Venclose™ Clinical Protocol VENC17A

EU Post Market Clinical Follow-Up Study of the Venclose System for Saphenous Vein Incompetence

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PROTOCOL AGREEMENT PAGE

I, the Investigator, agree to:

- Assume responsibility for the proper conduct of the study and not to deviate from the procedures described in the protocol;
- Be thoroughly familiar with the procedures as described in the protocol and any other information sources provided by the Sponsor;
- Conduct the study in compliance with the protocol and all applicable regulatory requirements;
- Permit monitoring and auditing of the study by the Sponsor and/or representatives, and inspections by appropriate regulatory authority(ies); and
- Ensure that all persons assisting with the conduct of the study are properly qualified for their function.

_____
Investigator Name (Print)

_____ _____
Investigator Signature Date

_____
Sponsor Name (Print)

_____ _____
Sponsor Signature Date

1 PROTOCOL SYNOPSIS

Protocol Number	VENC17A
Protocol Title	EU Post Market Clinical Follow-Up Study of the Venclose System for Saphenous Vein Incompetence
Sponsor	Venclose, Inc. 2570 N. First Street, 2nd Floor - #221 San Jose, CA 95131, USA
Study Type	Post Market Clinical Follow-up
Study Design	This is a prospective, non-randomized study in which patients who meet eligibility criteria and consent to participate will undergo a minimally invasive procedure using radiofrequency (RF) energy for ablation of the great saphenous vein (GSV).
Primary Objective	To confirm the safety and performance of the Venclose System for radiofrequency segmental thermal ablation of incompetent Great Saphenous Veins (GSVs).
Study Duration	Up to 3 months to enroll plus one year to complete follow-up
Participant Duration	Twelve months post-procedure
Study Site(s)	One study site located in Germany
Sample Size	Up to 25 subjects treated with the Venclose System
Study Visits	Baseline Visit, Treatment Visit, Follow-Up Visits (3-day, 3-month, 6-month, and 1 year post procedure)
Primary Endpoints	1. Vein Occlusion Rate (percentage of limbs with occlusion of the treated vein) at 3-day, 3-month, 6-month, and 12-month Follow-up Visits. 2. Reflux-free Rate (percentage of limbs without reflux, as determined by Duplex Ultrasound Scan) at 3-day, 3-month, 6-month, and 12-month Follow-up Visits.
Secondary Endpoints	Clinical signs and symptoms of lower limb venous disease at baseline, 3 months, 6 months, and 12 months as measured by:

	1. Clinical Etiologic Anatomic Pathophysiologic (CEAP) Classification; 2. Venous Clinical Severity Score (VCSS). Side effects/adverse events after treatment through 12-month follow-up.
Inclusion/ Exclusion Criteria	<u>Inclusion Criteria</u> 1. Subject is male or female and 18 to 80 years old (inclusive) at time of enrollment (signing of consent). 2. Subject has significant venous reflux by DUS, defined as reverse flow with reflux duration greater than 0.5 seconds after the Valsalva maneuver or distal augmentation while the patient is standing or in reverse Trendelenburg position. 3. Subject is eligible for endovascular treatment, as determined by the treating investigator. 4. Subject's general physical condition allows for a significant amount of ambulation after the procedure, as determined by the treating investigator. 5. Subject is willing and able to complete study requirements, including all follow-up visits and assessments. 6. Subject voluntarily provides written informed consent to participate in this study. <u>Exclusion Criteria</u> 1. There is evidence of old or fresh thrombus in the subject's diseased vein segment to be treated, as determined by DUS within 2 weeks prior to the index procedure. 2. In the judgment of the treating investigator heat energy delivery to the subject would be contraindicated. 3. Subject is concurrently participating in another interventional clinical trial. 4. Subject is pregnant or plans to be pregnant or lactating at the time of the treatment procedure. 5. Subject has known or suspected allergies or contraindications to any general or local anesthetic agents and/or any antibiotic medication that cannot be adequately pre-treated.

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2 BACKGROUND AND OBJECTIVES

The primary objective of this Post-Market Clinical Follow-up (PMCF) prospective, non-randomized study is to confirm the safety and performance of the CE-marked Venclose System for radiofrequency segmental thermal ablation of incompetent Great Saphenous Veins (GSVs).

These types of post-market studies are recommended by MEDDEV 2.12-2 rev 2 for all medical devices for which there is not medium- to long-term clinical evidence available at the time of gaining approval to market in the EU, and for medical devices that have relied on clinical data from equivalent devices for conformity with the Essential Requirements of the Medical Device Directive (MDD). It is hypothesized that the safety and performance of the Venclose System will be similar to the equivalent, alternative CE-marked ClosureFast System, which Venclose relied on for clinical data for conformity with the Essential Requirements.

The data and conclusions derived from this PMCF study will be used to provide additional data for updating the clinical evaluation in order to assess whether the device continues to comply with the Essential Requirements. Such an assessment may result in corrective or preventive actions, for example: changes to the labeling/instructions for use, changes to manufacturing processes, changes to the device design, or public health notifications.

This study has been designed in accordance with MEDDEV 2.12/2 rev 2.

3 TECHNOLOGY SUMMARY

The Venclose™ Radiofrequency (RF) System (Generator and Catheters) is intended for use in endovascular coagulation of blood vessels in patients with superficial vein reflux. The Venclose System uses resistive radiofrequency ablation via bipolar energy delivery to heat the wall of an incompetent vein with temperature-controlled RF energy to cause irreversible luminal occlusion, followed by fibrosis and ultimately resorption of the vein. The blood then naturally reroutes to healthy veins.

The technique involves percutaneous access and insertion of the endovenous sectional radiofrequency (EVSRF™) catheter into the target vein under ultrasound guidance and relies on the use of local anesthesia and thermal energy, from a radiofrequency generator, applied to the target vein. After each treatment, the EVSRF catheter is withdrawn a single length of the heating coil and another treatment is performed, until the entire vessel has been treated. This sectional treatment involves thermal damage that is inflicted upon the venous endothelium and into the wall, resulting in contraction and ultimately destruction of the vessel.

The procedure can be performed in an outpatient setting, without the need for general anesthesia, allowing for a walk-in/walk-out procedure with minimal postoperative recovery time.

The Venclose System consists of two (2) main components: 1) The EVSRF Ablation catheter (model VC-10A2.5-6F-60, 60cm or VC-10A2.5-6F-100, 100cm) with integrated cable connector which, using sectional ablation, treats the vein in 10 cm or 2.5 cm segments, and 2) the Venclose digiRF generator (model VC-RFG-1) which delivers RF energy to the EVRSF catheter.

The Venclose System is comprised of the following accessories:

- Power cord for generator for the geographical region that the generator is sold
- Optional foot pedal (model VC-FP-1)

The following supplies are necessary for the procedure, but are not provided with the Venclose System:

- Duplex or B-mode ultrasound console
- Supplies for sterile procedure
- Tilt table (recommended)
- 6F introducer sheath, with matching dilator, guidewire and percutaneous access needle (access kit/ introducer kit)
- Local or general anesthesia
- Post-operative compression as recommended by physician

EVSRF catheters have a handle with logic circuitry and a button for starting treatment cycles. The generator is a 60-Watt multi-voltage (24V or 9V) power delivery system that uses digital radiofrequency at 460 kHz. The system will be used to perform endovenous ablations at 120°C for 20 seconds per cycle, matching a treatment protocol that has been widely studied over the last 10 years[1].

4 RISKS AND BENEFITS

Bipolar segmental radiofrequency ablation technology has years of history of clinical safety and effectiveness in humans in the delivery of radiofrequency energy to peripheral veins in the leg. Procedures utilizing radiofrequency ablation devices are associated with consistently high successful vein closure rates, with side effects that are low in frequency,

[1] Proebstle TM, Alm BJ, Gockeritz O, Wenzel C, Noppeney T, Lebard C, Sessa C, Creton D, Pichot O. Five-year results from the prospective European multicenter cohort study on radiofrequency segmental thermal ablation for incompetent great saphenous veins. *BJS* 2015; 102: 212-218.

mostly minor/transient and common to catheter-based procedures in general. Radiofrequency ablation sessions are usually performed in an outpatient setting with local anesthetic and typically require no sedation. Patients are fully ambulatory following treatment, and the recovery time is short for the majority of patients.

Potential complications include, but are not limited to the following: vessel perforation, skin discoloration, nerve injury, phlebitis, hematoma, thrombosis, infection, skin burn and pulmonary embolism. Other adverse events are often related to and can be complicated by the progression of the underlying incurable and progressive nature of venous disease, the presence of co-morbid conditions, and/or the risks of tumescent anesthesia. Risks related to the use of catheters in general and thermal interventions in particular are considered to be manageable (minor, transient and treatable) when compared to the possible benefits of controlled and selective destruction of diseased peripheral vasculature. These risks may be minimized through adherence to the device instructions for use, proper patient selection and monitoring of the patient's status during treatment and follow-up. Radiofrequency ablation provides a minimally-invasive and outpatient-based treatment alternative for patients with varicose veins and peripheral venous insufficiency that is well-established and widely-used in the medical community.

The benefits of treatment with ablative radiofrequency energy include reduction in the overall severity of venous symptoms and improved quality-of-life with typically only mild postoperative discomfort.

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary study endpoints are percentage of limbs with vein occlusion in the treated vein and the absence of reflux in the treated vein, as determined by Duplex Ultrasound Scan (DUS).

Primary endpoint analysis will be accomplished by measuring the treated vein recanalization and reflux rates at 3 days (+/- 2 days), 3-months (+/- 2 weeks), 6 months (+/- 3 weeks) and 12 months (+/- 4 weeks) post-procedure. Recanalization will be determined by DUS and clinical assessment during follow-up. A twelve-month follow-up is sufficient to assess a stable occlusion in the treated vein, as it is the typical final follow-up time frame for varicose vein treatment when assessing technical and symptomatic recurrence.

Specific primary endpoint measurements will be:

1) Vein Occlusion Rate – percentage of limbs with occlusion of the treated vein: Occlusion is defined as the absence of any flow from 3 cm inferior to the Saphenofemoral Junction (SFJ) along the entire length of the treated vein as documented on the post-procedure and follow-up DUS. The 3 cm limit was selected

to represent the occlusion status of the proximal Great Saphenous Vein (GSV) and to allow precise evaluation with a typical 4 cm linear ultrasound probe. In line with the equivalent ClosureFast device clinical studies[2,3] flow in the stump of the GSV up to 3 cm below the SFJ is considered normal and does not constitute a failure.

2) Reflux-Free Rate – percentage of limbs without reflux in the treated vein: Reflux is measured by Duplex Ultrasound imaging along the entire treated vein segment(s). Reflux is defined as reversal flow >0.5 seconds with subject standing or in reverse Trendelenburg position of at least 15° after distal augmentation.

5.2 SECONDARY ENDPOINTS

Secondary endpoints are the clinical outcomes (patient symptoms, patient recovery) and evaluation of side effects/adverse events after the treatment:

5.2.1 Patient Outcome (Symptoms/Recovery)

Clinical signs and symptoms of lower limb venous disease will be evaluated using standardized scales and subject responses to pre and post-procedure questions using the Clinical Etiologic Anatomic Pathophysiologic (CEAP) clinical classification and the 2010 revised Venous Clinical Severity Score (VCSS).[4]

Clinical Etiologic Anatomic Pathophysiologic (CEAP): Status of clinical signs and symptoms of lower limb venous disease as measured by CEAP Classification at baseline, and 3-day, and 3-, 6- and 12-month follow-up visits.
CEAP clinical categories are as follows[5]:

C0: no visible or palpable signs of venous disease.

C1: telangiectasies or reticular veins.

C2: varicose veins.

C3: edema.

C4a: pigmentation or eczema.

C4b: lipodermatosclerosis or atrophie blanche.

C5: healed venous ulcer.

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[2] Proebstle T, van den Bos R. Endovenous ablation of refluxing saphenous and perforating veins. *Vasa*. 2017 May;46(3):159-166. doi: 10.1024/0301-1526/a000610. Epub 2017 Feb 27. Review. PMID: 28238282

[3] Creton D, Pichot O, Sessa C, Proebstle TM; ClosureFast Europe Group. Radiofrequency-powered segmental thermal obliteration carried out with the ClosureFast procedure: results at 1 year. *Ann Vasc Surg*. 2010 Apr;24(3):360-6. doi: 10.1016/j.avsg.2009.09.019. Epub 2010 Jan 29. PMID: 20116207

[4] Vasquez et al., Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg.* 2010 Nov;52(5):1387-1396.

[5] Eklöf, B. et al, Revision of the CEAP classification for chronic venous disorders: Consensus statement, *Journal of Vascular Surgery*, Volume 40, Number 6, 1248-1252

C6: active venous ulcer.

Venous Clinical Severity Score (VCSS): VCSS will be measured at baseline, 3-day, and 3-, 6- and 12-month follow-up visits. VCSS assesses 10 factors of venous disease for which each factor is graded on a severity scale of 0-3 (least to worst). The higher the VCSS score the most severe the clinical signs and symptoms of venous disease are in a patient. VCSS improvement over time is presented by a decrease in VCSS total score (maximum score = 30; minimum score = 0).[6]

Although ClosureFast studies utilized the original 1996 CEAP and 2000 VCSS scales, the Venclose post-market study will utilize the official 2004 and 2010 revised version of the scales, respectively, for consistency with the current state-of-the-art of clinical assessment for endovascular coagulation of blood vessels in patients with superficial vein reflux. Comparison efforts between the Venclose and ClosureFast studies will focus on similar percentages of score reduction, and may include an analysis of the differences in scale composition, as needed.

5.2.2 Side Effects and Complications

Side effects, adverse events and complications associated with the procedure will be recorded and analyzed. See Section 11.0 for Reporting of Adverse Events.

6 OVERVIEW OF STUDY DESIGN

Potential subjects presenting with signs and symptoms of chronic lower limb venous disease and significant reflux in the GSV will be further screened for study participation and enrollment. All enrolled subjects will meet study eligibility criteria as described in the inclusion and exclusion criteria sections below.

After voluntarily providing informed consent to participate, eligible subjects will undergo a minimally invasive procedure, which involves delivering controlled radiofrequency energy for ablation of the great saphenous vein (GSV). All procedures will be performed by surgeons determined to be experienced with the Venclose System and will take place at a single study site, Venenzentrum am Bruehl, Nikolaistr. 55, 04109 Leipzig. The study will enroll up to 25 treated subjects. The study site will receive the Venclose System components for the treatment of study patients, free of charge.

After the treatment procedure, subjects will be evaluated four (4) times to determine the incidence of adverse events, and to assess vein recanalization and reflux. Follow-up visits occur at 3 days (+/-2 days), 3-months (+/- 2 weeks), 6 months (+/- 3 weeks) and 12 months (+/- 4 weeks) post-procedure. Each follow-up visit will consist of a clinical examination,

[6] Vasquez et al., Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg.* 2010 Nov;52(5):1387-1396.

CIVIQ-20 Patient Questionnaire (except 3-day visit), patient satisfaction survey, and Duplex Ultrasound (DUS) examination of the treated limb in the reverse Trendelenburg position. A supine (rather than standing) position for DUS examinations is preferred in order to allow comparison with vein diameters obtained during the procedure.

6.1 INCLUSION CRITERIA

1. Subject is male or female and 18 to 80 years old (inclusive) at time of enrollment (signing of consent).
2. Subject has significant venous reflux by DUS, defined as reverse flow with reflux duration greater than 0.5 seconds after the Valsalva maneuver or distal augmentation while the patient is standing or in reverse Trendelenburg position.
3. Subject is eligible for endovascular treatment, as determined by the treating investigator.
4. Subject's general physical condition allows for a significant amount of ambulation after the procedure, as determined by the treating investigator.
5. Subject is willing and able to complete study requirements, including all follow-up visits and assessments.
6. Subject voluntarily provides written informed consent to participate in this study.

6.2 EXCLUSION CRITERIA

1. There is evidence of old or fresh thrombus in the subject's diseased vein segment to be treated, as determined by DUS within 2 weeks prior to the index procedure.
2. In the judgment of the treating investigator heat energy delivery to the subject would be contraindicated.
3. Subject is concurrently participating in another interventional clinical trial.
4. Subject is pregnant or plans to be pregnant or lactating at the time of the treatment procedure.
5. Subject has known or suspected allergies or contraindications to any general or local anesthetic agents and/or any antibiotic medication that cannot be adequately pre-treated.

7 PRE-SURGICAL ASSESSMENT (Baseline Study Visit)

Potential subjects will be examined by the Investigator or his/her designee and evaluated according to the inclusion/exclusion criteria for participation in this study. Demographics, medical history (including previous venous interventions, risk factors/co-morbidities, and

concomitant conditions/medications), and a venous Duplex Ultrasound will be performed during pre-surgical assessment, and the results recorded on the *Baseline Case Report Form*.

7.1 INFORMED CONSENT

For subjects who potentially meet study eligibility criteria, study participation will be carefully explained. Subjects who choose to continue in the evaluation will be asked to read the *Study Informed Consent Form* and will be given the opportunity to review the information and ask questions.

It is the responsibility of the treating physician or his/her designee to obtain voluntary written informed consent (according to local legal requirements and regulations). The information is intended to give each participant a thorough understanding of the purpose and nature of the PMCF study, the study requirements and visit commitments, and the potential benefits and risks of the study treatment. As part of the informed consent process, the investigator is instructed to inform the patient that he/she is free to refuse participation or to withdraw from the study at any time, without consequence. The patient is to understand that participation in the study is not required in order to receive treatment with the CE-marked Venclose System, and that alternative treatments (e.g., treatment with another endovenous ablation system or alternative method such as foam sclerotherapy) are available for venous insufficiency. A consent form in a language understood by the patient will be made available. The signed informed consent is retained in the patient's medical file(s) along with documentation of the informed consent conversation and process by the person who obtained consent. A copy of the informed consent will be provided to the patient. Signing of the Study Informed Consent Form formally enters the subject as a study participant and indicates the participant's willingness to comply with the pre-procedure, treatment, and follow-up study requirements. If participants withdraw from the study prior to treatment with the treatment device, additional patient(s) may be enrolled in order to achieve a total of 25 treated patients.

7.2 BASELINE STUDY ASSESSMENTS, CHRONIC VENOUS INSUFFICIENCY QUALITY OF LIFE QUESTIONNAIRE (CIVIQ-20)

Once the subject has agreed to participate in the study and signed the Study Informed Consent Form, the investigator will perform an assessment using the Clinical Etiologic Anatomic Pathophysiologic (CEAP) Classification and the Venous Clinical Severity Score (VCSS).

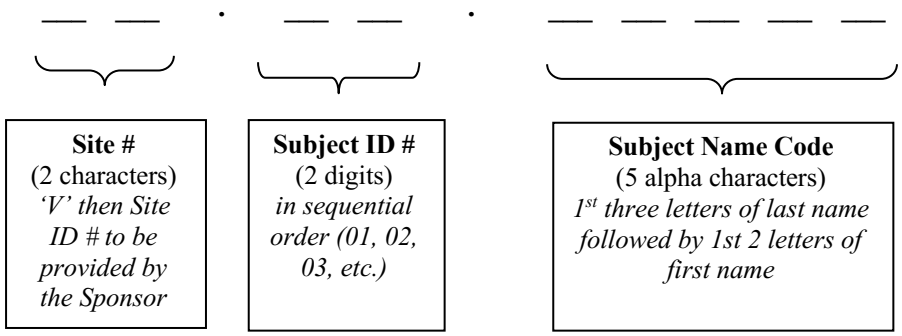
The subject will complete a self-administered questionnaire called the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ-20). The questionnaire assesses quality of life for patients with chronic venous disease using 20 questions in which the patient rates symptoms on a scale from 1 (no pain) to 5 (severe pain).

7.3 SUBJECT CONFIDENTIALITY AND IDENTIFICATION

All information concerning subjects or their participation in this study will be considered confidential. Only authorized Venclose personnel and designated consultants and regulatory agencies (in the event of a regulatory audit) will have access to these confidential files. The investigator and designated study personnel will assign a unique identifier that will be used to maintain confidentiality of subjects' medical information. Subject's full names or initials and other protected health information (PHI) will not be captured on the case report forms, except patient self-reported questionnaires/surveys. For patient self-reported questionnaires/surveys, the site will retain the original document and will redact a copy that will be provided to Venclose or Venclose representatives. In addition, any images or reports submitted from the participating site to Venclose or Venclose representatives will be redacted of all subject identifiers.

Subjects' identifying information will be recorded on a Master Enrollment Log with access restricted to the Investigator and designated study personnel.

On all source documents, case report forms, and any other documents provided to the Sponsor, the following subject identification coding for enrolled subjects will be used:



EXAMPLES

V 1 . 0 1 . J O N A D_

V 1 . 0 2 . M I L S T_

V 1 . 0 3 . S T U J E_

Note: Data for patients treated in bilateral limbs may be analyzed on a per-patient or per-limb basis, as appropriate. Patients treated in bilateral limbs will be counted as one subject for data analyzed per-patient (and for the purposes of adverse event data). For data analyzed per-limb, the two limbs will be analyzed separately.

Subjects will be given a date for surgery(s) during the Pre-Surgical Assessment (Baseline Visit) (with 14 allowable days between baseline assessments and the procedure).

8 SURGICAL PROCEDURE

In accordance with routine clinical commercial practice, study investigators will receive in-service training by Venclose personnel or its representatives for the use of the Venclose System as well as product labeling and training materials, which include the Venclose digiRF User Manual (LB00003) (generator) and Venclose Catheter IFU (LB00002).

The surgical procedure with the Venclose System will be conducted in accordance with the EU approved Venclose Catheter IFU and the Venclose digiRF User Manual (generator). The typical training program for the commercial device includes information about supplies, patient preparation, vein access, skin marking and measurement, device preparation, insertion, placement and local anesthetic, energy delivery and post-surgery recovery. Training that is specific to the performance of the study includes documentation requirements and procedures for the timely transmission of data. Procedure details and adverse events assessment will be recorded on the *Treatment Visit Case Report Form and Adverse Event Case Report Form.*

The Venclose procedure will be performed on the GSV per standard of care. For the GSV, no other treatment modalities are allowed (i.e. no phlebectomy or sclerotherapy).

Adjunctive procedures for treatment of side branches (i.e. anterior accessory saphenous vein) may be performed per standard of care including phlebectomy and sclerotherapy.

9 POST-PROCEDURE FOLLOW-UP CARE

The study site will follow standard of care post-procedure instructions including:

1) Post-operative compression as prescribed by physician.
2) For DVT prophylaxis, the subject will be instructed to ambulate frequently for several days after treatment.
3) It is recommended that the subject not drive for 24 hours after treatment.
4) It is recommended that the subject refrain from standing for long periods of time, and elevate the treated leg frequently in the first few days after treatment.
5) It is recommended that the subject refrain from strenuous activities (such as heavy lifting) for several days.
6) The bandage over the compression stocking may be removed in the evening on the day

of the treatment. After three days the pressure inserts may be removed; small bandages will remain over the incisions and the subject may shower with these bandages on.

7) Non-steroidal anti-inflammatory drugs are permitted as needed.
8) If full mobility is not achieved after 2-3 weeks, physical therapy is recommended.

10 FOLLOW-UP STUDY VISITS

As shown in Table 1, Study Visit Schedule, all subjects will undergo four (4) follow-up examinations to assess the safety and efficacy of the treatment procedure. The visits will be scheduled at 3 days (+/-2 days), 3-months (+/- 2 weeks), 6 months (+/- 3 weeks), and 12 months (+/- 4 weeks) post-procedure. Each follow-up visit will consist of a clinical examination that includes DUS examination of the treated limb in the reverse Trendelenburg position, assessments using the Clinical Etiologic Anatomic Pathophysiologic (CEAP) Classification and the Venous Clinical Severity Score (VCSS), patient satisfaction survey, and CIVIQ-20 patient questionnaire (except 3-day visit). All follow-up data will be recorded on the *Follow-Up Visit Case Report Form.*

Table 1: Study Visit Schedule

	Pre-surgical Assessment/ Baseline	**Treatment Procedure**	**3 Days Post-Procedure (+/-2 days)**	**3 Months Post-Procedure (+/- 2 weeks)**	**6 Months Post-Procedure (+/- 3 weeks)**	**12 Months Post-Procedure (+/- 4 weeks)**
Informed Consent	√					
Medical History and Physical Exam	√					
DUS	√		√	√	√	√
CEAP	√		√	√	√	√
VCSS	√		√	√	√	√
CIVIQ-20 Patient Question-naire	√			√	√	√

	Pre-surgical Assessment/ Baseline	Treatment Procedure	3 Days Post-Procedure (+/-2 days)	3 Months Post-Procedure (+/- 2 weeks)	6 Months Post-Procedure (+/- 3 weeks)	12 Months Post-Procedure (+/- 4 weeks)
Patient Satisfaction Survey			√	√	√	√
Treatment with Venclose System		√				
Medication Review	√	√	√	√	√	√
Adverse Event Assessment		√**	√	√	√	√
Study Exit						√

** Adverse events will be assessed during the immediate post-procedure period, prior to discharge.

10.1 3-DAY FOLLOW-UP VISIT

During the 3-day post-procedure follow-up visit, the pads, gauze bandage and wrapping will be removed. The surgical wounds will be evaluated, and complications or adverse events recorded. Duplex ultrasound of the treated limb will be performed for an assessment of the deep venous system, including an assessment of the treated GSV for closure, patency or recanalization. A patient self-reported satisfaction survey will be administered.

10.2 3-, 6-, AND 12-MONTH FOLLOW-UP VISITS

During the 3-, 6-, and 12-month follow-up visits Duplex ultrasound of the treated limb will be performed for an assessment of the deep venous system, including an assessment of the treated GSV for closure, patency or recanalization. Complications or adverse events will be recorded.

The CEAP and the VCSS assessments will be performed during the 3-, 6- and 12-month follow-up visits and will be recorded on the *Follow-Up Case Report Form*. The CIVIQ-20 patient questionnaire and a patient self-reported satisfaction survey will be administered during the 3-, 6- and 12-month follow-up visits.

10.3 ADJUNCTIVE PROCEDURES AND RE-INTERVENTION

Treatment of varices, perforators or side branches in the venous anatomy associated with the treated GSV segment is not allowed while subjects are in the follow-up period of this study (through 12-Month Follow-up Visit). This is done to avoid confusion post-operatively between morbidity due to index treatment and adjunctive procedures.

If an adjunctive procedure or re-intervention is performed at any time after the index procedure, the Investigator will complete an *Adjunctive Procedure Case Report Form* as well as a *Protocol Deviation Case Report Form.*

10.4 SUBJECT LOST-TO-FOLLOW-UP

In the event that a subject does not return for a follow-up visit, study personnel will make 3 attempts to contact the subject. The 3 attempts will be recorded in the subject's medical record, detailing date, method of attempted contact, and result.

If the study personnel are unable to contact the subject, or if the subject refuses to return for follow-up, a *Study Exit CRF* will be completed, specifying that the subject is lost-to-follow-up, and will include information on the 3 attempts to contact the subject (date, contact method, result).

10.5 EARLY WITHDRAWAL OF SUBJECTS

If a subject decides to withdraw from the study early, he/she must contact the investigator (contact information is provided on the first page of the Study Informed Consent Form). Study personnel will document the early withdrawal on the *Study Exit CRF* including a reason for withdrawal.

The investigator or sponsor may end a subject's study participation at any time if the subject is not compliant with required tests and visits, if it is in the subject's best interest medically, if a research-related injury occurs, or for administrative reasons. If a subject is terminated from the study early, the investigator will notify the subject and the subject will still receive necessary follow-up care.

11 ADVERSE EVENT REPORTING

The Investigator is responsible for recording and reporting adverse events observed during the study. Adverse Event information will be recorded on the *Adverse Event Case Report Form* (AE CRF) and will be reported to the Ethics Committee (EC), as per the EC reporting requirements and to the Study Sponsor, as per the following instructions.

To aid the Investigator and site staff, a list of known potential Adverse Events is provided in **Appendix 1.**

11.1 DEFINITION OF AN ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. An AE may be any of the following:

- A symptom
- A disease or new illness diagnosed while enrolled in a trial, excluding screening diagnosis/diagnoses
- An exacerbation of a sign or symptom of a pre-existing condition or of a concomitant illness
- An increase in frequency/intensity of a pre-existing condition
- An abnormal laboratory measurement of clinical relevance, excluding screening results
- A laboratory measurement that changes from baseline and is of clinical relevance
- A pre-existing physical finding (including vital sign measurements) that worsens compared with baseline and is of clinical relevance
- An accident
- Unrelated to participation in the trial or an effect of the trial procedures or study device
- A combination of one or more of the above factors

Information recorded on the AE CRF will include the nature of the event, date of onset, seriousness, severity, relationship to device, relationship to procedure, action taken, and outcome.

11.2 DEFINITION OF A SERIOUS ADVERSE EVENT

An AE is considered a serious adverse event (SAE) if the AE:

a) led to a death, injury or permanent impairment to a body structure or a body function.

b) led to a serious deterioration in health of the patient, that either resulted in:

- a life-threatening illness or injury, or

- a permanent impairment of a body structure (not including permanent damage intended by the procedure, such as obliteration by endovenous thermal ablation) or a body function (not including permanent impairment that is a known complication of the intended procedure, such as small local paresthesia after endovenous thermal ablation), or

- in-patient hospitalization or prolongation of existing hospitalization, or

- medical or surgical intervention to prevent life threatening illness or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. A serious injury does not include reversible damage or injury (such as endovenous heat induced thrombosis that is less than 50% occlusive of the deep vein (EHIT 2) and that resolves with or without treatment, not requiring surgical intervention).

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

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

11.3 DEFINITION OF AN UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

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

11.4 EVALUATING ADVERSE EVENTS

11.4.1 Severity of Adverse Event

The investigator must assess the severity of each AE reported during the study and will assign it to one of the following severity categories:

Mild:	An event that does not interfere with activities of daily living. No medical intervention is required.
Moderate:	An event that interferes with activities of daily living, limits usual activities. No or minimal medical intervention is required.
Severe:	An event that prevents normal every day activities. Medical intervention or therapy is required.

The term 'severity' is used to describe the intensity of an event (as in mild, moderate, severe); the event itself may be of relatively minor medical significance, such as a severe headache. 'Severe' is not the same as 'serious'. Seriousness, not severity, serves as the guide for defining regulatory reporting obligations.

11.4.2 Causality of Adverse Event (Relationship to Device and Procedure)

The investigator must assess the relationship to the device and to the procedure for each AE that is reported during the study. Causality will be categorized using the criteria in Tables 2 and 3.

Table 2: Assessment of Relationship to Device

Relationship	Description
Not Related	No relationship exists with the use of the device or the event is clearly related to other factors.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause.
Possibly Related	The relationship with the use of the device is weak but cannot be ruled out completely.
Probably Related	The relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause.
Causal	The event is associated with the device beyond a reasonable doubt.

Table 3: Assessment of Relationship to Procedure

Relationship	Description
Not Related	No relationship exists with the procedure or the event is clearly related to other factors.
Unlikely	The relationship with the procedure seems not relevant and/or the event can be reasonably explained by another cause.
Possibly Related	The relationship with the procedure is weak but cannot be ruled out completely.
Probably Related	The relationship with the procedure seems relevant and/or the event cannot reasonably be explained by another cause.
Causal	The event is associated with the procedure beyond a reasonable doubt.

11.5 RECORDING AND DOCUMENTING ADVERSE EVENTS

Each adverse event must be promptly recorded and sufficiently documented by the investigator on the *Adverse Event Case Report Form*, even if the adverse event is assessed by the investigator as unlikely to be related to the subject's participation in the study protocol. The investigator should make every attempt, if possible, to establish a diagnosis based on presenting signs and symptoms. At each visit, after the participant has had an opportunity to spontaneously mention any problems, the investigator should inquire about adverse events.

If any event meets the definition of a SAE, the investigator or designee will notify Venclose (or designee) by telephone or email within 48 hours after site study personnel becomes aware of the event.

The investigator or designee will notify Venclose (or designee) by telephone or email within 24 hours after site study personnel becomes aware of any UADE. The event will be reviewed per Venclose's Complaint Handling Procedures, which establish the requirements for reporting medical device incidents under the European Union's (EU) Medical Device Vigilance System for medical devices distributed in the EU under a CE mark.

All unresolved SAEs or UADEs that are ongoing at a subject's trial completion (12-Month Visit) or early termination will be followed by the Investigator until the event(s) is resolved, stabilized, the participant is lost to follow-up, or the event is otherwise explained. Documentation of this effort will be recorded on the *Adverse Event Case Report Form*.

11.6 CRITERIA FOR INTERRUPTION OR EARLY TERMINATION OF STUDY

If an event meets the following criteria it will be reviewed as an Unanticipated Adverse Device Effect (UADE):

- A serious adverse event (SAE);
- That is unanticipated (per UADE definition in Section 11.3);
- And is possibly related, probably related, or causal to the device or the procedure (per Section 11.4.2).

Venclose will immediately evaluate each UADE. After evaluating a UADE, if Venclose determines the effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible. Study termination will occur no later than 5 working days after Venclose makes this determination and no later than 15 working days after Venclose first received notice of the UADE.

12 DEVICE MALFUNCTIONS

All device malfunctions (a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions) whether or not the malfunction resulted in an adverse event will be reported to Venclose immediately. Malfunctioning devices are required to be returned to Venclose for analysis following internal Returned Merchandise Authorization Process Procedures. Venclose will attempt to confirm the malfunction/failure and the details of the malfunction will be reviewed per Venclose's Complaint Handling Procedures, which establish the requirements for reporting medical device incidents under the Medical Device Vigilance System.

13 PROTOCOL DEVIATIONS

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. Any protocol deviations that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor as soon as a possible, but **no later than within 5 working days** of the protocol deviation and to the institution's Ethics Committee (EC) per their policy.

Protocol deviation is also used to refer to any other, unplanned, instance(s) of protocol noncompliance. For example, situations in which the Investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, will be considered protocol deviations. These protocol deviations must also be reported to the institution's EC per their policy.

All protocol deviations will be recorded on the *Protocol Deviation Case Report Form* and reported to the study monitor as soon as possible.

14 STUDY COMPLETION

Subjects exit the study after completion of the 12-month follow-up visit.
For each enrolled subject, study staff personnel will complete a *Study Exit Case Report Form*, on which the Investigator certifies that the Medical Record and Case Report Forms are complete and accurate. If a subject is terminated from the study by the investigator or Venclose, or the subject withdraws consent and therefore withdraws from the study, the circumstances of termination or withdrawal are recorded on the *Study Exit Case Report Form*.

The Master Enrollment Log and the Screening and Enrollment Log are updated to indicate that the subject has completed the study, withdrawn from the study or has been terminated from the study.

15 DATA ANALYSIS

Subject demographics will be reported using descriptive measures including count, percentage, mode, median or mean as appropriate for the level of measurement. Clinical outcomes and visit assessment data will be presented with frequency distributions and cross-tabulations with selected demographics or other study variables.

Endpoint analyses of CEAP classifications and VCSS scores will be performed on a per-subject and/or per-limb basis for the 3-day, 3-, 6- and 12-month follow-up visits. Descriptive analyses of when desired outcomes were achieved will be calculated with sub-

group comparisons as appropriate. Estimation methods may be used to report effect size along with confidence intervals for sub-group comparisons.

Any adjunctive procedures, adverse events or protocol deviations will be described and reported as required.

If a subject has had treatment and subsequently withdraws consent or is terminated/lost-to-follow-up, data gathered as part of the study protocol up to the date of consent withdrawal or termination may be utilized in the data analysis. The Informed Consent document makes clear to the subject that non-identifiable health data gathered as part of study activities before the date of consent withdrawal or termination may be utilized in the manner and with the protections described in the Consent document.

16 USE OF STUDY DATA

The data and conclusions derived from the PMCF study will be used to provide further clinical evidence for the clinical evaluation process. This may result in the need to reassess whether the device continues to comply with the Essential Requirements. Such assessment may result in corrective or preventive actions (e.g., changes to the labeling/instructions for use, changes to manufacturing processes, changes to the device design, or public health notifications).

17 MONITORING

Venclose or its designee will monitor the day-to-day activities of this study. Monitors will also periodically inspect the relevant study records, either remotely or in-person, to assure that the study is being conducted in accordance with the protocol and applicable regulations. Focused attention will be given to ensuring written informed consent is obtained prior to study procedures, verification of study data with source documentation, confirmation of accurate, complete, and legible completed Case Report Forms, and device accountability.

18 REGULATORY CONSIDERATIONS

The study protocol (and any amendments) will be reviewed and approved by the ethics committee responsible for research oversight conducted at the participating study site, and all subjects will be required to provide written informed consent prior to study participation. This PMCF study will be registered at ClinicalTrials.gov and on the German Clinical Trials Register (DRKS) website (www.drks.de).

All investigators are experts in their field, with the device, and with the disease condition, as evidenced by CV, medical license, device training certificate, publications, and participation in previous research studies. This documentation will be provided to the ethics committee (EC) as part of the EC submission.

19 RECORDS

The PMCF study site will maintain a Regulatory & Study Operations Binder, the contents of which contain:

- An EC-approved Clinical Protocol (and amendments, if applicable),
- Protocol Agreement Page signed by the Investigator(s) and Sponsor (initial Clinical Protocol and any amendments, if applicable),
- The EC-approved Informed Consent Form
- EC approval letter(s) and correspondence
- Regulatory (Notified Body) correspondence
- Signed/dated Curriculum Vitae of each participating clinical site personnel
- A copy of current medical license for treating physicians
- Study Personnel Signature and Delegated Responsibility Log
- Training Logs
- Signed Investigator Agreement by the Principal Investigator
- Signed Financial Disclosure Form by the Principal Investigator and Sub-Investigator(s)
- Sponsor Insurance
- Correspondence file
- Screening and Enrollment Log
- Instructions for Use (IFU) for the Venclose EVSRF catheter and digiRF User Manual for the generator
- Adverse Events
- Protocol Deviations
- Notes-to-File
- Device Usage Log (to record subject ID, Venclose catheter lot number, and date used)
- Site Visit Log

The PMCF study site will maintain a study record (*i.e.,* research chart and/or medical record) for each enrolled subject for ten (10) years after the study is complete or terminated. The records will include a section for source documentation (e.g., medical and visit notes, duplex ultrasound reports), signed consent form, adverse events, and the required study Case Report Forms.

20 PROGRESS REPORTS AND INTERIM REPORTING

A final PMCF study report with conclusions relating back to the original objective(s) will be prepared and submitted to the Notified Body upon completion of the PMCF study, unless (as described in MEDDEV 2.12-2 rev 2, section 8) the Notified Body specifies that data from the PMCF study should be transmitted between scheduled assessment activities, or in cases where safety and performance information about the device is obtained during

the study which has the potential to negatively alter the benefit/risk profile of the device (Section 4).

Data gathered by the manufacturer from this PMCF study, whether favourable or unfavourable, will be used to actively update the risk management system for the Venclose System as new clinical safety and performance information about the device is obtained during its use. Analysis and review of this PMCF study data is part of the risk management process and is performed by Venclose on a routine basis via established processes and procedures for periodic management/product reviews and periodic risk/benefit re-analysis.

APPENDIX 1 - List of Potential Adverse Events

Based on the overall experience reported in the medical literature with endovenous thermal ablation by radiofrequency or laser, the following potential adverse events are provided as a guide:

1. Reaction to Local Anesthesia:

   Some people may have hypersensitivity or allergic reaction to certain types of local anesthesia. Prescreening the subject with a small amount of anesthesia can be performed. Venclose defers to physician judgment in selecting the appropriate agent and amount.

2. Deep Vein Thrombosis or Pulmonary Embolism:

   Potential for deep vein thrombosis (DVT) exists, usually less than 1 in 100 treated limbs. If a DVT blood clot breaks loose it can travel to the lung and cause pulmonary embolism (PE), usually less than 1 in 10,000 limbs.

3. Allergy to Product Component:

   The catheter has undergone biocompatibility testing to ensure safety of the components. Some people may have a hypersensitivity or allergic reaction to one or more of the components.

4. Perforation of the Saphenous Vein:

   The saphenous vein may be perforated during advancement of the catheter. Minimal mechanical injury to the soft tissue and hematoma may result.

5. Thermal Skin Injury:

   A burn is the partial or complete destruction of skin caused by some form of energy, usually thermal energy.

6. Skin Discoloration or Pigmentation:

   Blood degradation in the soft tissues may result in skin discoloration. The majority of these skin changes resolve spontaneously over several months to a year. Some discoloration may be permanent.

7. Infection:

   There is always a small chance of infection with any surgical procedure, however, the catheter is sterilized and is meant for one-time use. Aseptic (sterile) technique will be used during the procedure.

8. Neurological Injury:

   Motor nerves that could cause partial paralysis are typically avoided in endovenous thermal ablation procedures, and reports of such paralysis are extremely rare at less than 1 in 1,000,000 limbs.

9. Parasthesia:

   Parasthesia is defined as abnormal physical sensations such as numbness, prickling or tingling. This usually goes away within a few months, but can be permanent.

10. Superficial Venous Thrombophlebitis:

    Superficial venous thrombophlebitis may appear within 1- 3 weeks after the ablation procedure as a tender red firm spot along the skin. A great degree and length of compression may help to decrease the incidence of phlebitis.

11. Pain:

    There is a potential for post-treatment soreness for 1 or 2 weeks after treatment. Soreness may result from thrombosed or inflamed vessels. Other sources of pain include, but are not limited to compression-related problems, nerve injury, and pain at the access site.

12. Edema:

    Endovenous thermal ablation can correct the blood flow condition that can cause fluid swelling (edema), but it is possible for swelling of the treated area to be caused by changes in the pressure inside versus outside the vein or changes in vein wall fluid transport. Edema may also occur if compression is not applied gradually. Edema is usually self-limited and requires no specific therapy.

13. Compression-related Problems:

    Blisters may occur with the use of any tape on the skin. Occlusion of any hairy area can promote the development of folliculitis. Folliculitis is more likely to occur in the summer months or when patients are active and perspire under the dressing.

14. Ecchymosis:

    Defined as discoloration (bruising) of an area of the skin resulting from trauma to the underlying blood vessels.

15. Hematoma:

    Defined as a mass of clotted or coagulated blood. It differs from a simple bruise or contusion because the area is swollen, raised, or painful.

16. Erythema:

    Redness of skin along vein track that results from vascular irritation or capillary congestion in response to irritation; may be a precursor to phlebitis.