haptoglobins as described in Section 8.1

[b] Intravascular coagulations include Plasma fibrinogen level, Plasma D-dimer level platelet count, Prothrombin time (PT), Partial thromboplastin time (PTT) as described in Section 8.1.

[c] Plasma D-dimer level assessments will be conducted at: Baseline (Visit 2) immediately post Treatment (Visit 3) and at Week 1 follow-up (Visit 4); then, only at subsequent follow-up visits [Week 6 (Visit 5) and Week 12 (Visit 6)] if the D-dimer level is higher than it was at Baseline.

7.2. Pre-visit Patient Instructions

When scheduling a patient for a study visit, advise the patient to be mobile for at least 2 to 3 hours prior to arriving at the Investigational Study Site; this will facilitate obtaining precise measurements of incompetent saphenous vein.

Refer to the Appendix C VICARES Clinical Study Procedure Manual for instruction on the preparation and ultrasound procedure

7.3. Screening (Visit 1)

The study IRB approved informed consent form must be signed and dated before any screening procedures are performed, except for any laboratory tests performed as part of standard of care within the study screening window.

Patients will be evaluated against study inclusion and exclusion criteria. Patients must meet all inclusion and none of the exclusion criteria at Screening to be eligible for the study. For details of assessments, refer to Table 3.

At the Investigational site, prior to ultrasound assessment of the venous system, the patient will be asked to stand or walk for 10-15 minutes.

During Screening visit (Visit 1), the Investigator/Investigational Staff will:

1. Perform all Visit 1 assessments per Table 3
2. At the end of the Screening Visit, *if the patient fails to be eligible* per the Inclusion/Exclusion criteria, the patient will be considered a screen failure and the reason for failure must be documented in the screening log.

7.4. Baseline (Visit 2)

The Baseline visit will occur -10 to -7 days prior to the Day of Treatment.

At the Investigational site, prior to ultrasound assessment of the incompetent saphenous vein, the patient will be asked to stand or walk for 10-15 minutes.

During the Baseline visit (Visit 2), the Investigator/Clinical Study Staff will:

1. Perform all Visit 2 assessment per Table 3.
2. Review the preliminary ultrasound mapping of the bilateral superficial venous systems and the selected incompetent saphenous vein (which was obtained during the initial Screening (Visit 1)
3. Perform unilateral ultrasound imaging studies of the incompetent saphenous vein selected for treatment with patient in the standing position to determine:
   a. access site (e.g., lowest point of reflux, as appropriate); and
   b. treatment section length (TSL) and treatment section diameter (TSD) measurements.
4. Review the VEINES-QOL Sym with the patient. Instruct patient to answer the HASTI Symptom questions for 7-consecutive days prior to the arrival at the Day of Treatment visit (Visit 3).

5. At the end of the Baseline Visit, *if the patient fails to be eligible* per the Inclusion/Exclusion criteria, the patient will be considered a screen failure and the reason for failure must be documented in the screening log.

7.5. Day of Treatment (Visit 3)

On the Day of Treatment prior to treatment procedure review the VEINES-QOL Sym questionnaire; confirm that the patient has completed the HASTI symptom items daily for 7 consecutive days prior to Visit 3. Perform urine pregnancy test and document result. Reconfirm the patient is eligible for treatment. If the patient fails to be eligible per the Inclusion/Exclusion criteria, the patient will be considered a screen failure and the reason for failure must be documented in the screening log.

7.5.1. Prior to Treatment

1. Perform all Visit 3 assessments per Table 3
2. Review the Baseline ultrasound images and report
3. Perform a limited ultrasound exam to; (refer to Appendix C VICARES Clinical Study Procedure Manual)
    a. confirm the vein to be treated and the access site; and
    b. confirm TS (treatment section length) and TSD (treatment section diameter)
4. At the end of the screening, if patient is eligible for Treatment, prepare patient for the procedure
5. Investigator should follow their institution's protocol for vascular access.

7.5.2. Treatment Procedure

Refer to Appendix C VICARES Clinical Study Procedure Manual for the study treatment procedure.

Following the treatment procedure, apply compression stocking on the treated leg.

Instruct the patient of the following:

a. The compression stocking must be worn for 72 hours (3 days) post treatment; and
b. After 72 hours post treatment, patient is to wear the compression stocking only during the daytime for 2 weeks.

7.6. Post Treatment Follow up Period: Week 1, Week 6 and Week 12

At the post treatment follow up visits, the assessments must be completed as detailed in Table 3.

7.7. End of the Study for Patient

End of Study for a patient occurs when the patient has completed the Week 12 post-treatment follow-up visit, withdraws consent, or is lost to follow-up.

7.7.1. Discontinuation of Study Treatment/Procedure

Patients may voluntarily discontinue from the study for any reason at any time. If a patient decides to discontinue from the study, the Investigator will make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. A patient may be considered withdrawn if the patient states an intention to withdraw, fails to return for study visits, or becomes lost to follow-up for any other reason.

The Investigator should discontinue the study procedure for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment may be discontinued if any of the following occur:

- Adverse event
- Physician's decision
- Patient/guardian decision
- Protocol deviation
- Technical problems

Patients must be discontinued if any of the following occur:

- At the time, a patient discontinues from the study, a visit should be scheduled as soon as possible, or no later than within 14 days of the decision to permanently discontinue from the study.
- If the decision to withdraw the patient occurs on Day of Treatment (Visit 3) following the initiation of the treatment procedure and the patient is determined to be evaluable as defined in Section 6.1, the patient should be followed up for safety and efficacy at Week 1, Week 6 and Week 12.
- If the decision to withdraw the patient occurs on Day of Treatment (Visit 3) following the initiation of the treatment procedure and the patient is determined to not be evaluable as defined in Section 6.1, that patient should be followed up for safety at Week 1.

7.7.2. Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, does not want to have any further visits or assessments and does not want any further study related contact.

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation.

If a patient withdraws consent, the Investigator will make every reasonable effort (telephone, e--mail, letter) to determine the primary reason for this decision and record this information.

No further assessments will be conducted.

8. ASSESSMENT TYPES

8.1. Safety and Tolerability

Safety assessment will include overall evaluation of safety of ClariVein RES. Safety will be assessed based on:

- Adverse events
  - Type, incidence, severity (mild, moderate, severe), timing, seriousness, relatedness, outcome, action taken with study product, and treatment will be assessed and documented by the Investigator throughout the study
  - All spontaneous AEs will be monitored, processed, and reported per Sponsor's Standard Operating Procedure for handling AEs
- Vital signs (i.e., oral temperature, respiratory rate, heart rate and blood pressure)
- Clinical laboratory assessments
  - Hematological Assessment:
    - hemolysis
    - hematocrit,
    - reticulocyte count,
    - haptoglobins,
  - Intravascular Coagulation Assessment
    - plasma fibrinogen level
    - plasma D-dimer level platelet count
    - PT – prothrombin time
    - PTT – partial thromboplastin time

In addition, safety assessment will include evaluation of the following specific events:

- Allergic reactions, including anaphylaxis
- Neurological events including: stroke, TIA, visual symptoms, migraines
- Venous Thromboembolic Events (VTE) in the treated leg
- Post-treatment local effects including hyperpigmentation, granuloma formation, ulceration in the treated leg
- Thrombus formation in deep veins (e.g., femoral vein) in the treated leg
- Post-ablation superficial thrombus extension (PASTE) in the treated leg

8.2. Efficacy Assessments

8.2.1. Assessment of Symptoms

Efficacy assessment of patient improvement as compared to the baseline using the following scales at the post treatment follow up per Table 3:

- VEINES-QOL/Sym Questionnaire (subset of Q1; i.e. five symptoms referred to as HASTI [Heaviness, Achiness, Swelling, Throbbing, Itching])
- Clinical-Etiology-Anatomy-Pathophysiology (CEAP) Classification
- European Quality of Life scale (EQ-5D-5L)
- Revised Venous Clinical Severity Score (rVCSS)
- Wong Baker Visual Analog Pain Scale (VAS)

8.2.2. Elimination of Saphenous Vein Reflux

Elimination of saphenous vein reflux at Week 12 post treatment, as demonstrated by duplex ultrasound based on vein closure and/or vein competency.

Vein Closure is defined as no discrete open segment of vein > 5cm in length within the treatment section of the selected saphenous vein as assessed by duplex ultrasound.

Vein Competency is defined as absence of retrograde flow >500 ms (0.5 sec) within the treatment section of the selected saphenous vein as assessed by duplex ultrasound.

The endpoint is achieved when ultrasound images demonstrate vein closure and/or vein competency as read by an independent vascular core lab.

Refer to the Appendix C VICARES Clinical Study Procedure Manual for details.

8.2.3. Improvement in Patient Symptoms

Improvement in patient reported symptoms will be assessed at Week 12 post-treatment based on the responses to a subset of questions from VEINES-QOL/Sym questionnaire (an instrument of Varicose Vein Symptom Burden in patients with Superficial Venous); i.e., the 7-day average of five symptoms from Question 1 of the questionnaire referred to as HASTI symptoms (Heaviness, Achiness, Swelling, Throbbing, Itching).

The patient will record responses to HASTI symptom questions for 7 consecutive days at specific time points during the study as follows:

- For 7 days prior to the Day of Treatment
- For 7 days post Day of Treatment
- For 7 days, prior to Week 6 follow-up
- For 7 days, prior to Week 12 follow-up

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9. WITHDRAWAL OF PATIENTS FROM THE STUDY

9.1. Prior to Randomization and Treatment

Individuals who withdraw from the study prior to randomization and treatment are not considered to be enrolled patients in the study, will not be used for assessment, and no follow up is necessary. Therefore, these individuals may be replaced.

9.2. Post Randomization and Treatment

Individuals who sign the Informed Consent and are randomized are considered enrolled patients and will be included in the Intent-To-Treat (ITT) analysis.

Possible reasons for withdrawal (discontinuation) of a patient from the study include:

Adverse Event (AE). An adverse event, which in the opinion of the Investigator, indicates that discontinuation from study would be in the best interest of the patient. Patient will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. The reason for termination will be documented by the Investigator on the patient's source documents.

Patient withdrawal of consent (or assent). Patient may be withdrawn from the study at any time if the patient, the Investigator, or the Sponsor feels that it is not in the patient's best interest to continue. If the patient withdraws prior to completing the Week 12 Post Treatment Follow up Visit, patient is considered Lost-to-Follow up. In this event the Investigator should make at least two documented attempts to contact the patient and to have an early discontinuation visit. The reasons for patient withdrawal should be documented on the patient's source documents, if known.

Patient noncompliant with study procedures. If a patient is withdrawn prior to treatment due to lack of compliance with study procedures, the reason for withdrawal will be documented by the Investigator on the patient's source documents.

Sponsor requests early termination of study. If patient discontinuation (post randomization and treatment) is due to early termination of the study by the Sponsor, patient will be followed per the follow-up schedule to completion of the post-treatment Week 12 visit. The reason for termination will be documented by the Investigator on the patient's source documents.

10. SAFETY MONITORING DURING THE STUDY

10.1. Vital Signs

Vital signs will be taken at Visits 1 through Visit 6 (Screening through Week 12 post-treatment Visits). This should include temperature, pulse, respiratory rate, and blood pressure when patient is seated. Height and weight are required only at Screening Visit.

10.2. History/Varicose Vein History/Physical Examination

Medical and Vein history will be collected at the Screening (Visit 1). A physical examination will be performed and documented on the appropriate eCRF at Screening Visits.

10.3. Clinical Laboratory Safety Assessments

Hematological Assessments include: hemolysis, hematocrit, reticulocyte count, haptoglobins as described in Section 8.1.

Intravascular coagulations include: Plasma fibrinogen level, Plasma D-dimer level platelet count, Prothrombin time (PT), Partial thromboplastin time (PTT) as described in Section 8.1. Plasma D-dimer level assessments will be conducted at: Baseline (Visit 2) immediately post Treatment (Visit 3) and at Week 1 follow-up (V isit 4); then, only at subsequent follow-up visits [Week 6 (Visit 5) and Week 12 (Visit 6)] if the D-dimer level is higher than it was at Baseline as described in Section 8.1.

Other parameters and/or increased frequency of examinations may be needed, depending on the findings during the clinical study.

10.4. Post-treatment Local Effects

Local effects such as hyperpigmentation, granuloma formation, and ulceration will be monitored.

10.5. Identification and Description of Thromboembolic Events

Identification, description and assessment of venous-thromboembolic events, including as follows:

- Deep Vein Thrombus (DVT) – Clinical assessment and ultrasound imaging will be performed.
- Pulmonary Embolism (PE) - Clinical assessment will be performed to evaluate for PE. If clinical assessment is suspicious for PE imaging will be obtained to confirm.
- Post Ablation Superficial Thrombus Extension (PASTE) – Clinical assessment and ultrasound imaging will be performed.

10.6. Assessment of Adverse Events

Any observed or reported Adverse Event (AE) regardless of treatment group or suspected causal relationship to the ClariVein RES investigational product will be reported as described in Section 10.7.

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE; and to assess whether it meets the criteria for classification as a Serious AE (SAE). requiring immediate notification to Sponsor or its designated representative.

10.7. Adverse Event Definition

10.7.1. Pharmaceutical Product

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that patient and is considered clinically significant.

A suspected adverse reaction means any AE for which there is a *"reasonable possibility"* that the drug caused the AE. For reporting under this protocol, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

Pre-existing conditions, illnesses present prior to the p signing the Informed Consent Form, are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and recorded as such on the eCRFs.

Pregnancy is not considered an AE; however, a patient who becomes pregnant after Treatment should be followed as described in Section 10.12.

If the patient experiences a worsening or complication of a concurrent condition that was present before exposure to the study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., worsening of "…").

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of study drug exposure are not considered AEs. However, if a pre-planned procedure is performed earlier than anticipated (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

Elective procedures performed where there is no change in the patient's medical condition should not be recorded as AEs, but should be documented as concomitant procedures.

10.7.2. Medical Device

A Medical Device Report, "MDR reportable events" are events that manufacturers become aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Serious Injury - An injury must meet the definition of "serious injury" in 21 CFR 803.3 for an event to be reportable as a serious injury. A "serious injury" is an injury or illness that [21 CFR 803.3]:

- Is life threatening; or
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

"Permanent" means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage [21 CFR 803.3]. Note that not all cosmetic damage will be considered trivial. Furthermore, a life-threatening injury meets the definition of serious injury, regardless of whether the threat was "temporary." It should also be noted that a device does not have to malfunction for it to cause or contribute to a serious injury. Even though a device may function properly, it can still cause or contribute to a death or serious injury.

"Malfunction" means the failure of a device to meet its performance specifications or otherwise perform as intended [21 CFR 803.3]. Performance specifications include all claims made in the labeling for the device.

A malfunction is reportable if any one of the following is true:

- The chance of a death or serious injury occurring as a result of a recurrence of the malfunction is not remote;
- The consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury;
- The malfunction results in the failure of the device to perform its essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness, which could cause or contribute to a death or serious injury or other significant adverse device experiences required by regulation. (The essential function of a device refers not only to the device's labeled use, but also to any use widely prescribed within the practice of medicine.);
- The malfunction involves:
  - a long-term implant or
  - a device that is considered to be life-supporting or life-sustaining and thus is essential to maintaining human life; or
- The manufacturer takes, or would be required to take, an action under section 518 or 519(g)10 of the FD&C Act as a result of the malfunction of the device or other similar devices (see explanation of "similar device" below, and see section 2.21 of this guidance for an explanation of "remedial action").

10.8. Definition of Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. The patient is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospital admission for elective surgery scheduled prior to study entry is not considered an SAE.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered serious AEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.9. Follow-up Information on a Serious Adverse Event

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the Investigator. For all SAEs, the Investigator will make at least two documented efforts for a follow up, when necessary and provide information to Vascular Insights.

In addition, an Investigator may be requested by Vascular Insights to obtain specific information in an expedited manner. This information may be more detailed than that captured on the AE form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes such as concomitant medication and illnesses must be provided. Event will be followed up until resolved.

10.10. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the Investigator.
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
- Test result leads to discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Test result is considered an AE by the Investigator or Sponsor.

10.11. Relationship to Study Treatment

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the Investigator (or designated sub-Investigator) per his/her best clinical judgment. The criteria listed in Table 4 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in Table 4.

Table 4: Adverse Event Causality Guidelines

Relationship	Criteria for Assessment
Definitely related	There is evidence of exposure to the test drug; and – The temporal sequence of the AE onset relative to administration of the test drug is reasonable. – The AE is more likely explained by the test drug than by another cause. – Dechallenge (if performed) is positive. – Rechallenge (if feasible) is positive. – The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
Probably related	There is evidence of exposure to the test drug; and – The temporal sequence of the AE onset relative to administration of the test drug is reasonable. – The AE is more likely explained by the test drug than by another cause. – Dechallenge (if performed) is positive.
Possibly related	There is evidence of exposure to the test drug; and – the temporal sequence of the AE onset relative to the administration of the test drug is reasonable; and – the AE could have been due to another equally likely cause.
Not related	There is evidence of exposure to the test drug; and – there is another more likely cause of the AE, – dechallenge (if performed) is negative or ambiguous, – rechallenge (if performed) is negative or ambiguous. The patient did not receive the test drug; or Temporal sequence of the AE onset relative to administration of the test drug is not reasonable; or There is another obvious cause of the AE.

10.12. Pregnancy

At Screening, pre-menopausal females of childbearing potential will be informed that active pregnancy and breast feeding are exclusion criteria for participation in this study. As such, these individuals must agree to pregnancy testing at Screening, Baseline, and (prior to treatment) at Day of Treatment visits; agree to use effective medical means of preventing contraception from Screening to completion of the Week12 post-treatment follow-up visit; and must not breast feed until completion of the Week 12 post-treatment follow-up visit. Urine pregnancy tests will be conducted at Screening (Visit 1) and prior to treatment on Day of Treatment (Visit 3). A serum pregnancy test will be performed at the Baseline (Visit 2).

If a patient is confirmed pregnant post Treatment and prior to completing the study, (completion of the Week 12 post treatment visit), the Investigator must immediately notify the Study Medical Monitor of this event and record the pregnancy on the appropriate pregnancy form. Initial information regarding a pregnancy must be immediately forwarded by the study monitor or designee to Sponsor's Drug Safety and Pharmacovigilance contact or its designated representative.

The Investigator should follow the patient to the end of the pregnancy and must immediately report follow-up information to the Sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study.

10.13. Monitoring and Recording of Adverse Events

AE data collection will begin after a patient signs the ICF and will continue until completion of their Week 12 post-treatment follow-up visit (Visit 6). Any AE or SAE having an onset after the completion of Visit 6 (end of the study visit) will not be collected or reported unless the Investigator feels that the event may be related to the study drug.

Patients will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The Investigator will assess all AEs regarding any causal relationship to the study drug (Section 10.11), the intensity (severity) of the event, action taken, and patient outcome.

The following criteria will be used to guide the assessment of intensity (severity):

- **Mild**: An adverse event that is asymptomatic or barely noticeable to the patient; not interfering with patient's daily activity performance or functioning; generally, not requiring alteration or cessation of study drug administration; and/or ordinarily not needing therapeutic intervention
- **Moderate**: An adverse event of sufficient severity as to possibly make the patient moderately uncomfortable; some interference with the patient's daily activity performance or functioning; generally, not impairing the patient's ability to continue in the study; and/or possibly needing therapeutic intervention.
- **Severe:** An adverse event generally causing severe discomfort; major interference with the patient's daily activity performance or functioning; generally requiring alteration or cessation of study drug administration; life-threatening; resulting in

significant disability or incapacity; and/or generally requiring therapeutic intervention.

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure (IB) will be used as the reference document to designate event expectedness. An AE is considered unexpected if the AE is not listed in the current IB or is not listed in the IB at the specificity or severity observed.

Withdrawal from the study because of an AE and any therapeutic measures that are taken shall be at the discretion of the Investigator. If a patient withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the patient is deemed by the Investigator to be lost to follow-up.

10.14. Reporting of Serious Adverse Events

Serious AEs (SAE) which occur from the time the patient provides informed consent to the end of the study, require immediate notification to VI's Compliance Department or its designated representative. All SAEs must be reported within 24 hours of discovery, by faxing or emailing the report.

The written report should be submitted on the SAE form provided for this purpose. The report must include the Investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided.

Documentation regarding the adverse event should be made as to the nature, date of onset, end date, severity, and relationship to the investigational product, action(s) taken, seriousness, and outcome of any sign or symptom observed by the Investigator or reported by the patient upon direct questioning.

Expected outcomes related to the procedure should not be recorded as adverse events.

10.15. Sponsor Responsibility for Expedited Safety Reports

Vascular Insights or designee will notify Investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the Investigator must review and retain the notice with other study-related documentation.

The Investigator and Institutional Review Board (IRB)/Ethics Committee (EC) will determine if the informed consent form requires revision. The Investigator should also comply with the IRB/EC procedures for reporting any other safety information.

Suspected serious adverse reactions and other significant safety issues reported from the investigational product development program shall be reported to the relevant competent health authorities in all concerned countries per local regulations (either as expedited safety reports and/or in aggregate reports), by the Sponsor or its designated representative.

For use of central IRB for the study, the Sponsor or its designated representative is responsible for submission (or ensuring the submission) of the expedited safety reports to the appropriate IRB for the study.

For this blinded trial, treatment will be unblinded by the Sponsor as necessary to determine the need for expedited reporting, in accordance with global requirements.

11. PLANNED STATISTICAL METHODS FOR ASSESSMENT OF EFFICACY AND SAFETY

11.1. General Considerations

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. All statistical tests will be performed at the 0.05 significance level (p -value $\leq$ 0.050) unless otherwise indicated.

For efficacy analyses, missing post-treatment data will be imputed using last observation carried forward (LOCF). Missing safety data will not be imputed.

11.2. Analysis Populations

11.2.1. Safety Population

The safety population will include all patients who are treated with ClariVein RES. Patients will be analyzed per the treatment they received.

11.2.2. Modified Intent-to-Treat (MITT) Population

The MITT population will include all randomized and treated patients in the safety population who have baseline and at least one post-treatment assessment for the primary efficacy variable. Patients will be analyzed per their randomized dose of STS.

11.3. Primary Efficacy Endpoint

Improvement in patient reported symptoms at Week 12 post-treatment as compared to Baseline using the weekly average HASTI (Heaviness, Achiness, Swelling, Throbbing, Itching) symptom score from the VEINES-QOL/Sym, an instrument of Varicose Vein Symptom Burden in patients with Superficial Venous.

11.3.1. Secondary Efficacy Endpoint

Elimination of saphenous vein reflux at Week 12 post-treatment as demonstrated by duplex ultrasound.

11.4. Tertiary Endpoints

Assessment of patient improvement as compared to the Baseline assessment using the following scales at post treatment Week 12 on the following Quality of Life or patient improvement assessment:

- Clinical-Etiology-Anatomy-Pathophysiology (CEAP) Classification
- European Quality of Life scale (EQ-5D-5L)
- Revised Venous Clinical Severity Score (rVCSS)
- Wong Baker Visual Analog Pain Scale (VAS)

11.5. Exploratory Endpoints

11.5.1. Week 1

Assessment of change in VEINES-QOL/Sym (Questions 1 through 8) at post treatment follow-up visit at Week 1 as compared to Baseline

11.5.2. Week 6

Assessment of change in VEINES-QOL/Sym (Questions 1 through 8) at Week 6 post treatment follow-up visit as compared to Baseline

11.5.3. Week 12

Assessment of change in VEINES-QOL/Sym (Question 1, excluding HASTI, through Question 8) at Week 12 post treatment follow-up visit as compared to Baseline

11.6. Determination of Sample Size

The sample size of 50 patients (25 patients per treatment group) is based on both efficacy and safety considerations. The primary endpoint is change from baseline in the weekly average symptom score of a subset of the VEINES-QOL/Sym questionnaire (based on HASTI symptoms from Question 1: Heaviness, Achiness, Swelling, Throbbing, Itching) at Week 12 for both treatment groups combined.

Assuming a true mean change from baseline to 12 weeks of -5.44 and a standard deviation of 3.52 for the change from baseline, a sample size of 50 would provide at least 99% power to reject the null hypothesis that the mean change from baseline equals 0, based on a one-sample t-test with a 0.050 two-sided significance level. A sample size of 25 (that is, by treatment group) would also provide at least 99% power to reject the null hypothesis that the mean change from baseline equals 0.

11.7. Analysis of Primary Efficacy Endpoint

The null hypothesis is that the mean change from baseline for the primary efficacy endpoint equals 0. The alternative hypothesis is that the mean change does not equal 0.

The primary analysis will be a one-sample t-test for both treatment groups combined, to test the null hypothesis that the mean change from baseline equals 0.

To evaluate a dose-response relationship, two analyses will be performed. First, the primary analysis will be performed for each treatment group separately. Second, an analysis of covariance (ANCOVA) will be performed to compare the change from baseline for STS 1% versus STS 3% with treatment as a class variable and with the baseline weekly average HASTI symptom score as a covariate in the model.

Missing data for the Week 12 weekly average HASTI symptom score will be imputed using the last observation carried forward (LOCF) method.

11.8. Analysis of Other Efficacy Endpoints

The primary analysis for each endpoint will use LOCF methodology for the imputation of missing data.

Continuous endpoints will be summarized using descriptive statistics and will be analyzed using a one-sample t-test to test the null hypothesis that the mean change from baseline equals 0.

The secondary efficacy endpoint, the elimination of saphenous vein reflux at Week 12 post-treatment, will be summarized for both treatments combined using the count and percentage, together with a 95% Wilson (score) confidence interval for the proportion.

To evaluate a dose-response relationship, two analyses will be performed for each endpoint. First, the analyses performed for both treatments combined will be repeated for each treatment group separately. Secondly, for continuous endpoints, an ANCOVA will be performed to compare the change from baseline for STS 1% versus STS 3% with treatment as the class variable and with baseline score as the covariate. For vein closure rate, the treatment difference for STS 1% versus STS 3% for the proportion will be assessed by a chi-square test together with a 95% Wilson (score) confidence interval for the treatment difference.

For each continuous endpoint, the change from baseline to each scheduled visit will be analyzed in the same manner as the Week 12 assessment. Both LOCF and observed cases analyses will be performed.

The correlation between Week 12 efficacy endpoints will be explored using a Spearman correlation coefficient for pairs of quantitative variables, and Kendal's tau for the correlation of the elimination of saphenous vein reflux (yes, no) with quantitative variables.

11.9. Analysis of the Safety Endpoints

Safety will be assessed based on adverse events (including selected events of interest), clinical laboratory tests, physical examination, vital signs, and concomitant medications. Safety data will be summarized by treatment group and overall. No statistical testing will be performed for safety data.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent events are those adverse events that begin or worsen after initiation of the treatment procedure. The number and percentage of patients reporting treatment-emergent adverse events will be summarized by MedDRA System Organ Class (SOC) and Preferred Term. Treatment-emergent adverse events will be further summarized by severity and relationship to the treatment procedure.

Physical examination data will be listed per patient. No summaries will be provided.

Vitals signs data will be summarized by descriptive statistics for baseline, each post-treatment visit, and the change from baseline to each post-treatment visit.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant medications are medications taken on or after the treatment day, regardless of when they were started. Prior medications are medications taken before the treatment day, regardless of when they ended. The number and percentage of patients using

concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) 3 classification and preferred name.

Overall safety assessment will include evaluation of the following specific events:

- Neurological events including: stroke, TIA, visual symptoms, migraines
- Venous Thromboembolic Events (VTE) in the treated leg
- Post-treatment local effects including hyperpigmentation, granuloma formation, ulceration in the treated leg
- Thrombus formation in deep veins (e.g., femoral vein) in the treated leg
- Post-ablation superficial thrombus extension (PASTE) in the treated leg
- Local and systemic allergic reactions, including anaphylaxis

11.10. Protocol Deviations/Violations

Protocol deviations will be identified prior to database lock and will be listed by treatment group in the clinical study report. A protocol violation occurs when the patient, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion/exclusion criteria, patient safety, or primary endpoint criteria.

Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to attend two post treatment visits: of which one is Week 12

Failure to comply with Good Clinical Practice (GCP) guidelines will result in a protocol violation. Sponsor will determine if a protocol violation will result in withdrawal of a patient from the study.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

12. ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

The study will be conducted according GCP guidelines and the applicable regulatory requirements, and in accordance with the ethical standards that have their origin in the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). To ensure ethical conduct of this clinical study, Investigators will be expected to adhere to the basic principles in recognized guidelines such the Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

To maintain confidentiality at the Investigational site, all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number and patient's initials only. All study records will be kept in a locked file cabinet. Coded sheets linking a patient's name to a patient identification number will be stored in a separately locked file cabinet. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

12.1. Institutional Review Board or Ethics Committee Approval

The protocol and the informed consent document must have the initial and at least annual (when required) approval of an IRB/EC. The signed IRB/EC approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit patients should also be reviewed by the IRB/EC. The Sponsor will not ship clinical supplies until a signed approval letter from the IRB/EC has been received and a Clinical Trial Agreement has been signed by the Sponsor and the clinical site.

12.2. Informed Consent

Informed consent form (ICF) will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

A master ICF template will be provided by VI or its representative to each investigational study site. The Investigator will review and modify this document, if necessary. If any modifications are made, they must be approved by VI or its representative. The Investigator will provide the final informed consent form, assent, and HIPAA authorization to the Sponsor or designee for approval prior to submission to the IRB/EC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/EC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/EC-approved copy of the Informed Consent Form to the Sponsor (or designee) for

the study file. In case of Central IRB approval, the process may be handled by the Sponsor or Sponsor's Representative and a copy of the approval provided to the Investigator.

A properly executed, signed ICF will be obtained from each patient prior to enter the patient into the trial. Information should be given in both oral and written form, and the patient (or patient's legal representatives in the case of language translation needed) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/EC, assent from the patient will also be obtained. If a patient is unable to sign the ICF and the HIPAA authorization, a legal representative may sign for the patient. A copy of the signed ICF (and assent) will be given to the patient or legal representative of the patient and the original will be maintained with the patient's records.

The Investigator is responsible for maintaining each patient's consent form(s) in the Investigator's site file and providing each patient, or the patient's parent or legal representative (for minors), with a copy of the signed and dated consent form(s).

Nothing in this protocol or the regulations is intended to limit the authority of an Investigator to provide emergency medical care under applicable regulations. In addition, the Investigator should be aware that some regulations require that he/she permit regulatory agencies to conduct inspections and review records pertaining to this clinical investigation.

12.3. Patient Confidentiality

All unpublished information that the Sponsor gives to the Investigator, and all information generated about the study, shall be kept confidential and shall not be disclosed to a third party without the prior written consent of the Sponsor or published prior to the Sponsor's review in accordance with the terms of the Clinical Trial Agreement. When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies. The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor.

12.4. Data Monitoring Committee(s)

A Data Monitoring Committee is not planned for this Phase 2 Pilot study.

13. REGULATORY/ADMINISTRATIVE PROCEDURES AND DOCUMENTATION

13.1. Quality Control and Quality Assurance

The Sponsor (Vascular Insights, LLC) performs quality control and assurance checks on all clinical studies that it sponsors. Prior to enrolling any patients into this study, the Sponsor personnel or its designee and the Investigator will review the protocol, the Clinical Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs.

A qualified representative of the Sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone. During the visits, information recorded in the eCRFs will be verified against source documents. The Sponsor's Medical Monitor will review the data for safety information. The Sponsor's clinical data associates or designees will review the data for legibility, completeness, and logical consistency. Additionally, the Sponsor's clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be added to the electronic database and reviewed by the investigational site for resolution. The Sponsor may visit the investigational site and perform a quality check of the eCRFs against source documents.

13.2. Investigators and Study Administrative Structure

The Investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- An executed Clinical Trial Agreement
- FDA Form 1572
- Documentation of financial disclosure
- Principal Investigator's Curriculum Vitae
- IRB/EC approval of the protocol
- IRB/EC approved consent form
- And any other documentation required by US rules and regulations and/or good clinical practice

If any Investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to another person (Sponsor, IRB/EC, or other Investigators) who accepts the responsibility. The Sponsor must be notified in writing and must agree to the change. An updated FDA Form 1572 will be filed with the Sponsor and the FDA for any changes in the study personnel reported in the current FDA Form 1572.

13.3. Study Monitoring

The study will be monitored by representatives of the Sponsor. Site visits are made before the study begins, at regular intervals during the study, and at the study closeout. Communication by

telephone, mail, and e-mail may be used as needed to supplement site visits. The Investigator and study personnel will cooperate with the Sponsor, provide all appropriate documentation, and be available to discuss the study. The purpose of site visits is to verify:

- Adherence to the protocol (the Investigator should document and explain any deviation from the approved protocol)
- Completeness and accuracy of the eCRFs and the dispensing and inventory record (adequate time and space for these visits should be allocated by the Investigator)
- Compliance with regulations (the verification will require comparison of the source documents to the eCRFs)

13.4. Data Collection and Electronic Case Report Forms

Study-specific eCRFs will be made available to the Investigative site. Study data contained in source documentation will be entered in the eCRFs for all patients enrolled in the study. All pertinent data records are to be submitted to the Sponsor during and/or at completion or termination of the study.

13.5. Access to Source Documentation

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Patients will not be identified by name in any reports stemming from the study, and confidentiality of information in medical records will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) that permits the release of the patient's medical records will be included in the informed consent document:

Representatives of regulatory agencies, IRB/EC, the Sponsor, and the patient's personal Investigator may review the patient medical records and all information related to this study as permitted by law. Patient identity will remain confidential unless disclosure is required by law.

13.6. Study Documentation and Retention of Records

Trial documents (including correspondence related to this clinical study, patient records, source documents, eCRFs, study drug inventory records, and IRB/EC and Sponsor correspondence pertaining to the study, original patient, laboratory, and study drug inventory records relating to the study) should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years or at least 2 years have elapsed since the formal discontinuation of clinical development of the product). Trial documents should be retained for a longer period if required by applicable regulatory requirements or by agreement with the Sponsor. Thereafter, records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records, at the Sponsor's cost and expense.

14. DISCLOSURE OF DATA AND PUBLICATION

The Investigator must notify the IRB/EC of the conclusion of the clinical trial within 3 months of the completion or termination of the study. The final report sent to the IRB/EC should also be sent to the Sponsor. This report, along with the completed eCRFs, constitutes the final summary to the Sponsor, thereby fulfilling the Investigator's regulatory responsibility.

Section 801 of the FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical trials of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition for publication of research results generated by a clinical trial (http://www.icmje.org [Accessed08 December 2016).

15. REFERENCES

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ANDA 40541

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APPENDIX A. ASSESSMENT OF EFFICACY AND SAFETY

Description of Selected Scales for Efficacy Assessment presented in Table 5.

Table 5: Description of Selected Scales for Efficacy Assessment

Scale	Relevance for its Selection for Study Assessment
VEINES QOL	The VEINES-QOL/SYM is a commonly used instrument to assess the effects of venous disease on patient quality of life and is well-accepted tools for the assessment of quality of life for patients with venous disease. VEINES QOL-SYM has been found to be a reliable and valid patient outcome measures.
VAS	The pain VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations. The pain VAS is a continuous scale comprised of a horizontal line 100 mm in length, anchored by 2 verbal descriptors, “no pain” (score of 0) and “worst imaginable pain” (score of 100). The patient indicates the level of pain intensity by the position of a mark on the line.
EQ-5D-5L	The EuroQOL-5 Dimensions 5-Level questionnaire (EQ-5D-5L) is a standardized instrument for measuring generic health status. It is one of the most commonly used generic health status measurements, and its validity and reliability have been reported in various health conditions. In the description part of the EQ-5D, health status is measured in terms of five dimensions (5D): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Mobility dimension asks about the person's walking ability. Self-care dimension asks about the ability to wash or dress by oneself, and usual activities dimension measures performance in "work, study, housework, family or leisure activities". In pain/discomfort dimension, it asks how much pain or discomfort they have, and in anxiety/depression dimension, it asks how much anxious or depressed they are. The respondents self-rate their level of severity for each dimension using the five-level (EQ-5D-5L) scale. In the evaluation part, the respondents evaluate their overall health status using the visual analog scale (VAS)
rVCSS	Chronic venous disease (CVD) has benefited from the institution of several assessment instruments designed to clarify elements of the disease process. Among these is the revised Venous Clinical Severity Score (rVCSS), which has proven to be a valuable tool for evaluating changes in condition over time with or without intervention. This revision increased the sensitivity and value of the VCSS in interpreting the language of venous disease. VCSS was originally designed and validated as an objective measure of disease severity in patients with CVD. The recent revision resolved ambiguity in the clinical descriptors and improved clarity and ease of use. The rVCSS consists of 10 items with scores ranging from 0 = Absent to 3 = Severe. The

	rVCSS is calculated by the sum of the scores for the 10 items with a max score of 30.
CEAP	The CEAP classification is a method for evaluating venous disease of the leg based on clinical, etiologic, anatomic, and pathophysiologic data.

APPENDIX B. CLINICAL SUPPLIES

CLINICAL SUPPLIES

ClariVein RES (Study Drug and Delivery System)

- STS (1% and 3%/)– Each shelf carton contains five (5) 2mL ampules. The study drug will be double blinded; i.e., to drug concentration will be blind to the Investigator/Site personnel and to the patient.
- ClariVein® (45,65, 85 cm) - Each shelf carton contains one (1) ClariVein infusion catheter within a Tyvek tray within a sealed pouch; 5 pouches within a shelf box. The study drug delivery system will not be blinded as the physician will select size based on patient anatomy.

Sodium Tetradecyl Sulfate (STS) 1% and 3% Solution

The ampules and cartons are double blinded using a blinded label; each ampule and carton carries a specific code for inventory accounting of the investigational drug at the ampule and the carton level.

ClariVein (45, 65, and 85cm length models)

The ClariVein product is commercially available in the USA under the name ClariVein IC. For inventory control purposes of this study, the package will carry a label specifying for investigational use. Blinding of the ClariVein product is not considered necessary to maintain integrity of the study, except for length all models are identical.

Procedural Accessories

The Sponsor may provide commercially available procedural accessories to the investigational sites for use during this study, as a convenience for the study sites.

These supplies are not being evaluated in this clinical study; therefore, they will not be blinded and will not be labeled for investigational use. Accessory products may include those identified in Table 6.

Table 6: Clinical Supplies

VICARES - Clinical Supplies
Clinical Study Product - ClariVein RES
• STS package contains: (5) 2ml ampules of 1% or 3% solution • ClariVein® IC tray package contains: (1) ClariVein IC (catheter assembly with check valve and motor drive unit) (1) 5 ml syringe
Commercially Available Procedural Accessories
Pre-Treatment (Visit 1 -Screening; Visit 3 - Treatment Day)
(2) Urine Pregnancy Kits
Sterile Procedure Accessories
(1) Vascular Access set with 0.018" guidewire (1) Gauze Pad: 2" x 2" (1) Gauze Pad: 4" x 4" (1) 1-inch 30-g needle (2) Filter needles (to draw up saline, and sclerosant) (1) 3 cc syringe (for local anesthetic) (1) 5 cc syringe (extra syringe for sclerosant) (1) 10 cc syringe (for saline purge) (1) Normal Saline (USP .09%) 10ml Vial (1) Local Anesthetic (Lidocaine 1%) (4) Writeable Syringe Labels (1) Sterile Marking Pen (1) Sterile Ultrasound Probe Cover (3) Sterile Ultrasound Gel Packs (1) Measuring Tape (centimeter scale) (2) Antiseptic Swab Sticks (e.g., Chloraprep)
Post-treatment (Treatment Day)
(1) Compression Hose

APPENDIX C. VICARES - PROTOCOL CL-001 CLINICAL STUDY PROCEDURE MANUAL VERSION 1.1

VICARES - Protocol CL-001

Clinical Study Procedure Manual
Version 1.1

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1. INTRODUCTION

This VICARES Clinical Study Procedure Manual is an adjunct to the VICARES™ clinical study protocol CL-001.

1.1. VICARES CLINICAL STUDY OVERVIEW

The VICARES is prospective, randomized, controlled, multi-center, double blind study of the ClariVein RES for treatment of venous insufficiency associate with incompetent saphenous veins due to superficial venous reflux in adults.

- The VICARES clinical study is limited to the treatment of one incompetent saphenous vein per treatment procedure.
- Ancillary procedures will not be allowed per protocol until after completion of the Week 12 post treatment follow-up visit.

Carefully read and understand the VICARES clinical study protocol CL-001, Investigator Brochure, and this Procedure Manual.

Please contact the Sponsor or designated representative with **any** questions regarding the study protocol, the study product, or any study related matter.

2. STUDY PRODUCT AND CLINICAL SUPPLIES

2.1. Clinical Study Product

The study product, ClariVein RES, consists of STS solution and the ClariVein infusion delivery system. Both STS and ClariVein will carry a label specifying: "Caution: Limited by Federal (or United States Law) to Investigational Use Only".

2.1.1. STS Solution

STS will be provided as blinded supplies of STS solution (1% or 3%) in 2 mL ampules, packaged in a carton of 5 ampules. Each carton will contain a total of 10 mL.

2.1.2. ClariVein

ClariVein infusion delivery system will not be blinded because it is not considered necessary to maintain integrity of the study. Except for length, all models are identical. Physician will select catheter model based on individual patient anatomy. Supplies of ClariVein (45, 65, or 85 cm length model), packaged one per pouch in a shelf box of 5 pouches. The pouch contains a covered tray holding: (1) Catheter assembly with check valve and Motor Drive Unit; and (1) syringe, 5 mL (for sclerosant).

2.1.3. Other Clinical Supplies

Commercially available, commonly used vascular procedural accessories will be provided to the investigational sites. These supplies are not being evaluated in this clinical study; therefore, they will not be blinded and will not be labeled for investigational use. Accessory products may include:

(2) Pregnancy Kits
Sterile Procedure Accessories

- (1) Vascular Access set with 0.018" guidewire and 5 Fr Introducer
- (1) Gauze Pad: 2" x 2"
- (1) Gauze Pad: 4" x 4"
- (1) 1 inch 30 G needle
- (2) 1.5 inch 21 G filter needles (to draw up saline, and sclerosant)

Sterile Syringes:

- (1) 3 mL syringe (for local anesthetic)
- (2) 5 mL syringes (one for sclerosant, one for saline prime and flush)

Other Supplies

- (1) Normal Saline (USP 0.9%) 10 mL Vial
- (1) Local Anesthetic (lidocaine 1%)
- (4) Writeable Syringe Labels
- (1) Sterile Marking Pen
- (2) Sterile Ultrasound Probe Cover

(3) Sterile Ultrasound Gel Packs
(1) Measuring Tape (centimeter scale)
(2) Antiseptic Swab Sticks (e.g., Chloraprep)

Compression Hose – 20 to 30 mmHg (Class 2 compression, knee-high / open-toe). (A range of sizes will be supplied to each investigational site.)

2.2. Storage and Dispensing of ClariVein® RES Product and Clinical Supplies

Supplies are to be stored at a controlled room temperature [20°C to 25°C (68°F to 77°F)] in a secure, dry place where the access is limited to Study personnel only. Do not freeze. Maintain all supplies in the same packaging as was provided until ready to use. Review all labeling prior to use. All supplies will be dispensed and transferred to the procedure room using the clinical study site practice for dispensing of the clinical study material. Maintain accounting of all supplies.

3. SCREENING PERIOD [VISITS 1 AND 2 - SCREENING AND BASELINE]

Refer to Schedule of Events as provided in the Study Protocol (CL-001).

3.1. Ultrasound Imaging

3.1.1. Imaging Format

Ultrasound imaging to be recorded in Digital Imaging and Communications in Medicine (DICOM) format and labeled to the location.

3.1.2. Ultrasound Equipment Required

Color flow Doppler ultrasound equipment with high frequency linear array transducer.

3.2. Visit 1 - Screening

The Screening (Visit 1) ultrasound exam is to be performed to determine patient eligibility per the study Inclusion/Exclusion criteria. The Superficial Venous System and the Deep Venous System of both legs will be assessed for reflux and obstruction. To obtain optimal assessment of a patient's venous system, prior to arriving at the clinic the patient should be hydrated and be mobile for at least 2 to 3 hours. At the clinic, the patient will be asked to stand or walk for 10-15 minutes prior to the ultrasound imaging examination.

3.2.1. Superficial Venous System

Reflux Assessment - Perform with patient in the standing position. Perform and record assessment using color flow Doppler ultrasound with pulse wave tracing in the longitudinal view, after a manual calf compression and relaxation (or after Valsalva's maneuver at the SFJ).

Reflux in Superficial System - defined as retrograde flow >500ms (0.5s).

Reflux - identify location using a pulse wave tracing on the target vein in the longitudinal view and measure duration

Refluxing Section Length - measure length in centimeters in the longitudinal view: 2 cm below the SFJ for the GSV or ASV, or at the fascial curve for the SSV; i.e., from the deep vein junction, or highest point of reflux, to the end of the refluxing pathway of the saphenous vein.

Refluxing Section Diameter - measure diameter in millimeters in cross-section view. Calculate average Treatment Section Diameter. Refer to **Table 1** for measurement locations.

Table 1: Measurement Locations to Determine Treatment Section Diameter

GSV Greater Saphenous Vein	ASV Accessory Saphenous Vein	SSV Small Saphenous Vein	SVS Saphenous Vein Segment
1. Proximal Thigh (2 cm below SFJ) 2. Mid-thigh 3. Distal-thigh (Knee) ---------- 1. Proximal Calf (Knee) 2. Mid-calf 3. Distal Calf at Lowest Point of Reflux	1. Proximal Thigh (2 cm below SFJ) 2. Mid-Treatment Section 3. Distal-thigh (Knee) at Lowest Point of Reflux	1. Proximal Termination or Junction 2. Fascial Curve (Top of the fascial curve or where termination is located) 3. Distal Calf at Lowest Point of Reflux	1. Proximal portion (1 cm below highest point of the reflux within the segment) 2. Midportion 3. Distal portion at Lowest Point of Reflux

Note: To determine the average TSD, measure the diameter at the initial position of the dispersion wire ball tip and the diameter midway between the position of the dispersion wire ball tip and the target access point. If a treatment section extends below the knee, take an additional measurement. Measure the diameter at the knee and carry out a three-point proximal GSV average TSD and a three-point distal GSV average TSD. Use the corresponding TSL to determine STS volume.

Obstruction Assessment - Perform with patient in the standing or supine position. Perform and record assessment in longitudinal and cross-section view. If obstruction or evidence of post-thrombotic changes in the superficial veins are found, document the location.

3.2.2. Deep Venous System

Reflux and Obstruction of the Deep Venous System including the common femoral, deep femoral, femoral, popliteal and calf veins will be evaluated and documented.

Reflux Assessment – Perform with patient in the standing position. Perform and record assessment using color flow Doppler ultrasound with pulse wave tracing in the longitudinal view, after a manual calf compression and relaxation (or after Valsalva's maneuver at the SFJ).

Reflux – identify location and determine if segmental, i.e., if reflux is located near the saphenofemoral and/or saphenopopliteal junctions alone. Reflux is defined as:

- retrograde flow lasting >1.0s: common femoral, femoral and popliteal veins
- retrograde flow lasting >0.5s: deep femoral and calf veins

Obstruction Assessment **-** Perform with patient in the standing or supine position. Perform and record assessment using longitudinal and cross-section view and record if obstruction is present.

3.3. Visit 2 - Baseline

The Baseline (Visit 2) ultrasound exam is to be performed to confirm patient's eligibility per the study Inclusion/Exclusion criteria and collect baseline data. The ultrasound assessment will be limited to the target saphenous vein. To obtain optimal assessment, prior to arriving at the clinic, the patient should be hydrated and be mobile for at least 2 to 3 hours. At the clinic, the patient and will be asked to stand or walk for 10-15 minutes prior to the ultrasound imaging examination.

The physician will refer to vein mapping completed at the Screening (Visit 1); and perform focused ultrasound evaluation of the target saphenous vein.

Reflux Assessment – Perform with patient in the standing position. Perform and record assessment using color flow Doppler ultrasound with pulse wave tracing in the longitudinal view, after a manual calf compression and relaxation (or after Valsalva's maneuver at the SFJ).

Reflux in Superficial System - defined as retrograde flow >500ms (.05s).

Reflux– identify location using a pulse wave tracing on the target vein in the longitudinal view.

Refluxing Section Length - measure length in centimeters in the **longitudinal view** the deep vein junction, or highest point of reflux, to the end of the refluxing pathway of the saphenous vein.

Refluxing Section Diameter - measure diameter in millimeters in **cross-section view.** Calculate average Treatment Section Diameter. Refer to Table 1.

Obstruction Assessment – Perform with patient in the standing or supine position. Assess using longitudinal and cross-section view and record if obstruction is present.

4. TREATMENT PERIOD

4.1. Visit 3 - DAY OF TREATMENT

Refer to **Schedule of Events** as provided in the Study Protocol (CL-001).

On the Day of Treatment (Visit 3) the physician is to perform a limited ultrasound scan of the target saphenous vein. To obtain optimal assessment, prior to arriving at the clinic, the patient should be well hydrated and be mobile for at least 2 to 3 hours. At the clinic, the patient and will be asked to stand or walk for 10-15 minutes prior to the ultrasound imaging examination. Prior to treatment, physician will reference Screening and Baseline vein mapping.

Using B-mode Duplex ultrasound in cross-section view with patient in the standing position, physician will perform an ultrasound scan to confirm precise treatment section length and treatment section diameter. These measurements will be used to determine STS volume for treatment procedure.

Prior to treatment obtain a cross section image of the target access site. Note vein diameter and location of access site relative to the knee. Include the name of the vein. The target access point is the lowest point of reflux. Record actual access point.

Confirm Treatment Section Length and Treatment Section Diameter. These measurements will be used to determine STS volume for infusion.

4.1.1. Patient Preparation

Typical patient position during the treatment will depend on the vein treated; i.e., for GSV (Great Saphenous Vein) or ASV (Accessory Saphenous Vein) patient is supine, for SSV (Small Saphenous Vein) patient is prone.

1. Use sterile technique per institutional protocol for endovenous procedures.
2. Medicate the patient as appropriate.
3. Prepare and drape the puncture site.
4. Administer local anesthetic (1% lidocaine) at the access site as needed per medical protocol.
5. A 5 F Introducer is provided in the accessory product supplies.

4.1.2. Preparation of Investigational Product

4.1.2.1. STS Solution Preparation

The study drug, sodium tetradecyl sulfate (STS) is supplied in 2 mL ampules for single use. Each 1% and 3% ampule contains:

- 1% ampules, 20 mg/2 mL (10 mg/mL)

- 3% ampules, 60 mg/2 mL (30 mg/mL)

The STS will be blinded and will be dispensed using a randomization procedure provided to each investigational site. Concentrations of 1% and 3% will be issued at a ratio of 1:1. Each ampule and carton carries a specific code for inventory accounting of the investigational drug at the ampule and carton level. The Investigator, Site Staff, and Patient will be blinded to the STS concentration.

4.1.2.2. Use of Aseptic Technique

Strict aseptic technique must be maintained while handling the study drug. STS is a single-use, sterile, non-pyrogenic solution for parenteral use. STS ready-to-use solution is intended for intravenous infusion via ClariVein catheter. The STS solution does not require any additional preparation. The solution must NOT be diluted for use. Once an ampule is opened, it must be used only for that procedure; after the procedure, any unused portion of the ampule must be discarded.

4.1.2.3. Withdrawal of STS from Ampules

All parenteral drug products, including the study drug should be inspected visually for particulate matter and discoloration prior to use and administration. The STS is supplied as clear colorless solution.

- Do not use if particulates, precipitation or discoloration is observed in the clinical drug supplies. Solutions that are discarded must be for accounted for during the disposition of the material.
- STS inventory will be replenished as needed.
- Site will report any product complaints to the study Sponsor or designee.
- Maintain sterility of the STS sclerosant.
  - The outside surface of the glass ampule is non-sterile.
  - The sclerosant must be accessed with a sterile needle and syringe across the sterile field.
  - An assistant must hold the ampule while the sterile-gloved physician extracts the sclerosant with sterile needle and syringe.

4.1.2.4. STS Volume per Treatment Procedure

STS volume for administration has been calculated based on Treatment Section Length (TSL) and average Treatment Section Diameter (TSD) as presented in **Table 2**.

The Investigator should consult this table for the target volume of STS solution, but may use his/her own discretion on volume per treatment procedure, provided that STS volume is **not less than the minimum** volume; and does **not exceed a maximum of 10 mL** for the single treatment procedure.

Table 2: Target STS Volume (mL) per Treatment Procedure

		Treatment Section Length (TSL) cm															
		10	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**
Average Treatment Section Diameter (TSD) mm	**4**	1	2	2	3	3	4	4	5	5	6	7	7	8	8	9	9
	5	1	2	3	3	4	5	6	6	7	8	8	9	10	10	10	10
	6	2	3	3	4	5	6	7	8	9	9	10	10	10	10	10	10
	7	2	3	4	5	6	7	8	9	10	10	10	10	10	10	10	10
	8	2	4	5	6	7	8	9	10	10	10	10	10	10	10	10	10
	9	3	4	5	7	8	9	10	10	10	10	10	10	10	10	10	10
	10	3	4	6	7	9	10	10	10	10	10	10	10	10	10	10	10
	11	3	5	7	8	10	10	10	10	10	10	10	10	10	10	10	10
	12	4	5	7	9	10	10	10	10	10	10	10	10	10	10	10	10

4.1.3. ClariVein® Device Preparation

The ClariVein is introduced through a micro introducer. Utilizing ultrasound vascular imaging, the Catheter Sheath with Dispersion Wire is navigated through the vasculature to the treatment site. Fluid delivered through the Catheter Assembly's Check Valve and Injection Port surrounds the Dispersion Wire and exits via an opening at the distal end of the catheter.

The ClariVein catheter assembly, check valve, and motor drive unit must be connected prior to use; do not attempt to disassemble the ClariVein after use. It is fully disposable as a unit upon completion of the treatment procedure.

Physician will select the ClariVein model based on patient anatomy; either a 45, 65 or 85 cm length model.

Inspect the ClariVein package prior to opening. **Do not** use if package is opened or damaged.

1. Use sterile technique to carefully remove the tray from the pouch and the contents from the try.
2. Inspect all components of the ClariVein® to be certain there are no visible signs of damage (**Figure 1**). **Do not** use if contents are damaged.
3. Remove Battery Terminal Insulator Tab from the Motor Drive Unit (**Figure 2, Item 12**). Check to see that the MDU has power by confirming the Green Indicator Light is illuminated (**Figure 2, Item 13**) and by engaging the Trigger momentarily (**Figure 2, Item** 10).
4. Set the Dispersion Wire Tip speed to "H" using the Speed Selector (**Figure 2, Item 8**) on the MDU. The four speed positions are labeled as follows:

   L – low, 2,000 RPM
   M1 – medium 2,500 RPM
   M2 – medium high, 3,000 RPM
   H – high, 3,500 RPM

   Note: The Dispersion Wire will **not** rotate if Green Indicator Light (LED) does not illuminate.

5. Attach the Check Valve (**Figure 3, Item 1**4) to the Injection Port (**Figure 1, Item 2**) on the Catheter Assembly by turning the Check Valve clockwise onto the Injection Port.
6. Using a 10 mL sterile syringe, prime the Catheter Assembly with sterile normal saline USP 0.9%, through the Check Valve and Injection Port checking to confirm connection is secure. **Caution:** If leak is detected, reconfirm connections of Syringe/Check Valve/Injection Port. **Do not** use product if leak continues.
7. Use the 5 mL syringe provided within the ClariVein tray to infuse STS. Refer to Table 2 and determine the volume of STS for administration per patient.
    a. Portion the dose by halves or thirds of the total STS volume for administration, load the syringe with ≤ 4 mL at a time, and slowly administer small aliquots in sequence throughout the treatment section to facilitate even distribution of the STS.

Figure 1: Catheter Assembly

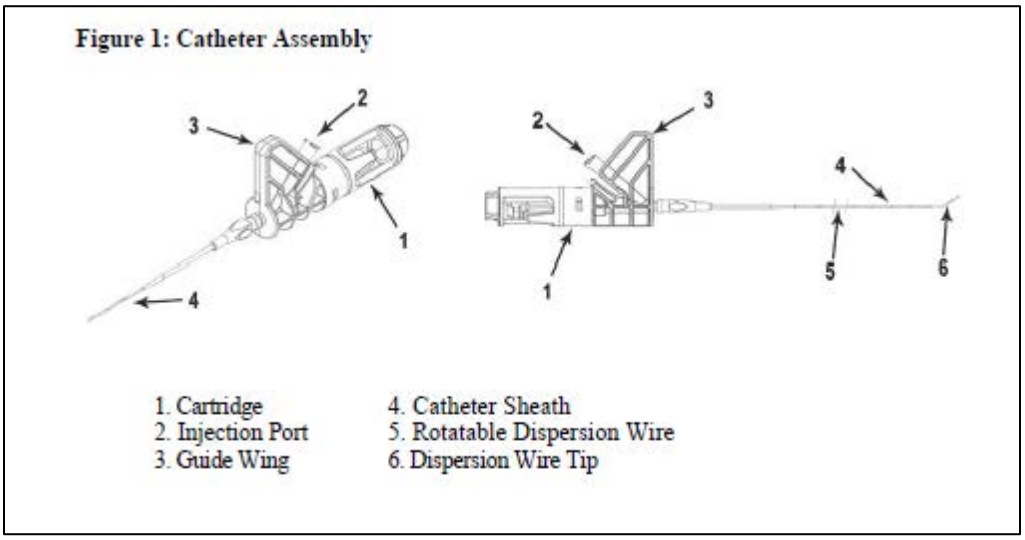


Figure 2: Motor Drive Unit

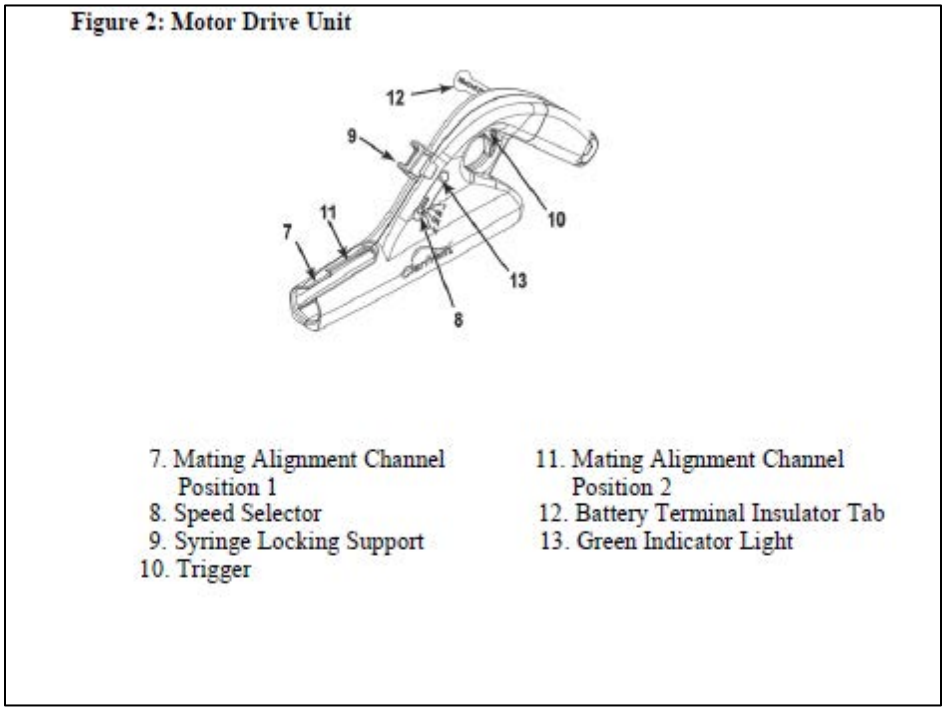
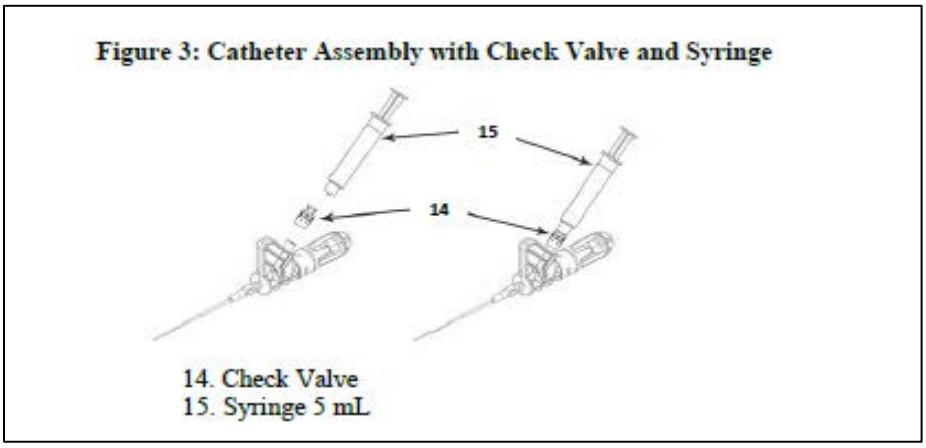


Figure 3: Catheter Assembly with Check Valve and Syringe



4.1.4. Catheter Assembly Positioning

1. Prior to joining the catheter assembly with the Motor Drive Unit (MDU), thread the ClariVein® Catheter Assembly through the access device and use ultrasound imaging guidance to confirm that the Catheter Tip (with the Dispersion Wire still within the sheath) is in the approximate desired location in the Treatment Section.

2. Once the Catheter Tip is in the approximate desired position (**Table 3**), join the Catheter Assembly and Motor Drive Unit.

Table 3: Initial Positioning of The ClariVein Catheter and Dispersion Wire

Target Vein	Position within the Treatment Section
Great Saphenous (GSV) and Accessory Saphenous Vein (ASV)	Position dispersion wire ball tip 2 cm below the saphnofemoral junction (SFJ) and the superficial epigastric vein (SEV).
Small Saphenous Vein (SSV)	Position dispersion wire ball tip at the top of the fascial curve. This is usually 2.5 to 3 cm from the saphenopopliteal (SPJ) junction if the SPJ exists.
Saphenous Vein Segment (SVS)	Position dispersion wire ball tip at the highest point of reflux within the segment.

NOTE: If using a second access point to complete infusion through the entire Treatment Section, move the Catheter Assembly **only after resheathing** the dispersion wire, i.e., move the Catheter Assembly to Position 1.

4.1.4.1. Catheter Sheath Marking

The ClariVein® has markings on the catheter to aid in location.

A single black 'hash' mark denotes 1 cm increments.

A double black 'hash' mark denotes 10 cm increments.

A single white 'hash' mark denotes approximately 8 cm from the Dispersion Wire Tip when the Dispersion Wire is unsheathed.

4.1.4.2. Joining Catheter Assembly to The Motor Drive Unit

1. While carefully maintaining position of the Dispersion Wire Tip within the Treatment Section, hold the Guide Wing (**Figure 1, Item 3**) and advance the MDU onto the Catheter Assembly's Cartridge for initial mating in the Alignment Channel Position 1 (**Figure 2, Item 7**). Ensure the orientation of the MDU is in straight alignment with the Catheter Assembly. Exercise care not to bend or kink the proximal end of the Catheter Sheath.

NOTE: Once joined, the Catheter Assembly is **not removable** from the MDU.

2. To expose the Dispersion Wire Tip, advance the MDU to secure the Guide Wing into the Mating Alignment Channel Position 2, by holding the Guide Wing and rotating the MDU slightly to the left. (**Figure 4**).

NOTE: The electrical circuit is now activated and the Dispersion Wire Tip is now unsheathed.

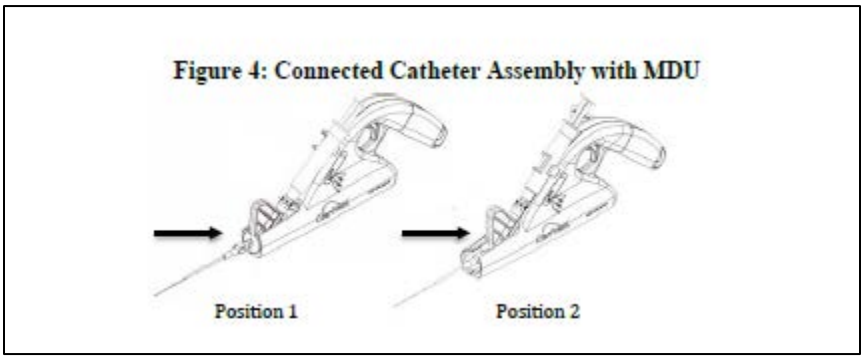
1. Connect the Syringe to the check valve connected to the Injection Port.
2. Snap the syringe into the syringe locking support. (**Figure 2, item 9**).

3. Ensure the syringe is fully engaged in the syringe locking support.

4.1.4.3. Immediately Prior to Treatment

1. Using ultrasound imaging guidance, confirm that the dispersion wire tip is in the desired position. Adjust as needed and reposition if necessary as described in **Table 3** above.

Figure 4: Connected catheter Assembly with MDU



4.1.4.4. Activating the Rotatable Dispersion Wire

1. Prior to activating rotation of the dispersion wire confirm the:
   a. position of the dispersion wire tip within the Treatment Section utilizing ultrasound imaging guidance
   b. dispersion tip is **not** within the vascular access device
   c. speed selection is at 3500 RPM
   d. patient is informed they will feel a slight vibration along the treated vein.
2. Activate rotation of the dispersion wire by depressing the trigger.

Caution: Only activate rotation of the dispersion wire while **simultaneously** slowly withdrawing (pulling back) the catheter assembly.

3. During the first 1 cm of pull back, activate the dispersion wire rotation, but do not infuse any fluid. For the remainder of the procedure, pull back with **simultaneous** dispersion wire rotation and infusion of fluid.
4. After the first 1 cm of pull back with wire rotation alone (without infusion of any fluid), slowly withdraw the device through the treatment area while simultaneously infusing the STS.
   a. The procedure is carried out using both hands moving simultaneously.

b. Depress the syringe plunger with the thumb of the same hand that is holding the MDU (**Figure 6**).
c. Perform a controlled pull back (withdrawal) of approximately 6 – 7 sec / cm.
d. While the Dispersion Wire is rotating, hold the MDU with one hand while using the other hand to gently grasp the catheter sheath between your thumb and index finger proximal to the access site; pull back slowly and smoothly with 2 hands ensuring the ClariVein® catheter sheath does not kink or become damaged.
e. Ensure the orientation of the MDU is in straight alignment and pointed towards the Catheter Assembly. The catheter must be kept straight between the Access Site and the point being grasped by the physician.

Note: For veins with diameters ≥10 mm, slight compression with the ultrasound probe is recommended. If the patient feels any discomfort, compression should be abandoned.

Caution: Do not forcefully compress the vein at the location of the rotating (spinning) dispersion wire tip either manually or with an ultrasound probe during the procedure. It is not recommended to continuously follow the rotating (spinning) dispersion wire tip with the ultrasound probe. Doing so may result in the dispersion wire becoming ensnared with the vein, damage to the device, and/or cause patient discomfort.

After approximately 10 cm of the Treatment Section has been infused with STS, stop wire rotation by releasing Trigger and stop STS infusion. Utilizing ultrasound, assess the 10 cm portion.

- If venous spasm is present, continue with the procedure as planned by reactivating the dispersion wire rotation and resume infusing STS.
- If the treated vein has not gone into spasm, **resheath** the dispersion wire into the catheter sheath by placing the Catheter Assembly in Position 1, then slowly advance the catheter to the proximal position in the Treatment Section and retreat that segment as appropriate. If the target volume of STS was less than 10 mL, the physician should deliver additional STS but **not exceed the maximum dose of 10 mL.** (See **Table 2**)

Caution: To minimize potential damage to the device and/or patient injury:

- Never advance the catheter when the Catheter Assembly is in Position 2; the Catheter Assembly must be in Position 1during advancement in the vein.
- Never advance the dispersion wire when it is rotating – it must NOT be activated during advancement in the vein.
- Do not create a bend with tension between the Catheter Assembly and the MDU.

Note: If patient experiences discomfort during pull back, temporarily reduce speed of dispersion wire rotation. After pulling dispersion wire tip through sensitive area, resume High speed wire rotation.

1. Evenly deliver sclerosant along the Treatment Section.

2. If resistance is encountered during pull back, see **Pull back Resistance** below.
3. When approximately half of the treatment has been completed, slide the access sheath back over the catheter to the most proximal end of the Catheter Assembly.
4. After emptying the syringe which contains the final amount of STS, flush the catheter with 1 mL of sterile normal saline. (This accounts for the dead space within the catheter system and thus ensures delivery of the full target volume of STS.)
5. When the single white hash mark on the catheter is visible, the dispersion wire tip is 8 cm from the access point. Be prepared to end fluid infusion after approximately 2 to 3 cm more pull back.
6. When the procedure is finished and prior to catheter removal from the patient, re-sheath the Dispersion Tip and disable the MDU by the following:
    a. Unsnap the Syringe from the Syringe Locking Support on the MDU (**Figure 5, Step 1**).
    b. Rotate the Catheter Assembly away from the Syringe Locking Support (**Figure 5, Step 2**).
    c. Push Guide Wing to its most distal position until it stops in Mating Alignment Channel Position 1 (**Figure 5, Step 3**).
    d. Continue to push to the most distal position until it stops (**Figure 5, Step 4)**

Note: Placing Catheter Assembly in Mating Alignment Channel Position 1 so that the Dispersion Wire will not rotate when removing device from patient. The Catheter Assembly cannot be separated from the MDU.

Remove the Catheter Assembly and access device as one unit from patient. Hold pressure at the access site as in any endovenous procedure. Then, apply a bandage to the Access Site.

4.1.4.5. Pull-back Resistance

During pull back, venous anatomy may interfere with the free rotation of the Dispersion Wire Tip. The user may detect one or more of the following:

- a change in the tone of the Motor Drive Unit indicating a reduction in Dispersion Wire rotation,
- the patient may complain of discomfort, or
- resistance to pull back.

If any of these occur, **immediately release the trigger** to stop the Dispersion Wire rotation**.**

While maintaining straight alignment of the catheter assembly, determine remedial action to be taken, including:

- Hold the catheter with a thumb and index finger at the Access Site; then pull the catheter past the area of resistance.

- Move the Catheter Assembly to Position 1; then move back to Position 2 and repeat.
- Move the Catheter Assembly to Position 1; then slowly rotate entire assembly clockwise up to 3 full rotations.

After taking remedial action, confirm the Dispersion Wire can rotate freely by gently sliding the catheter about 2 to 3 mm back and forth within the vein. When the user is certain that the Dispersion Wire is free within the vein, ensure the Catheter Assembly is in Position 2; then resume the procedure.

Figure 5: Re-sheathing of Dispersion Tip

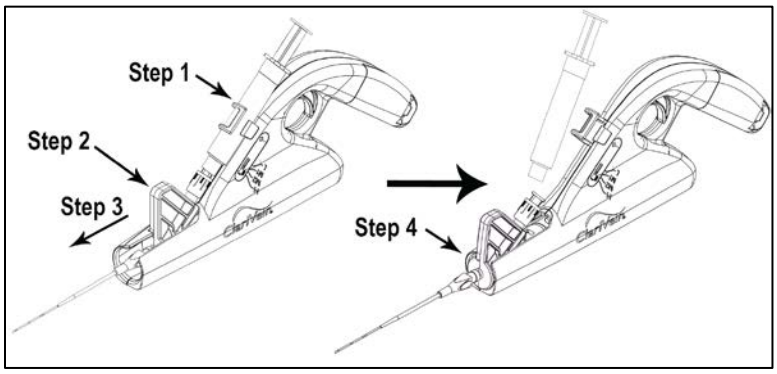


Figure 6: Fully Assembled ClariVein Device

4.1.5. Steps After Completion of STS and Removal of ClariVein

While the patient is on the procedure table, after completion of the STS delivery and removal of the ClariVein, the physician is to:

1. Have the patient to perform dorsiflexion / plantar flexion exercises (on the treated leg) at a moderate rate (approximately 10 times per minute for 2 or 3 minutes).
2. Place a moderate pressure (20 to 30 mmHg, Class 2) knee high compression stocking on the treated leg; and instruct the patient to wear the compression stocking continuously for 3 days (72 hours); then to wear the stocking only during the daytime for 2 weeks.

After the patient is off the procedure table, the physician is to:

1. Have the patient ambulate for 15 minutes, while still in the clinic.
2. Observe the patient in the clinic for **at least 30 minutes** following treatment.

   The Investigator **must be prepared** to treat any allergic reaction to substances utilized during the treatment procedure, including anaphylactic reactions.

   Emergency resuscitation equipment must be immediately available in the event of anaphylactic reactions.

4.1.6. Prior to Patient Discharge

1. Instruct the patient to ambulate 15 minutes per hour for the next 8 hours or until bedtime,
2. Instruct the patient to be hydrate throughout the remainder of the day,
3. Collect patient information per Schedule of Events, and
4. Review Schedule of Events for post-treatment follow-up with patient.

4.1.7. Product Disposal Instructions

4.1.7.1. Accountability of Investigational Product

After use, quarantine the product and return it to the secure area where clinical study supplies are maintained for product accountability purpose. Once the accountability is completed by the sponsor representative and permission granted for disposal, the product should be disposed using the instructions

4.1.7.2. Disposition of Investigational Product

Upon approval by the sponsor representative for disposal, dispose of the products used in the procedure per institution's procedures, taking note of the product specific instructions below and in accordance with hospital, administrative, and/or local government policy.

Any unused portion of the opened glass ampules of STS solution, as well as any empty glass ampules must be disposed of immediately, discarded per your institution's procedure. The fully assembled ClariVein contains a 9V DC battery in the MDU, which is not intended for removal. As such, the entire ClariVein delivery system, including the MDU is considered an infected medical device and is fully disposable as medical/biohazard waste and is **not** intended to be

included in used electronic equipment recycling programs. Discarded per your institution's procedure.

4.1.7.3. Inventory of Investigational Product

All unused Study Product and Clinical Supplies must be maintained according to sponsor procedures and placed in a restricted area for return and/or destruction.

5. FOLLOW-UP PERIOD

5.1. VISITS 4, 5, 6 - WEEKS 1, 6 AND 12 Post Treatment

Refer to **Schedule of Events** as provided in the Study Protocol (CL-001).

5.1.1. Ultrasound Imaging Post Treatment

With patient in the standing position, assess the Treatment Section of the selected saphenous vein for complete closure utilizing 2D ultrasound imaging with compression (split screen view) of the Treatment Section with the ultrasound probe, using color flow Doppler to confirm patency or occlusion.

5.1.1.1. Closure

Closure of the Treatment Section of the Target Vein will be assessed as follows:

1. Image the Treatment Section and record location and length of any open segments within the Treatment Section
    - GSV and ASV: 3 cm from the deep vein junction to the Access Point
    - SSV: 1 cm below the fascial curve to the Access Point
    - SVS: 1 cm below highest point of refluxing segment to the Access Point
2. Open segments >5 cm in length will be evaluated for reflux.
3. Indicate by notation and color coding the presence or absence of reflux.

5.1.2. Competence

Competence of the Treatment Section of the Target Vein will be assessed as follows:

1. Sweep along the entire Treatment Section of the Target Vein, using the ultrasound probe to compress the vein while imaging in cross-section.
2. In any compressible areas, switch to a longitudinal view; and document presence or absence of color flow in any compressible areas. If color flow is present, evaluate for reflux.
3. For this clinical study, reflux is defined as retrograde flow > 500ms (0.5s).
4. Screen for reflux utilizing color flow Doppler ultrasound, after a manual calf compression and relaxation (or after Valsalva's maneuver if evaluating the SFJ).
5. Assess for reflux in the longitudinal view with the patient in the standing position.
6. If reflux is present, utilizing Doppler ultrasound to document duration of reflux in each segment

5.1.3. Treatment Outcome

5.1.3.1. Success

Defined as Elimination of Saphenous Vein Reflux is defined as target vein closure and/or vein competency demonstrated by duplex ultrasound (color flow) at Week 12 post-treatment.

Vein Closure is defined as no discrete open segment of vein > 5 cm in length within the Treatment Section of the selected saphenous vein as assessed by duplex ultrasound.

Vein Competency is defined as absence of retrograde flow >500ms (0.5s) within the Treatment Section of the selected saphenous vein as assessed by duplex ultrasound.

5.1.3.2. Failure

Defined as the presence of retrograde flow >500ms in any discrete open vein segment >5cm within the Treatment Section of the saphenous vein; and a failure will be categorized as:

"complete" when the entire vein Treatment Section shows flow; and

"segmental" when there is at least discrete segment >5 cm in length within the vein Treatment Section shows retrograde flow.

6. MONITORING OF SELECTED VASCULAR SAFETY EVENTS

6.1. Identification and Description of Thromboembolic Events

1. Measure “stump length”, i.e., the distance from the junction to the first point of venous closure. Record image in long view of the junction indicating the “stump length”.
2. Record cross section images including junction with deep vein (split screen view with and without compression of the vein).
3. The study will use a two-point technique for assessing Deep Vein Thrombosis (DVT) in the common femoral, superficial femoral, and popliteal veins.
4. The study will also evaluate and record PASTE into the deep venous system. If PASTE is present categorize per **Table 4**.

Deep Venous System - The deep venous system will be evaluated to exclude deep vein thrombosis (DVT) using a two-point technique for assessing Deep Vein Thrombosis (DVT) in the common femoral, superficial femoral, and popliteal veins. The treated vein junction will also be evaluated for PASTE.

Evaluation for the presence of DVT and PASTE will be performed (in supine position) and images stored using the following protocol while scanning from the CFV to the calf veins:

- Evaluate above veins in B-mode; and in presence of PASTE in color flow mode
- Compress proximal, mid, and distal part of each vein segment. Record images in cross-section view using B-mode (split screen) with and without compression
- Evaluate above vein segments with color flow with distal augmentation

6.2. Post Ablation Superficial Thromboembolic Events (PASTE)

With patient in the supine position, clinician will carefully evaluate the SFJ and SPJ to look for post-ablation superficial thrombus extension from the GSV, ASV and SSV into the deep venous system.

- If post-ablation superficial thrombus extension is present, measurement and evaluation will be done with patient in the reverse Trendelenburg or standing position; and images stored.
- Characterization of the length of any post-ablation superficial thrombus extending into the deep venous system and the percentage of deep vein diameter that is affected will be assessed utilizing **Table 4**.

Table 4: Characterization of Post-Ablation Superficial Thrombus Extension (PASTE)

Type	Description	Action
Type 1	Confined to the junction (SFJ or SPJ), not extending into the deep vein system.	Treatment not required
Type 2	Past the junction (SFJ or SPJ,) extending into the deep vein system and occupying less than 50% of the deep vein cross sectional area.	Treatment could be required, if the patient is high risk, e.g. history of DVT.
Type 3	Into the deep venous system and occupying greater than 50% of the deep vein cross sectional area.	Treatable Follow institutional protocol.
Type 4	Into the deep system, fully across the diameter of the deep vein (e.g., at the SFJ or SPJ).	Treatable Follow institutional protocol.