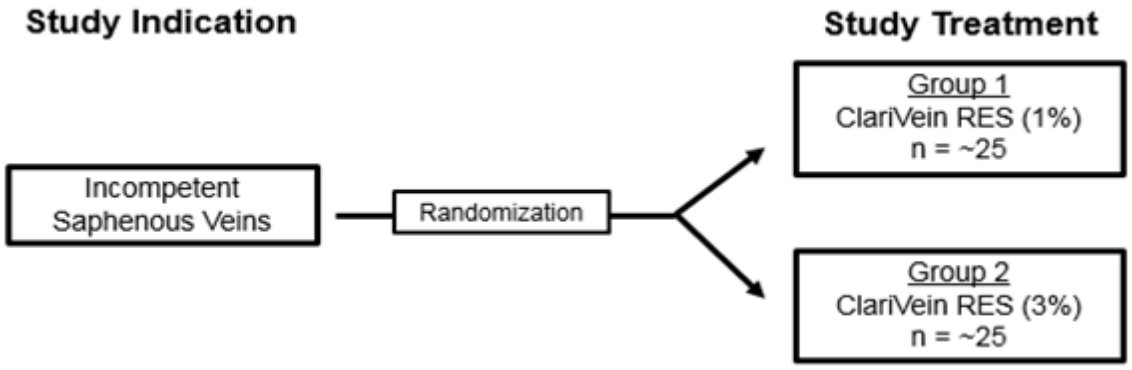
4. STUDY DESIGN

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.

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).

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

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.*

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)

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.

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

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.

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.

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.

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.

11.5. 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.

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

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.

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.

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.)

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

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

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.

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)

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

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.