AngioDynamics, Inc.
26 Forest Street
Marlborough, MA 01752

A Prospective Safety and Effectiveness Study: VenaCure Endovenous Laser Treatment (EVLT) 400 µm Fiber Procedure Kit for Treatment of Incompetent Perforator Veins

CIP Number: PV-VC300

Version: 1.3

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SeCure STUDY

PROSPECTIVE SAFETY AND EFFECTIVENESS STUDY:

Treating Incompetent Perforator Veins with VenaCure EVLT 400 µm Laser Fiber

SYNOPSIS

SPONSOR:	AngioDynamics, Inc. 26 Forest St Marlborough, MA 01752 USA
SPONSOR CONTACT:	Kate Pietrovito Director, Medical Affairs and Clinical Operations P: 508-658-7806 kpietrovito@angiodynamics.com
INVESTIGATIONAL DEVICE:	VenaCure EVLT 400 Micron (µm) Fiber Procedure Kit
CIP TITLE:	A Prospective **S**afety and **E**ffectiveness Study: Vena**Cure** Endovenous Laser Treatment (EVLT) 400 µm Fiber Procedure Kit for Treatment of Incompetent Perforator Veins
CIP NUMBER:	PV-VC300 Version 1.2
PRIMARY OBJECTIVE:	The primary objective of this study is to evaluate the safety and effectiveness of the VenaCure EVLT 400 µm Fiber Procedure Kit when used to treat Incompetent Perforator Veins (IPVs). The 10 day (± 3 days) acute primary ablation success rate associated with the VenaCure EVLT 400 µm Fiber Procedure Kit will be compared to an IPV ablation success rate performance goal (PG) of 70% (based on published experience with endovascular radiofrequency ablation).
SECONDARY OBJECTIVES:	The secondary objectives of this study are to investigate post-procedural clinical outcomes associated with safety and effectiveness as evaluated/measured through the following: • Procedural technical success rate • 1, 3, 6, 9, and 12 month primary ablation closure rates • Primary assisted ablation rates • Secondary (retreatment) ablation rates • Changes in Venous Clinical Severity Score (rVCSS) • Changes in clinical, etiologic, anatomic, and pathophysiologic (CEAP) symptoms • Changes in Quality of Life from Baseline QoL (VEINES QoL) • Pain assessment as related to the patient's venous disease measured by the Visual Analog Scale (VAS) • Ulcer Healing (when applicable) • Incidence of procedure related adverse events (AEs)

DESIGN: This is a single-arm, prospective, multi-center, non-blinded clinical trial. Study data will be summarized and submitted to FDA in a premarket notification once all treated subjects have completed the **3-Month** visit. Longer-term follow-up is being performed for publication purposes.

STUDY POPULATION: Patients diagnosed with Incompetent Perforators Veins (IPVs) and meeting all inclusion and none of the exclusion criteria will be eligible for this study. Diagnosis and definition of perforating vein insufficiency will be consistent with the SVS/AVF Clinical Practice Guidelines for the Care of Patients with Varicose Veins and Associated Chronic Venous Disease (Gloviczki, et al, 2011). A perforator will be considered to be incompetent when outward flow is >0.5 sec in duration immediately after manual release of manual compression. IPVs that measure ≥3.5mm (measured at the level of the fascia) located superior to the foot and distal ankle will be eligible for treatment. Only one limb per patient may be treated in this study, although, multiple IPVs within the study limb may be treated.

SAMPLE SIZE: For purposes of assessing safety and effectiveness, a minimum of 86 patients and a minimum of 119 IPVs will be treated and included in the primary effectiveness endpoint. In addition, up to 3 lead-in cases will be allowed per Investigator. The maximum number of IPVs allowed to be treated under this CIP will be 182, which accounts for a 15% possible drop-out rate and 3 lead-in cases across 7 sites assuming 2 investigators per site. Patients will be treated until the minimum number of IPV's required for primary endpoint analysis have been reached. Once the minimum number of patients/IPV's has been reached, patients that have started the screening process can still be treated under this protocol.

PATIENT SCHEDULE:

SCREENING: Patients that appear to meet the eligibility criteria will be consented for participation in the trial. Following consent, patients will be screened to confirm that they meet all eligibility criteria. Screening will include a complete medical and surgical history assessment complemented by duplex ultrasonography (DUS) scanning of the entire study limb.

BASELINE: Following Screening, all patients will undergo evaluation and documentation of Baseline assessments including a full physical examination and vital signs measurement, pain assessment as related to the patient's venous disease, quality of life assessment, and ulcer measurement(s) when applicable. Following completion of Baseline assessments, patients will be scheduled for the study procedure.

PROCEDURE: The study procedure will be conducted according to the Directions for Use (DFU) included with the VenaCure EVLT 400 µm Fiber Procedure Kit. Patients may only have one limb treated in this study; however, multiple IPVs in the study limb may be treated. All IPVs treated will be counted towards the primary endpoint, with the exception of lead-in cases. Concomitant venous procedures will be prohibited to avoid confounding results.

FOLLOW-UP: Following the study procedure, patients will be clinically evaluated between 7 and 13 days post-procedure for the primary effectiveness endpoint and followed for a minimum of **3-months** for the regulatory analysis. In addition, patients will be evaluated 6, 9, and 12 months post-procedure to collect longer-term outcome data for publication.

STATISTICS AND ASSESSMENTS:

STATISTICAL METHODS: Standard statistical methods will be employed to analyze all data. All data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, including counts, mean, median, standard deviation (SD), minimum and maximum. Where appropriate, 95% two-sided confidence intervals for the means will be presented. Categorical variables will be summarized by frequencies and percentages. Unless explicitly stated otherwise, percentages will utilize a denominator corresponding to the number of unique patients.

SAFETY ASSESSMENTS: Procedure related adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), serious adverse device effects (SADE), and unanticipated adverse device effects (UADE) will be followed. Device malfunctions will be reported by the investigator and reviewed by the Sponsor in compliance with applicable regulations

PRIMARY ENDPOINT EFFECTIVENESS ASSESSMENT: The primary effectiveness endpoint is “Acute Primary Ablation Success” defined as complete lack of flow or IPV disappearance in the entire treated segment. Success will be measured via DUS imaging performed 10 days (± 3 days) post procedure. Primary ablation success must be measured by a physician other than the physician that performed the study procedure.

SECONDARY ENDPOINT TECHNICAL SUCCESS ASSESSMENT: Technical Success, defined as successful access and entry into the IPV to be ablated and the ability to deliver the intended laser energy, will be evaluated as a secondary endpoint for inclusion in device labeling.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ADE	Adverse Device Effect
AE	Adverse Event
AVF	American Venous Forum
CCC	Complaint Call Center
CFR	Code of Federal Regulations
CEAP	Clinical, Etiologic, Anatomic, and Pathophysiologic
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CTMF	Clinical Trial Master Files
CV	Curricula Vitae
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
DUS	Duplex Ultrasonography
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EVLA	Endovenous Laser Ablation
EVRF	Endovascular Radiofrequency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSV	Great Saphenous Vein
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IPV	Incompetent Perforator Veins
IR	Interventional Radiologist
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRU	Medical Resource Utilization
NCS	Not Clinically Significant
OR	Operating Room
PAPS	Percutaneous ablation of perforators
PE	Pulmonary Embolism

Abbreviation	Meaning
PG	Performance Goal
PI	Principal Investigator
PSI	Pounds per Square Inch
PCIP	Per Clinical Investigation Plan
PT	Preferred Term
RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEPS	Subfascial Endoscopic Perforator
SIR	Society of Interventional Radiology
SVS/AVF	Society of Vascular Surgery/American Venous Forum
SVT	Supraventricular tachycardia
TEAE	Treatment Emergent Adverse Event
UADE	Unanticipated Adverse Device Effects
US	Ultrasound
rVCSS	Revised Venous Clinical Severity Score
VEINES	Venous Insufficiency Epidemiological and Economic Study
WHO DDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION AND RATIONALE

Varicose veins affect up to 25% of men and 40% of women in the United States. While many people seek treatment for varicose veins because they are unsightly, many also experience symptoms such as aching pain, night cramps, fatigue, heaviness or restlessness. If left untreated, nearly 50% of patients with significant superficial venous insufficiency will eventually experience chronic venous insufficiency characterized by lower extremity swelling, eczema, pigmentation, hemorrhage and ulceration (Homans, 1917).

The importance of incompetent perforator veins (IPVs) in the pathogenesis of chronic venous insufficiency has been recognized since the early 1900s first by Homans and later by Linton (Homans, 1917 and Linton, 1938). It is theorized that as perforating veins become incompetent, blood refluxes into the superficial venous system, worsening venous hypertension which results in relevant clinical manifestations. In two successive landmark studies over 90 years ago, Homans emphasized the value of interrupting IPVs as a component of reducing superficial venous hypertension for treating venous ulcerations; 20 years later, Linton developed the open surgical approach to ligate IPVs through a subfascial medial calf incision. Outcomes from numerous observational studies with high ulcer recurrence rates combined with a significant morbidity led to a decreased use of the procedure in the 1980s.

To avoid the complications associated with open surgery, German surgeon GH Hauer (Hauer, 1985) employed endoscopic techniques to gain access to the subfascial space; this led to future development of a laparoscopic modality, known as subfascial endoscopic ligation of incompetent perforators (Gloviczki, et al, 1996). In spite of this, the risk of complication associated with the procedure prevented its universal adaptation.

Newer methods for treating venous disease, including, endovenous laser and radiofrequency ablation as well as foam sclerotherapy now have positive clinical evidence available and have gained widespread support (Coleridge-Smith, 2009). Endovenous treatments are less invasive than conventional surgery, which may be advantageous in more elderly patients who are affected by leg ulcers (Coleridge-Smith, 2009).

Recent clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum suggest treatment of pathologic perforating veins (outward flow duration ≥500 ms, vein diameter ≥3.5 mm) located underneath healed or active ulcers (CEAP class C5-C6; GRADE 2B) (Gloviczki, et. al., 2011).

This study seeks to establish the safety and effectiveness of the VenaCure EVLT 400 µm Fiber Procedure Kit when used to ablate IPVs. A 2013 study Abdul-Haqq and colleagues demonstrated that patients who have IPVs treated along with the Great Saphenous Vein (GSV) fare better in a retrospective review of 95 C6 patients. Ulcer healing was accomplished to a significantly greater degree using Endovenous Laser Ablation (EVLA) of the GSV and IPV compared to GSV ablation alone.

A 2012 study of EVLA treatment of varicose perforating veins with 1470 nm diode found the procedure effective and safe. After one month, 95.6% of the treated veins were still occluded (67/69). During follow-up, researchers did not diagnose any DVT, PE or SVT in the area related to the treated perforating vein (Zerweck, et. al., 2012).

There are much existing data highlighting the safety and effectiveness of perforator vein ablation, as well as the important contributions of perforator vein treatment to reducing disease recurrence and improvements in venous ulcer healing.

There is a wide basis of literature establishing the effectiveness and safety of thermal ablation of perforator veins, as well as a sound argument within the historical literature for improving overall treatment effectiveness with ablation of IPVs. The concept of treating perforator veins is not new; liquid sclerotherapy was used to treat IPVs as early as 1974 (Hobbs, 1974). The term PAPS (percutaneous ablation of perforators) was coined in 2005 and collectively refers to IPV treatment (comprising laser, RF, and sclerotherapy).

While historical literature based on older interventions found questionable benefit from perforator vein treatment alone, recent data demonstrate incompetent perforator veins contribute to Chronic Venous Insufficiency (CVI) and indicate treatment of IPVs is beneficial to overall Chronic Venous Disease (CVD) improvement. A cross-sectional study demonstrated the contributions of IPVs to CVI, finding that the extent of venous insufficiency "correlated with an increase in the number and the diameter of perforators" and that clinical status worsened perforator insufficiency (Krnic, et. al., 2005). In an ultrasound study, perforator vein insufficiency was "common in limbs with complications" (Myers, et. al., 1995). Iafrati and colleagues (2002) demonstrated that aggressive treatment of both superficial and perforating vein reflux resulted in rapid ulcer healing and low 5-year recurrence rates in patients with C5 and C6 disease.

With more aggressive disease (CEAP class C5-C6), recent literature has shown that treating the superficial venous system alone is not enough. Among 64 limbs with pre-op IPVs, IPVs persist in 40% of limbs 2 years after superficial venous surgery alone (Blomgren, et. al., 2005). Rueda and colleagues 2013 article echoed this, their retrospective cohort analysis of 64 patients (C5 and C6) who underwent adjunctive IPV treatment from a prospective venous database collected over 6 years (64% Subfascial Endoscopic Perforator Surgery [SEPS], 36% Radiofrequency Ablation [RFA]-IPV). Over a mean patient follow-up of 37 months, 88% of SEPS-treated patients and 100% of RFA-IPV patients with C6 disease went on to completely heal their venous ulcers. The authors concluded that they support an "aggressive approach to patients with C5/C6 disease" which would include treatment of incompetent perforating veins when appropriate.

In a prospective evaluation, Oscar and colleagues evaluated outcomes following EVLA of 302 perforator veins predominantly in the internal part of the leg. Acute closure success was achieved for 97.6% of treated perforators and with recurrence observed in 15 perforators within 6 months (93% closure rate). The authors reported improved cosmetic

and symptomatic improvement. There was no incidence of deep venous thrombosis, no infections and no skin necrosis during the follow-up period.

Given the basis of the published literature, AngioDynamics believes there is a clinical basis for the proposed study of the VenaCure EVLT 400 µm Fiber Procedure Kit for the treatment of incompetent perforator vein ablation.

2 INVESTIGATIONAL DEVICE

2.1 VENACURE EVLT 400 µM FIBER PROCEDURE KIT

The VenaCure EVLT 400 µm Fiber Procedure Kit contains a 400 µm Optical Fiber with SiteMark and compression clamp, 21G Venous Access Needle, a 10cm x 4F Introducer Sheath and a .018 inch guidewire. All components contained in the Procedure Kit are single use, disposable devices, for use with a laser in the treatment of varicose veins.

2.2 CURRENT INDICATIONS

The VenaCure EVLT 400 µm Fiber Procedure Kit is indicated for use in the treatment of varicose veins and varicosities associated with superficial vein reflux of the Great Saphenous vein, and with veins in the lower limbs with superficial reflux.

3 RISKS AND BENEFITS OF EVLT

Potential complications associated with EVLT are listed below;

- Vessel Perforation
- Thrombosis
- Pulmonary Embolism
- Deep Venous Thrombosis
- Phlebitis
- Hematoma
- Infection
- Skin Pigmentation Alteration
- Neovascularization
- Paresthesia due to thermal damage of adjacent sensory nerves
- Complications associated with anesthetic tumescence
- Non-Target Irradiation
- Hemorrhage
- Necrosis
- DEHP Exposure
- Skin Burns and Pain
- Dysesthesia

The risks described above will be minimized via the selection of physicians that have experience performing interventional vascular procedures, specifically with the use of laser ablation. Patients will be selected and enrolled using clearly defined inclusion and exclusion criteria to ensure that patients with conditions and/or comorbidities that put them at a higher risk for procedural complications are excluded. Patient treatment and follow-up will be performed consistent with current medical best practices. Furthermore, risks will be minimized by requiring participants to report for routine clinic visits allowing for prospective diagnosis of potential procedure related complications. Participants will be given instructions on whom to contact in the event that they have questions regarding their medical care or experience health related problems.

Appropriate therapeutic intervention following medical best-practices will be used in the event of medical complications.

4 OBJECTIVES OF THE CLINICAL INVESTIGATION

4.1 STUDY OBJECTIVES

4.1.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the VenaCure EVLT 400 µm Fiber Procedure Kit when used to treat Incompetent Perforator Veins (IPVs). The 10 day (± 3 days) acute primary ablation success rate associated with the VenaCure EVLT 400 µm Fiber Procedure Kit will be compared to an IPV ablation success rate performance goal (PG) of 70% (based on published experience with endovascular radiofrequency ablation).

4.1.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to investigate post-procedural clinical outcomes associated with safety and effectiveness as evaluated/measured through the following:

- Procedural technical success rate
- 1, 3, 6, 9, and 12 month primary ablation closure rates
- Primary assisted ablation rates
- Secondary (retreatment) ablation rates
- Changes in Venous Clinical Severity Score (rVCSS)
- Changes in clinical, etiologic, anatomic, and pathophysiologic (CEAP) symptoms
- Changes in quality of life from Baseline QoL (VEINES QoL)
- Pain assessment as related to the patient's venous disease measured by the Visual Analog Scale (VAS)
- Ulcer Healing (when applicable)
- Incidence of procedure related adverse events (AEs)

5 DESIGN OF THE CLINICAL INVESTIGATION

5.1 PATIENTS

5.1.1 INCLUSION CRITERIA

Patients are required to fulfill all the following criteria to be included in the study:

1. Is ≥ 18 years of age
2. IPV(s) to be treated have an outward flow duration of ≥ 0.5 sec immediately after manual release of manual compression
3. IPV(s) to be treated have a diameter of $\geq$ 3.5 mm (measured at the level of the fascia) located superior to foot and distal ankle
4. Has been diagnosed with refractory symptomatic disease (CEAP Class 4b to Class 6) attributable to the IPV to be treated
5. Has palpable pedal pulses in the study limb
6. Any pathologic superficial saphenous veins have been previously eliminated and were done so at least more than 30 days prior to the study procedure
7. Is able to ambulate
8. Is able to comprehend and have signed the Informed Consent Form (ICF) to participate in the study
9. Is willing and able to comply with the CIP and follow-up schedule

5.1.2 EXCLUSION CRITERIA

Patients will be excluded from participation in the study if they meet any of the following:

1. Has venous insufficiency secondary to venous obstruction proximal to the intended treatment site
2. Has thrombus in the vein segment to be treated
3. Has known peripheral arterial disease
4. Has a BMI calculation (BMI = W / H^2) $\geq$40kg/m^2
5. Is undergoing active anticoagulant therapy for DVT or other conditions (e.g., warfarin, Q10 inhibitors or low molecular weight heparin) or has a history of DVT within the last 6 months or hypercoagulable state.
6. Has had prior venous procedures in the study limb within the last 30 days (including but not limited to, thrombolysis / thrombectomy / stenting / ablation / phlebectomy / sclerotherapy)
7. Has undergone or is expected to undergo any major surgery within 30 days prior to or within 90 days following the study procedure
8. Has a condition, judged by the treating physician, that may jeopardize the patient's well-being and/or confound the results or the soundness of the study
9. Is pregnant or lactating at the time of the study procedure or is intending on becoming pregnant within 90 days following the study procedure
10. Is participating in another clinical study that is contraindicative to the treatment or outcomes of this investigation

5.1.3 INFORMED CONSENT

Patients that appear to meet the eligibility criteria will be consented for participation in the trial. The patient will be asked to sign an Informed Consent Form (ICF) prior to performance of any study-specific procedures. The ICF must have prior approval from each respective Institutional Review Board (IRB). Failure to provide informed consent renders the patient ineligible for the study. A progress note indicating that the patient was consented for participation in the study should be included in the patient's medical record.

Participants enrolled at sites in the United States must also sign a Health Insurance Portability and Accountability Act (HIPAA) release of protected health information.

5.1.4 CRITERIA AND PROCEDURES FOR WITHDRAWAL OR DISCONTINUATION

Any patient may withdraw his or her consent at any time for any reason during the study. The investigator will also withdraw a patient if the Sponsor or local regulatory agency (e.g., FDA) terminates the study.

The investigator may withdraw a patient from the study for any of the following reasons:

- The investigator determines that it is not in the patient's best interest to continue in the study, or
- The sponsor or investigator terminates the study, or
- The patient requests to be discontinued from the study.

If a patient is withdrawn or discontinued from the study for any reason, the reason(s) for withdrawal or discontinuation will be recorded on the eCRF.

5.1.5 POINT OF ENROLLMENT

A patient is considered enrolled at the time of informed consent.

5.1.6 NUMBER OF PATIENTS REQUIRED

For purposes of assessing safety and effectiveness, a minimum of 86 patients and a minimum of 119 IPVs will be treated and included in the primary effectiveness endpoint analysis. In addition, up to 3 lead-in cases will be allowed per Investigator. The maximum number of patients allowed to be treated under this CIP will be 182, which accounts for a 15% possible drop-out rate and 3 lead-in cases across 7 sites assuming 2 investigators per site. Patients will be treated until the minimum number of IPV's required for primary endpoint analysis have been reached. Patients that are in the screening process when the minimum number of IPVs required has been reached will be treated.

5.2 SCREENING VISIT

Patients that appear to meet the eligibility criteria will be consented for participation. All patients must complete the Informed Consent process prior to starting any Screening assessments. A Screening visit will be conducted for all patients. All Screening assessments must be performed on or before the date of Baseline assessments and no more than 14 days prior to the date of the study procedure (except where noted below). Screening

assessments are not required to be performed on the same day. A full schedule of events can be found in Appendix 1.

Diagnosis and definition of perforating vein insufficiency will be consistent with the SVS/AVF Clinical Practice Guidelines for the Care of Patients with Varicose Veins and Associated Chronic Venous Disease (Gloviczki, et al, 2011). A perforator will be considered to be incompetent when outward flow is >0.5 sec in duration immediately after manual release of manual compression. IPVs that measure ≥3.5mm (measured at the level of the fascia) located superior to the foot and distal ankle will be eligible for treatment. A Patient that does not meet the eligibility criteria will be considered a Screen Failure. Reason(s) for Screen Failure will be documented in the eCRF.

The following Screening assessments will be performed and documented in the eCRF:

- Demographics
- Inclusion/exclusion criteria assessment
- Medical and surgical history, including current medical conditions
- Medications taken, current and prior 14 days
- DUS of entire study limb with assessment of superficial and deep system, including diameter (mm) of each perforator and duration of reflux (seconds) according to DUS Screening Protocol
- Venous Mapping, including anatomic location of each IPV to be treated (Appendix 4)
- Ipsilateral and contralateral standardized limb girth measurement
- CEAP Classification (Appendix 5)
- rVCSS Classification (Appendix 6)

5.3 BASELINE VISIT

Patients must have completed all Screening assessments prior to beginning any Baseline assessments, although both Screening and Baseline may occur on the same day. All Baseline assessments must be performed no more than 14 days prior to the date of the study procedure. Baseline assessments are not required to be performed on the same day. The following Baseline assessments will be performed and documented in the eCRF:

- Vital Signs (height, weight, blood pressure, pulse)
- Pain assessment as related to patients venous disease measured by the Visual Analog Scale (Appendix 7)
- Physical Examination
- Quality of Life score as measured by the VEINES QoL (Appendix 1)
- Ulcer Measurement (if applicable) (Appendix 9)

5.4 PROCEDURE

5.4.1 PROCEDURE ASSESSMENTS

All Screening and Baseline assessments must be completed prior to performing the study procedure, although Screening and Baseline may occur on the same day as the study procedure. Pre-procedure, Procedure and Post-procedure details will be captured.

5.4.1.1 Pre-procedure

The following pre-procedure assessments will be performed and documented in the eCRF:

- Confirmation of negative pregnancy test within 2 days of the study procedure (for women of child-bearing potential) or per IRB policy*
- Review of new or recurring medical conditions not documented during Screening and/or Baseline*
- Review of new medications or changes to current medications since Screening and/or Baseline*
- Vital Signs (weight, blood pressure, pulse)*
- Physical Examination (Abbreviated)*

*If the Screening/Baseline visit occurs on the same day as the study procedure, these assessments do not need to be repeated.

5.4.1.2 Procedure

Only one limb can be treated and included in this study; however, multiple IPVs within the study limb may be treated. All IPV's treated will be followed according to this CIP schedule.

The study procedure should be followed according to the VenaCure EVLT 400 µm Fiber Procedure KIT Directions for Use (DFU) included with the product.

The following procedure details will be collected and documented in the eCRF:

- Method and location of vein access for each IPV to be treated
- Anatomic location of each IPV to be treated
- Laser Details: Wavelength, Settings, etc.
- Energy Delivery (watts, duration, etc.)
- Total procedure duration
- Anesthesia details
- Concomitant Procedure(s)*
- Adverse event assessment

*Concomitant procedures are not allowed under this CIP and must be documented as a protocol deviation.

5.4.1.3 Post-procedure

The following post-procedure assessments will be performed and documented in the eCRF:

- Vital Signs (blood pressure, pulse)
- Adverse event assessment
- Post procedure medications
- Additional interventions performed

Following the study procedure, the treated limb should be dressed and wrapped per standard practice assuring direct pressure over the treated vein(s). The use of graduated compression garments is recommended. Immediately following the study procedure, the patient should ambulate for 15 – 20 minutes. Instruct the patient to avoid hot baths and vigorous activity for 7 days following the study procedure.

5.5 FOLLOW-UP VISITS

5.5.1 10 DAY FOLLOW-UP (DAY 10 ± 3 DAYS)

All patients will be seen 10 (+/- 3) days following the study procedure. The following assessments will be performed and documented in the eCRF:

- DUS for the primary effectiveness endpoint
    - DUS findings must be read and interpreted by a physician that has been trained according to the standardized DUS Post Procedure protocol
    - DUS findings must be read and interpreted by an independent physician that did not perform the study procedure
- Vital Signs (weight, blood pressure, pulse)
- Physical Examination (Abbreviated)
- Review of new medications or changes to current medications
- Interventions and/or procedures performed since the study procedure
- Ipsilateral and contralateral standardized limb girth measurement
- CEAP Classification
- rVCSS Classification
- Adverse event assessment

5.5.2 1, 3, 6, 9 AND 12 MONTH FOLLOW-UP

All patients will be seen at 1, 3, 6, 9 and 12 month post procedure. The following windows are acceptable for follow up visits:

- 1 month follow-up must be performed within 30 – 45 days post procedure
- 3 month follow-up must be performed within 90 (+/- 15) days post procedure
- 6 month follow-up must be performed within 180 (+/- 15) days post procedure
- 9 month follow-up must be performed within 270 (+/-15) days post-procedure
- 12 month follow-up must be performed within 365 (+/- 15) days post procedure

The following assessments will be performed at each follow-up visit and documented in the eCRF:

- DUS for evaluation of primary ablation, primary assisted ablation and secondary (retreatment) ablation closure according to standardized DUS Post Procedure Protocol
- Vital Signs (weight, blood pressure, pulse)
- Physical Examination (Abbreviated)
- Review of new medications or changes to current medications
- Interventions and/or procedures performed since the study procedure
- Ipsilateral and contralateral standardized limb girth measurement
- Ulcer Measurement (if applicable) (Appendix 9)
- CEAP Classification (Appendix 5)
- rVCSS Classification (Appendix 6)
- Pain assessment as related to the patient's venous disease measured by the Visual Analog Scale (Appendix 7)
- Quality of Life score as measured by the VEINES QoL (Appendix 8)
- Adverse Event(s) Assessment
- Study Exit (Only at 1 Year Follow-up or Early Withdrawal)

5.6 PRIMARY ASSISTED ABLATION

Any primary assisted ablation(s) will be documented in the eCRF. Primary assisted ablation is defined as successful retreatment of anatomic recanalization before clinical failure has occurred.

5.7 SECONDARY (RETREATMENT) ABLATION

Any secondary (retreatment) ablation(s) will be documented in the eCRF. Secondary (retreatment) ablation is defined as successful retreatment of patients with anatomic and clinical failure.

5.8 UNSCHEDULED VISITS

Unscheduled visits, as a result of the study procedure, may occur as deemed necessary by the treating Physician or the Patient. The following assessments should be performed and documented in the eCRF:

- Vital Signs
- Physical Examination (Abbreviated)
- Adverse Event Assessment
- Review of new medications or changes to current medications
- Interventions and/or procedures performed since the study procedure

5.9 LOST TO FOLLOW-UP PREVENTION

Follow-up visit expectations will be discussed with each patient before they are consented into the study. Prior to each follow-up visit, patients will be contacted via telephone to confirm the scheduled visit date and time. If a patient does not appear for their scheduled visit, a minimum of 2 telephone contact attempts will be made. If contact is not made via telephone after at least 2 attempts, a certified letter will be issued and sent to the patient's residence. All attempts to contact the patient will be documented in the eCRF. If patient contact was still unsuccessful after sending the certified letter, then the date the certified letter was mailed will be used as the date of study exit.

5.10 DISCONTINUATION / END OF STUDY

Patients will not be followed beyond 12 months except in the event that a procedure related AE or SAE extends beyond 12 months. Procedure related AEs/SAEs will be followed until resolved or stabilized. Once a patient completes their 12 month visit, they are considered to have completed the study. The patient's 12 month visit date will serve as the patient's date of study exit.

6 STATISTICAL CONSIDERATIONS

6.1 GENERAL CONSIDERATIONS

All data collected in this study will be documented using summary tables and patient data listings. Summary tables will be presented. Continuous variables will be summarized using descriptive statistics, including counts, mean, median, standard deviation (SD), minimum and maximum. Where appropriate, 95% two-sided confidence intervals for the means will be presented. Categorical variables will be summarized by frequencies and percentages. Unless explicitly stated otherwise, percentages will utilize a denominator corresponding to the number of unique patients.

A detailed Statistical Analysis Plan (SAP) will be developed and finalized prior to the locking of the database for this study.

6.2 DETERMINATION OF SAMPLE SIZE

In a review of the literature, the cumulative success rate observed for EVRF ablation is between 70.6% and 80.5% [95% CI]. In all studies, acute ablation success was based on follow-up duplex ultrasound scan.

Based on the lower 95% confidence interval for the cumulative success rate for EVRF ablation, A PG of 70% will be used for hypothesis testing. Assuming an EVLT primary ablation success rate of 80%, 119 IPVs must be treated in the study (sample size is based on an Exact test for a single proportion assuming a one-sided α of 0.05 and a power of 80%). For safety, it was determined that there is greater than an 80% chance to detect at least one medically significant adverse event if the true event rate is at least 2.2% with a sample size of 75 patients. Assuming a 15% drop-out rate, a minimum of 86 patients would be

treated to obtain the appropriate number of veins for the effectiveness endpoint and meet the minimum number of patients needed to detect at least one medically significant adverse event.

In addition, each investigator will be allowed to treat up to 3 patients as "lead-in" cases. Lead-in cases will be analyzed separately for safety and effectiveness and will not be included in any of the analysis populations.

Assuming an expected 15% drop-out rate and assuming 2 investigators across 7 sites performing 3 "lead-in" cases, the maximum number of veins that may be treated under this protocol is 182 as calculated using this formula:

182 veins = ((119 veins /0.85)) + (7 sites * 2 investigators * 3 lead-in cases)

6.3 BASELINE AND DEMOGRAPHICS CHARACTERISTICS

Descriptive statistics will be used to summarize the baseline and demographic characteristics as well as vessel, lesion and procedural characteristics. For continuous variables, the variables will be summarized using frequencies and percentages. 95% confidence intervals will be utilized as appropriate.

6.4 ANALYSIS POPULATIONS

The following analysis populations are planned for the study:

6.4.1 ITT POPULATION (INTENTION TO TREAT)

The ITT Population will consist of all enrolled patients where vein access was attempted and energy was delivered with the VenaCure EVLT 400 µm Fiber Procedure Kit. The ITT population will be used as the primary analysis for the effectiveness endpoints, secondary technical success endpoint and other clinical outcome data. Lead-in patients are not included in the ITT population.

6.4.2 PCIP POPULATION (PER-CLINICAL INVESTIGATION PLAN)

The Per-Clinical Investigation Plan (PCIP) population is a subset of the ITT population. Patients will be included in the PCIP population if they have had a technically successful procedure and completed the study without major CIP deviations. The PCIP population will be used as the secondary or supportive analysis for the effectiveness endpoints and other clinical outcome data. Lead-in patients are not included in the PCIP.

The following will be considered major CIP deviations:

- Major inclusion/exclusion criterion deviation
- Major procedural deviation
- Missing primary endpoint data (no US performed)
- Significant CIP non-compliance that may confound the incidence of adverse events

6.4.3 SAFETY POPULATION

The safety population will include all enrolled patients where vein access was attempted with the VenaCure EVLT 400 µm Fiber Procedure Kit. Lead-in patients are included in the safety population.

6.5 STUDY ENDPOINT ANALYSES

6.5.1 PRIMARY ENDPOINT EFFECTIVENESS ANALYSIS

The primary endpoint effectiveness analysis will be based on the 10 day follow-up visit (± 3 days) and will include the ITT and PCIP populations with the ITT population being of primary interest. Primary ablation success will be determined via DUS and must be measured by a physician other than the physician that performed the study procedure.

Primary ablation success will be compared to an objective Performance Goal (PG) of 70%. The PG has been established based on the acute closure success rate associated with EVRF published within the historical literature but also with input/concurrence of experienced endovascular interventionalists. The hypothesis of the study is as follows:

H_0: $P_{VenaCureEVLT} < 0.70$

H_A: $P_{VenaCureEVLT} \geq 0.70$

Where $P_{VenaCureEVLT}$ is the proportion of treated IPVs demonstrating acute primary ablation success.

The proportion of IPVs in the treatment group being classified as “Acute Primary Ablation Successes” will be compared to the performance goal of 70% using a one sample proportion test with a significance level of 0.05. In conjunction with the proportion test, a 95% one-sided lower confidence bound for the treatment success rate will be constructed.

6.5.2 SECONDARY TECHNICAL SUCCESS ANALYSIS

Assuming the primary endpoint has been met, the secondary analysis for labeling will be evaluated. The secondary endpoint technical success analysis will be based on procedural technical success defined as successful access and entry into the IPV to be ablated and the ability to deliver the intended laser energy and will include the ITT and PCIP populations. The hypothesis for the secondary technical success analysis is as follows:

H_0: $TS_{VenaCureEVLT} < 0.75$

H_A: $TS_{VenaCureEVLT} \geq 0.75$

Where $TS_{VenaCureEVLT}$ is the proportion of treated IPVs demonstrating technical success. For this analysis, IPVs will be summarized by count and percentage for technical success with the rate of technical successes compared to the performance goal of 75% using a one sample proportion test with a significance level of 0.05. In conjunction with the proportion test, a 95% one-sided lower confidence bound for the treatment success rate will be constructed. With a sample size of 119 IPVs, assuming a one one-sided α of 0.05 and a power of 80%, the null hypothesis will be rejected if $TS_{VenaCureEVLT}$ is equal to or greater than 85%.

6.5.3 ADDITIONAL TREATMENT OUTCOMES

6.5.3.1 Primary Ablation, Primary Assisted Ablation, and Secondary (retreatment) Ablation

Treated IPVs will be summarized by time-point, count and percentage for primary, primary assisted and secondary (retreatment) closure rates.

6.5.3.2 Change from Baseline in rVCSS

Descriptive statistics (i.e., N, mean, median, standard deviation, 25th percentile, 75th percentile, min, and max), will be presented and for the changes from baseline at each time point where collected. A signed-rank test will be performed to evaluate the change from baseline values at each time point to see if they are significantly different from their respective baseline values.

6.5.3.3 Change from Baseline in CEAP

Descriptive statistics (i.e., N, mean, median, standard deviation, 25th percentile, 75th percentile, min, and max), will be presented and for the changes from baseline at each time point where collected. A signed-rank test will be performed to evaluate the change from baseline values at each time point to see if they are significantly different from their respective baseline values.

6.5.3.4 Quality of Life Assessments

The VEINES-QOL/VEINES-SYM survey will be given to patients to assess their quality of life. Both the VEINES-QOL and VEINES-SYM scores will be computed for patients. Descriptive statistics (i.e., N, mean, median, standard deviation, 25th percentile, 75th percentile, min, and max), will be presented for these scores and for their changes from baseline at each time point where collected. A signed-rank test will be performed to evaluate the change from baseline values at each time point to see if they are significantly different from their respective baseline values.

6.5.3.5 Ulcer Healing

Patients will be summarized by count and percentage for ulcer healing. The denominator for this calculation will be the count of patients who had an ulcer.

6.5.4 SAFETY OUTCOMES

6.5.4.1 Evaluation of Procedure Related Adverse Events

Standard adverse event rate tables based on MedDRA will be created and presented. Tabulations include the following:

- Tables presenting adverse event rates by {body system X preferred term} overall
- Tables presenting adverse event rates by {body system X preferred term X strongest relationship to therapy} overall
- Tables presenting adverse event rates by {body system X preferred term X maximum severity} overall

Adverse events leading to death or to discontinuation from the study, serious adverse events, and UADEs will be listed separately.

6.5.4.2 Evaluation of Vital Signs

Descriptive statistics of vital signs will be calculated at each scheduled time point and will include the change from baseline (e.g., value at daily assessment minus value at baseline). The summary of descriptive statistics at each time point will be displayed by visit and the change from baseline within treatment group tested using the signed rank test.

6.5.4.3 Evaluation of Device Malfunctions

Device malfunctions will be tabulated and listing in a manner similar to methods described for the adverse events. Device malfunctions will not be coded but will be categorized into like events. Any device malfunction leading to an AE or to study termination will be listed separately.

6.6 MISSING DATA

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. While the primary endpoint is evaluated at 10 days, it is not anticipated that there will be much missing data. However, missing observations will be described in detail and evaluated for assessment of possible bias. It is assumed that data will be missing at random. However, to examine this assumption, an analysis will be performed to compare baseline characteristics and symptomatic status (at earlier time points) between those participants with missing data and those who completed the study. A sensitivity analysis of missing data will be performed. Methods of imputation such as:

1) “last observation carry forward (LOCF)”,
2) “missing-equals-failure”, and
3) multiple imputation methods (e.g., SAS PROC MI) will be considered for handling of missing data provided statistical assumptions of these methods are satisfied. In addition, a tipping point analysis could be performed for the primary study endpoint which will allow assessment of sensitivity without need for postulating any missing data mechanism. For this analysis, all possible combinations of missing data will be considered, and the point at which significance is no longer achieved will be identified. Missing data techniques will be described more fully in the Statistical Analysis Plan (SAP).

All data collected on safety or adverse events will be reported to the extent it is available, regardless of the active/withdrawn status of patients..

7 AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor. The CIP amendment(s) must be signed by the investigator and approved by the IRB before implementation. The CIP amendment(s) will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

Substantial changes will require approval from the Sponsor, FDA, and IRB prior to implementation.

8 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The investigator will not deviate from the CIP except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies the Sponsor must be notified within 2 working days of the incident. Periodic monitoring of CIP compliance will be performed for each site. The Sponsor has the right to suspend enrollment at sites deemed to have excessive CIP compliance issues.

All deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment must be appropriately documented and reported. Other CIP deviations to be considered include non-adherence to the CIP that results in a significant additional risk to the patient, or non-adherence to FDA regulations and/or ISO 14155.

The investigator must document and explain any CIP deviation in the patient's source documentation. CIP deviations should be reported to the IRB according to their requirements. Deviations will also be documented by the monitor during site visits and those observations will be reviewed with the investigator.

If the investigator believes that any exception to the CIP is justified for an individual patient or if the investigator has a question concerning a patient who may not meet an eligibility criterion, they should contact their Clinical Research Associate (CRA). The Sponsor will evaluate circumstances where the investigator deviates from the study CIP and will retain the right to remove either the investigator or the investigational site from the study.

9 DEVICE ACCOUNTABILITY

Investigators or qualified, trained designees will be responsible for maintaining device accountability from the time of receipt of product at the clinical site through use or return of product to AngioDynamics. All investigational devices must be accounted for using the Device Accountability Logs designed to keep track of investigational devices in this study. The investigator is responsible for maintaining accurate records of the three transactions key to material transfer in this study:

- Device received (Sponsor to investigator)
- Device used (investigator to patient)
- Device returned (investigator to Sponsor), or discarded

The necessary documents can be found in the Investigator Site File (ISF) binder.

The site monitor will verify accountability of the study devices during routine monitoring visits to the site.

Investigational devices must be stored according to the conditions set forth for the device on the label in a controlled, locked area. All device shipment records (packing lists, etc.) must be maintained at the site.

10 STATEMENTS OF COMPLIANCE

10.1 ROLE OF THE SPONSOR

As the study Sponsor of this clinical trial, AngioDynamics has the overall responsibility for the conduct of the study, including assurance that the study meets the requirements of the appropriate regulatory bodies. In this study, the Sponsor will have certain direct responsibilities and may delegate other responsibilities to the CRO.

10.2 ETHICAL CONDUCT OF THE STUDY

The investigator agrees that the study will be conducted according to the applicable FDA regulations (21CFR). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

10.3 INSTITUTIONAL REVIEW BOARD

Federal regulations and 21CFR require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to patient enrollment, a signed copy of the IRB approval letter must be submitted to AngioDynamics. In addition, the CIP, informed consent, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient and/or the patient's legal authorized representative, must be approved by the IRB. Documentation of all IRB approvals will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairperson or designee and must identify the IRB by name and address, the clinical CIP by title and/or CIP number, and the date approval was granted.

The Investigator is responsible for submitting and obtaining initial and continuing review of the trial at intervals not exceeding 1 year or as otherwise directed by the IRB. The investigator must supply the Sponsor or its designee written documentation of continued review of the study.

11 INFORMED CONSENT PROCESS

A written informed consent in compliance with Title 21 of the Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient prior to participating in the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent form (ICF) template will be provided by the Sponsor or designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent must be reviewed by the Sponsor prior to IRB submission. Once reviewed, the consent will be submitted by the investigator to their IRB for review and approval prior to the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient and/or patient's legal authorized representative will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal representative understands the implications of participating in the study, the patient/legal representative will be asked to give consent to participate in the study by signing the ICF.

The investigator shall provide a copy of the signed ICF to the patient/legal representative. The original form shall be maintained in the patient binder at the site.

ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND PROCEDURE-RELATED COMPLICATIONS

12.1 DEFINITIONS

12.1.1 ADVERSE EVENT

An adverse event (AE) is defined as any untoward medical occurrence in a patient. This definition does not imply a relationship between the adverse event and the study procedure.

12.1.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any event that:

- Leads to death
- Leads to serious deterioration in the health of a patient that:
  - results in a life threatening illness or injury
  - results in a permanent impairment of a body structure or a body function
  - requires in-patient hospitalization
  - results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function

12.1.3 ADVERSE DEVICE EFFECTS

An adverse device effect (ADE) is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in instructions for use or deployment of the device. This definition also includes any event that is a result of user error.

12.1.4 SERIOUS ADVERSE DEVICE EFFECTS

A serious adverse device effect (SADE) is defined as an ADE that results in any of the consequences characteristic of an SAE or that may lead to any of these consequences if suitable action is not taken or intervention is not made.

12.1.5 UNANTICIPATED ADVERSE DEVICE EFFECT

An unanticipated adverse device effect (UADE) is defined as any SADE on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death has not been 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 patients.

12.1.6 DEVICE COMPLAINTS

Should a problem be encountered with the study device at any time during the course of this trial, it should be reported to AngioDynamics following the usual complaint process, as well as documented in the eCRF if applicable

Device kit contents are supplied sterilized and should not be used if the sterile barrier is damaged. If damage is found, or any other issues with the device or kit components are identified, the following number should be called to report the issue:

Complaint Call Center (CCC)

Phone: 1-800-772-6446 (select option #2 for Customer Service)
E-mail: Complaints@angiodynamics.com

All device kits should be inspected prior to use to verify that no damage has occurred during shipping.

These complaints will be reported following 21 CFR Part 803.53.

12.1.6.1 Procedure-Related Complications-Event Severity

Complications will be classified using the Society of Interventional Radiology (SIR) classification system for grading minor or major complications (Kundu, et al, 2009):

Minor Complication:

- No therapy, no consequence
- Nominal therapy, no consequence; includes overnight admission for observation only

Major Complication:

- Require therapy, minor hospitalization (<48 hours)
- Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours)
- Permanent adverse sequelae
- Death

12.1.6.2 Recording Procedure-Related Complications

All procedure-related complications observed during the study procedure and during the course of follow-up, regardless of severity, will be recorded on the Adverse Event eCRF. To the extent possible, the event to be recorded and reported is the event diagnosis as opposed to event symptoms, e.g., thrombophlebitis vs swelling. Medical interventions administered to address procedure-related complications will be documented within the eCRF.

The Investigator shall notify the reviewing IRB of all major procedure-related complications occurring in the study according to the IRB's requirements for serious adverse event reporting.

Device failures or problems not associated with procedure-related complications will be documented separately on the Device Malfunction eCRF.

12.1.7 DEVICE MALFUNCTIONS

All device malfunctions involving the study device will be documented on the Device Malfunction eCRF and reported to AngioDynamics within 24 hours. The product involved should be retained if feasible. AngioDynamics will advise whether the device(s) should be returned for analysis.

12.2 ADVERSE EVENT REPORTING

Only procedure related AEs will be collected. AEs will be reported by the investigator and reviewed by the Sponsor in compliance with applicable regulations. AEs may be volunteered by patients, elicited by the investigator or designee, or collected via observation by the investigator.

AEs will be assessed by the investigator who will determine whether or not the event is related to the study procedure or related to the study device, and whether or not the event meets serious criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE eCRF. Source documents must be submitted to the Sponsor within a timely manner to ensure timely assessment of the event as appropriate.

In addition, patients will be instructed to contact the investigator or a member of their care team if any significant AEs occur between study visits.

An AE assessment will be performed at each visit. AEs are reported starting from the day of study procedure until patient participation has ended (i.e. completion of study or withdrawal of consent). All AEs must be followed until resolution, AE has stabilized, or the study has been completed.

Pre-existing medical conditions or symptoms observed prior to the study procedure date will not be recorded as an AE and should be collected in the patient's medical history. In the event there is a change (i.e. worsening) in the pre-existing medical condition or symptoms after the study procedure, then an AE must be reported. Whenever possible, the adverse event diagnosis (and not the signs or symptoms) should be recorded on the CRF (i.e. leg edema with leg pain associated with a DVT should be recorded as a DVT).

12.2.1 SERIOUS ADVERSE EVENT REPORTING

A completed SAE eCRF must be entered in the clinical study database (EDC system) for all SAEs within 24 hours of knowledge of the event. The site will also be responsible for submitting relevant source documentation for the SAE. If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary must also be included with the SAE source documentation. In case of death, the investigator must make every effort to obtain a copy of the death certificate to submit to the Sponsor. When submitting copies of source documentation, all patient identifying information must be redacted and only the unique patient number will be used to label the forms for identification purposes.

Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator. All SAEs will be followed until resolution, SAE has stabilized, or the study has been completed. All device or procedure related SAEs will be followed until resolution.

AngioDynamics will notify the regulatory agency of any unexpected, fatal, or life-threatening experience (expedited report) associated with the study as soon as possible in

accordance with regulatory requirements in each country after becoming aware of the event.

Copies of any reports to regulatory agencies regarding serious and unexpected AEs will be provided to the investigators for review and submission to the IRB. The investigator is responsible for informing the IRB of any SAEs and/or UADEs. Copies of SAE/UADE correspondence with the investigators, regulatory authorities, and Sponsor must be retained with study records.

12.2.2 UNITED STATES REPORTING OBLIGATIONS

All UADEs must be reported to the FDA and governing IRB within 10 working days after the Sponsor is first made aware of the event. Reporting to the FDA will be consistent with 21 CFR Part 803.53 and 21 CFR Part 812.150.

12.3 ADVERSE EVENT RELATEDNESS

The investigator will be responsible for making a determination on the causal relationship of the AE. Specifically, the investigator will report whether the AE was related to the study procedure.

The causal relationship for each adverse event will be rated as follows:

- Unrelated: The event is not related to the procedure or the study device.
- Possibly Related: The temporal sequence is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the patient's condition. There is a possibility of any relation between the event and the procedure or the study device.
- Related: The temporal sequence is relevant or the event abates upon completion of the procedure/study device, or the event cannot be reasonably explained by the patient's condition or comorbidities. The event is related or most likely associated with the procedure or the study device.

12.4 ADVERSE EVENT SEVERITY

The severity of the AE will be rated based upon the following grades:

- Mild: an experience that is usually transient, & requires no special treatment or intervention
- Moderate: an experience that is alleviated with simple therapeutic treatments
- Severe: an experience that requires therapeutic intervention

12.5 ADVERSE EVENT CODING

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

13 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

Although AngioDynamics, Inc. intends to complete the study, they reserve the right to discontinue the study at any time for clinical or administrative reasons, or if required by the local regulatory authority, with suitable written notice to the investigators and regulatory authorities as appropriate.

Similarly, investigators may withdraw from the study providing written notification to AngioDynamics, Inc. within 30 days of their intent to withdraw. However, AngioDynamics, Inc. and investigators will be bound by their obligation to complete the follow-up of patients already enrolled into the trial. Patients must be followed according to the clinical CIP and information obtained during patient follow-up shall be reported on the eCRF.

14 QUALITY CONTROL AND ASSURANCE (STUDY MONITORING)

14.1 QUALITY CONTROL

In accordance with applicable regulations, GCP, and AngioDynamics procedures, AngioDynamics monitors (or their designees) will contact the site prior to the start of the study to review with the site staff the CIP, study requirements, and their responsibilities to satisfy regulatory, ethical, and AngioDynamics requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

AngioDynamics, or their designees, will monitor the study to ensure that the:

- data are authentic, accurate, and complete.
- the safety and rights of patients are being protected.
- the study is conducted in accordance with the currently approved CIP and any other study agreements, GCP, and all applicable regulatory requirements.

14.2 MONITORING

This study will be monitored in accordance with applicable regulatory requirements and guidance by AngioDynamics to ensure compliance with the study CIP. Site monitoring will be conducted by the qualified monitor (CRA) on behalf of the Sponsor. This will include conducting study initiation visits, interim monitoring visits, and study closure visits, as well as device reconciliation procedures for each participating clinical site.

The monitor will ensure that the applicable data points on the eCRFs match the source documents, and resolve differences. Records of each visit will be documented in the appropriate monitoring report format and will include a statement of findings, conclusions, and any actions taken to correct any deficiencies noted during the visit.

The monitor will report to the Sponsor any non-compliance with the signed Investigator Statement, the study CIP, applicable GCP requirements, or any conditions imposed by the

IRB or local regulatory authority. If compliance cannot be secured, device shipments to the Investigator may be discontinued and the Investigator's participation in the investigation terminated.

The frequency of monitoring visits will be determined by the Sponsor, but should not be less than one site visit annually.

Investigators and site coordinators are expected to make source files and other records and reports available to the CRAs as required.

14.3 ACCESS TO SOURCE DOCUMENTATION

The Sponsor or its designee may perform periodic site and study file audits to evaluate compliance with its own clinical standard operating procedures (SOP) and Good Clinical Practice (GCP) standards. Investigators and institutions involved in the study will permit trial-related monitoring, audits, IRB review, and regulatory inspection by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, representatives of the Sponsor, the FDA, or other regulatory authorities access to all study records.

The investigator should promptly notify the Sponsor of any audits scheduled by the regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

15 ADMINISTRATIVE AND DATA MANAGEMENT

15.1 PATIENT CONFIDENTIALITY

All data used in the analysis and reporting of the study will be without identifiable reference to the patient. Only the unique patient number will be used to identify patient data submitted to the Sponsor, and only the investigating site will be able to link the unique patient ID to the patient's name.

Collecting and analyzing data is considered processing of personal data under the law. All information and data sent to the Sponsor concerning study patients or their participation in this trial will be considered confidential. Only authorized personnel will have access to these confidential files. All records will be kept in secure storage areas and on password-protected computers. Patient identification and confidentiality will be ensured according to the terms and definitions in ISO 14155.

This includes, but is not limited to the following:

- Patients will be identified on all eCRFs by a unique patient ID
- eCRFs are confidential documents and will only be available to the Sponsor (including delegates, such as CRAs), the investigator, the biostatistician, and if requested, to regulatory authorities. The investigator will maintain, as part of the investigation file, a list identifying all patients entered into the trial.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. Clinical information will not be released without the written permission of the patient and/or the patient's legal authorized representative, except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA, or the IRB.

The investigator and all site staff involved in this study may not disclose (or use for any purpose other than performance of the study), any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Participants enrolled at sites in the United States must also sign a HIPAA (Health Insurance Portability and Accountability Act) release of protected health information.

15.2 CASE REPORT FORMS AND CLINICAL INVESTIGATION RECORDS

15.2.1 ELECTRONIC CASE REPORT FORMS (CRFS)

This trial will utilize Electronic Data Capture (EDC) to collect patient data. Data will be recorded on electronic CRFs (eCRFs) during the course of the trial. The EDC database will reside on a central server accessible via the Internet. Paper copies may be printed off the EDC website.

The investigator is responsible for the accuracy and completeness of data reported on the eCRFs. Each set of patient eCRFs must be reviewed and signed by the investigator in the EDC system. The investigator also agrees to maintain accurate source documentation as part of the patient's medical records. These source documents may include chart notes, laboratory reports, images, etc.

15.3 RETENTION OF DATA

Investigators shall maintain all study-related documentation for a period of two (2) years following completion of the study, or as per the local regulatory authority's guidelines and practices.

15.4 STUDY REPORTING REQUIREMENTS

By participating in this study, the investigator agrees to submit safety reports according to the timeline and method outlined in this CIP. In addition, the investigator agrees to submit annual reports to his/her IRB as appropriate.

Upon completion or termination of the study, the principal investigator (PI) must submit a final written report to the Sponsor and IRB. The report must be submitted within 3 months (90 days) of completion or termination of the trial.

The Sponsor will submit all reports required by the appropriate regulatory authorities, including unanticipated adverse device effects, withdrawal of IRB approval, list of current investigators, annual progress reports, recall information, final reports and CIP deviations.

15.5 SELECTION OF INVESTIGATORS

The Sponsor will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide all investigators with the information necessary to conduct the study.

15.6 FINANCIAL DISCLOSURE

Investigators and sub-investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under Title 21 CFR 54. In addition, the investigator must notify the Sponsor promptly of any relevant changes that occur during the course of the study, at the completion of the study and 1 year following the completion of the study.

15.7 INVESTIGATOR DOCUMENTATION

Prior to beginning the study, the investigator will be asked to comply with ISO14155 and Title 21 CFR by providing the following essential documents, including but not limited to:

- An original investigator-signed Investigator Agreement page of the CIP
- An IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient
- IRB approval of the investigator, CIP, and acknowledgement of the instruction manuals
- Curricula vitae (CV) for the PI and each investigator participating in the study.
- Financial disclosure information (as stated above) and a commitment to promptly update this information if any relevant changes occur
- Normal ranges for any local laboratories used by the site in accordance with Title 42 CFR 493

15.8 SITE TRAINING

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or its designee. To ensure proper device usage, uniform data collection, and CIP compliance, the Sponsor or designee will present formal training sessions to relevant study site personnel. The Sponsor reserves the right to enforce retraining for sites who have demonstrated study or procedure compliance issues.

15.9 DEVICE RETURNS

Any unused or damaged devices must be returned to the study Sponsor. To initiate the return, the site will contact the AngioDynamics clinical affairs representative.

16 PUBLICATION POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of AngioDynamics. The investigator must discuss any

publication or presentation with AngioDynamics prior to release and obtain written consent on the intended publication.

AngioDynamics recognizes the right of the investigator to publish the results upon study completion. However, the investigator must send a draft manuscript of the publication or abstract to AngioDynamics thirty (30) days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably.

In case of a difference of opinion between AngioDynamics and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

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18 APPENDICES

APPENDIX 1 SCHEDULE OF EVENTS

	Screening[a]	Baseline[a]	Procedure			10 Day Follow-up[b]	1[c], 3[d], 6[d], 9[d] Month Follow-up	12 Month Follow-up[d]	Unsch.
			Pre	Intra	Post				
Informed Consent	X								
Inclusion / Exclusion	X								
Medical/Surgical History	X								
Medication History[1]	X								
Duplex Ultrasound (Screening)	X								
Venous Mapping	X								
Limb Girth Measurements	X					X	X	X	
CEAP	X					X	X	X	
rVCSS	X					X	X	X	
Pregnancy Test[2]			X						
Demographics		X							
Vital Signs		X	X		X	X	X	X	X
Visual Analog Pain Scale Score		X					X	X	
Physical Examination (Full)		X							
VEINES QoL		X					X	X	
Ulcer Measurement		X					X	X	
Physical Examination (Abreviated)			X			X	X	X	X
Procedure Details				X					
Concomitant Medications			X	X	X	X	X	X	X
Concomitant Procedures				X	X	X	X	X	X
Duplex Ultrasound (Post Procedure)						X	X	X	
Adverse Event(s) Assessment				X	X	X	X	X	X
Study Exit								X	

1. Document medications currently taken and within the last 14 days

2. Must be completed within 2 days of procedure

a. Must be completed within 14 days prior to the study procedure

b. Window + or - 3 days

c. Must be completed between 30 and 45 days of study procedure

d. Window + or - 15 days

APPENDIX 2 SPONSOR / PRINCIPAL STUDY INVESTIGATOR APPROVAL

Clinical Investigation Plan Title:	A Prospective Clinical Study Evaluating the Safety and Effectiveness of the VenaCure Endovenous Laser Treatment (EVLT) 400 µm Fiber Kit for Ablation of Incompetent Perforator Veins
CIP Number:	PV-VC300
Version:	1.3

This Clinical Investigation Plan was subject to critical review and has been approved by the sponsor and the Principal Study Investigator. The following personnel contributed to writing and/or approving this Clinical Investigation Plan:

Signed:_____ Date: 1/11/17

Mark Adelman, MD, FACS – Chief, Division of Vascular and Endovascular Surgery, Principal Study Investigator

Signed: Kate Pietrovito Date: 1/12/2017

Kate Pietrovito – Director, Medical Affairs and Clinical Operations, AngioDynamics, Inc.

APPENDIX 3 INVESTIGATOR'S SIGNATURE

Clinical Investigation Plan Title:	A Prospective Clinical Study Evaluating the Safety and Effectiveness of the VenaCure Endovenous Laser Treatment (EVLT) 400 µm Fiber Kit for Ablation of Incompetent Perforator Veins
CIP Number:	PV-VC300
Version:	1.3

Investigator Agreement and Certification

SeCure Study: A Prospective Safety and Effectiveness Study: Treating Incompetent Perforator Veins with the VenaCure EVLT 400 µm Fiber Procedure Kit

I hereby agree to participate in the SeCure Study, a clinical investigation of the VenaCure EVLT 400 µm Fiber Procedure Kit sponsored by AngioDynamics Inc. (hereinafter "Study Sponsor"). I agree to conduct this investigation in accordance with this agreement, the investigational plan, 21 CFR Part 812, other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA. I agree to supervise all use of the investigational device and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study. The rights, safety, and well-being of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the 21 CFR Part 50. This shall be understood, observed, and applied at every step of the investigation.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. I am also aware that I may be inspected by a representative of the regulatory authorities/agencies to verify compliance with applicable requirements related to clinical research on human subjects.

I am aware that Study Sponsor reserves the right to discontinue this investigation at any time. In the event that I decide to discontinue my participation as an Investigator in this study, I will notify AngioDynamics Inc. 30 days prior of my intent to discontinue. I understand that I am obligated to complete the follow up of the subjects already participating in the investigation.

I agree to provide to the Study Sponsor a current curriculum vitae along with the curriculum vitae of those physicians at this institution who will be using this investigational device or participating in this study as sub-Investigators under my supervision. These CVs include the extent and type of our relevant experience with pertinent dates and locations. I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of Study Sponsor, this institution's IRB or FDA.

I understand that this investigation, protocol, and trial results are confidential and I agree not to disclose any such information to any person other than a representative of Study Sponsor or a regulatory authority (IRB/FDA/ Office of Human Research Protections-OHRP) without the prior written consent of the Study Sponsor.

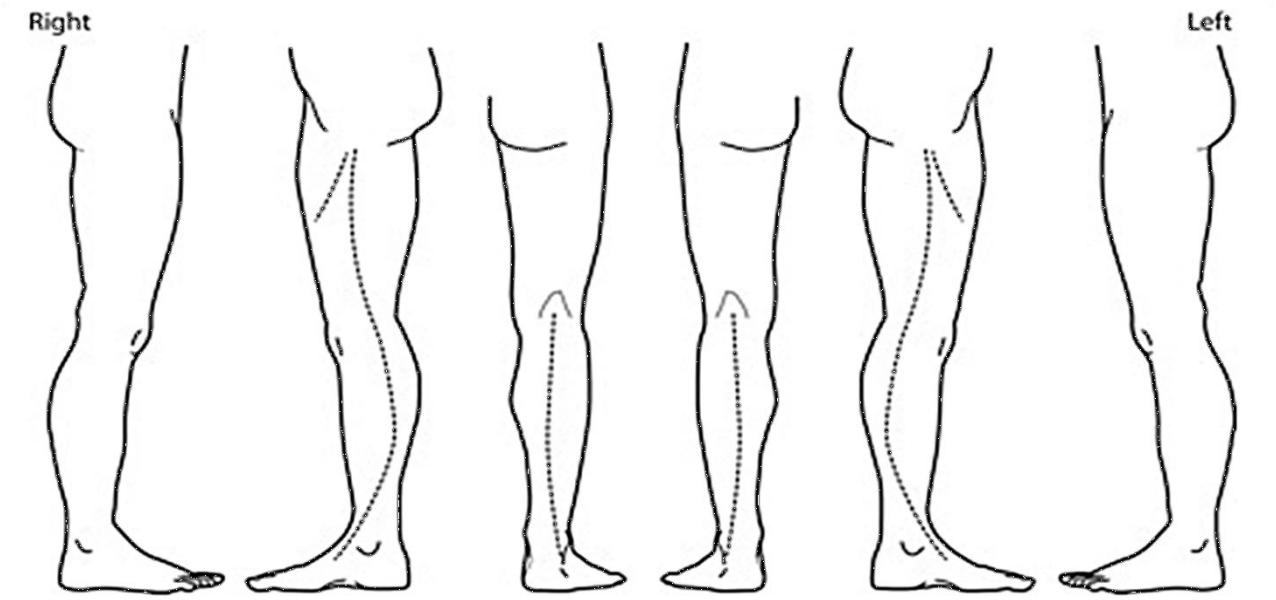
I will provide financial information, as indicated in U.S. Code of Federal Regulations: 21 CFR Part 812.43 (c)(5) and 21 CFR Part 54.

Accepted by:

Signed:_____ Date:_____

Principal Site Investigator

APPENDIX 4 LOWER EXTREMITY VENOUS MAPPING



Please use the following legend for completing the venous map

RED -Reflux	BLUE-Thrombophlebitis	BLACK – Previously Treated	RF, Laser, Chemical Ablation, Ligation & Stripping	----- Recanalization	Neovascularization
Deep VVs >5mm depth	Superficial VVs <5mm depth	Reticular Vein	Telangiectasia	Incompetent Perforator	Venous Ectasia
SVT - Superficial Venous Thrombophlebitis DVT – Deep Venous Thrombosis	SFJ - Sapheno-Femoral Junction SPJ - Sapheno-Popliteal Junction		B – Bulging Varicose Vein NB – Non-bulging Varicose Vein	Small Caliber Vein - 1-2mm diameter Medium Caliber- 2-3mm diameter Large Caliber - >3mm diameter	
DTA - Distal to access	A - Aplastic H - Hypoplastic	U – Active Ulcer HU – Healed Ulcer	CP – Corona Phlebectasia	PC – Pigment Changes	NE - Not Evaluated NV - Not Visualized

APPENDIX 5 CEAP CLASSIFICATION

Clinical Classification	
C0:	no visible or palpable signs of venous disease
C1:	telangiectases or reticular veins
C2:	varicose veins
C3:	edema
C4a:	pigmentation or eczema
C4b:	lipodermatosclerosis or atrophie blanche
C5:	healed venous ulcer
C6:	active venous ulcer
S:	symptomatic, including ache, pain, tightness, skin, irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A:	asymptomatic

Etiologic Classification	
Ec:	congenital
Ep:	primary
Es:	secondary (post thrombotic)
En:	no venous cause identified

Anatomic Classification	
As:	superficial veins
Ap:	perforator veins
Ad:	deep veins
An:	no venous location identified

Pathophysiologic Classification	
Pr:	Pr: reflux
Po:	Po: obstruction
Pr,o:	Pr,o: reflux and obstruction
Pn:	Pn: no venous pathophysiology identifiable

APPENDIX 6 REVISED VENOUS CLINICAL SEVERITY SCORE (RVCSS)

The revised Venous Clinical Severity Score (rVCSS) will be used as an assessment tool to evaluate the severity of the venous disease of the patient. The rVCSS includes 9 hallmarks of venous disease, each scored on a severity scale from 0 to 3.

	None: 0	*Mild: 1*	*Moderate: 2*	*Severe: 3*
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin		Occasional pain or other discomfort (ie, not restricting regular daily activities)	Daily pain or other discomfort (ie, interfering with but not preventing regular daily activities)	Daily pain or discomfort (ie, limits most regular daily activities)
Varicose veins "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position.		Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	≥3
Active ulcer duration (longest active)	N/A	<3 mo	>3 mo but <1 y	Not healed for >1 y
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2-6 cm	Diameter >6 cm
Use of compression therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

Table taken from: Vasquez, M, 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; 52(5): 1387-1396.

APPENDIX 7 VISUAL ANALOG SCALE

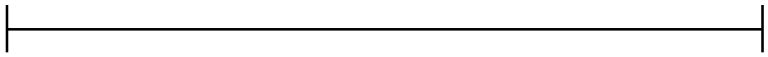
The visual analog scale (VAS) will be used as an assessment tool to determine the amount of pain that the patient is feeling. This assessment will be performed after the Patient Informed Consent Form is obtained. The assessment can be administered by either an investigator or research coordinator. The VAS will not be used in any analysis at this time.

VAS Instructions

- Site personnel should complete the header information and date completed prior to handing the forms to the subject.
- Have the subject write on a hard surface with a black ball point pen.
- Have the subject read the instructions on the form.
- Ask the subject if they have any questions regarding the instructions.
- Have the subject complete the form on their own. Site personnel cannot mark the form.
- Inform the patient that the vertical mark that they make must cross through the horizontal line
- When the subject has completes the VAS, review it to ensure the vertical mark crosses the horizontal line and that there is only one mark on the line.
- If there is more than one mark on the horizontal line have the patient draw a line through the mark that they wish to eliminate and have them initial and date the correction.
- Site personnel should never instruct or suggest where the mark should be placed on the vertical line.
- Record the mark measure in mm with the ruler provided by AngioDynamics. This measurement **must** be made in millimeters.
- Please also record your initials and date the measurement was made.

Visual Analog Scale (VAS)*

Place a single vertical mark on the line below indicating the total amount of leg pain you currently are feeling.



No Pain **The worst pain you could imagine**

Below to be completed by your healthcare professional

Measurement (mm): _____

Date of Assessment: _____

Measured By: _____

*A 10-cm baseline is recommended for VAS scales.
From: Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0032; February 1992. Agency for Healthcare Research & Quality, Rockville, MD; pages 116-117.

APPENDIX 8 VEINES QOL

The Veines-QOL/Sym Questionnaire will be used as an assessment tool to determine the patients Chronic Venous Disorders of the Leg (CVDL) symptomology, limitations in daily activities due to CVDL, and psychological impact, as well as questions asking about the time of day the leg problem is most intense. This assessment will be performed after the Patient Informed Consent has been obtained. The assessment can be administered by either an investigator or research coordinator. The scores of the VEINES-QOL/Sym will be calculated for patients. The scores will be evaluated to determine the difference of the baseline scores to the various scores collected at follow up time points.

Patient Instructions

You have Chronic Venous Disorder of the Leg. In this survey, we are interested in finding out more about the effects of your leg problem on your daily activities, both at home and at work. This information will give us a better idea about how to treat such problems.

Thank you for participating in this study. This questionnaire includes questions about your health in general and about your leg problem, as well as questions about your life and usual activities. It will take about 10 minutes to complete.

Thank you for your help.

P1

3

INSTRUCTIONS
HOW TO ANSWER:
Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

Below are some questions about your views about your legs. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. During the past 4 weeks, how often have you had any of the following leg problems?

(check one box on each line)	**Every day**	**Several times a week**	**About once a week**	**Less than once a week**	**Never**
1. Heavy legs	1	2	3	4	5
2. Aching legs	1	2	3	4	5
3. Swelling	1	2	3	4	5
4. Night cramps	1	2	3	4	5
5. Heat or burning sensation	1	2	3	4	5
6. Restless legs	1	2	3	4	5
7. Throbbing	1	2	3	4	5
8. Itching	1	2	3	4	5
9. Tingling sensation (e.g.pins and needles)	1	2	3	4	5

2. At what time of day is your **leg problem** most intense ? *(check one)*

1 On waking
2 At mid-day
3 At the end of the day
4 During the night
5 At any time of day
6 Never

P1

4

3. Compared to one year ago, how would you rate your **leg problem** in general now? *(check one)*

1 Much better now than one year ago
2 Somewhat better now than one year ago
3 About the same now as one year ago
4 Somewhat worse now than one year ago
5 Much worse now than one year ago
6 I did not have any leg problem last year

4. The following items are about activities that you might do in a typical day. Does your **leg problem** now limit you in these activities? If so, how much ?

(Check one box on each line)	**I do not work**	**YES, Limited A Lot**	**YES, Limited A Little**	**NO, Not Limited At All**
a. Daily activities at work	0	1	2	3
b. Daily activities at home (e.g. housework, ironing, doing odd jobs/repairs around the house, gardening, etc...)		1	2	3
c. Social or leisure activities in which you are standing for long periods (e.g. parties, weddings, taking public transportation, shopping, etc...)		1	2	3
d. Social or leisure activities in which you are sitting for long periods (e.g. going to the cinema or the theater, travelling, etc...)		1	2	3

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your **leg problem**?

(check one box on each line)	**YES**	**NO**
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

6. During the past 4 weeks, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbors or groups? *(check one)*

1 Not at all
2 Slightly
3 Moderately
4 Quite a bit
5 Extremely

P1

5

7. How much leg pain have you had during the past 4 weeks? *(check one)*

1 None	4 Moderate
2 Very mild	5 Severe
3 Mild	6 Very severe

8. These questions are about how you feel and how things have been with you during the past 4 weeks as a result of your **leg problem**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(check one box on each line)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Have you felt concerned about the appearance of your leg(s) ?	1	2	3	4	5	6
b. Have you felt irritable ?	1	2	3	4	5	6
c. Have you felt a burden to your family or friends ?	1	2	3	4	5	6
d. Have you been worried about bumping into things ?	1	2	3	4	5	6
e. Has the appearance of your leg(s) influenced your choice of clothing ?	1	2	3	4	5	6

Thank you for your help.
Please return this questionnaire to us by mail using the envelope provided or give it to your doctor.

Please write today's date: _____/_____/_____ *(day/month/year)*

APPENDIX 9 ULCER MEASUREMENT

Use the ruler to measure the longest and widest aspect of the wound surface in centimeters; multiply length x width.

Pick the depth, thickness, most appropriate to the wound using these additional descriptions:

1 = tissues damaged but no break in skin surface.
2 = superficial, abrasion, blister or shallow crater. Even with, &/or elevated above skin surface (e.g., hyperplasia).
3 = deep crater with or without undermining of adjacent tissue.
4 = visualization of tissue layers not possible due to necrosis.
5 = supporting structures include tendon, joint capsule.

Record the date of measurement

Measurement	Baseline	1 month	3 month	6 month	9 month	12 month
L x W cm						
Depth						
Date						

PROTOCOL REVISION HISTORY

Date	Version	Description of Modifications	Rationale for Modification
May 28, 2014	1.0	Initial Release	IDE protocol submitted to FDA for approval
September 18, 2014	1.1	Statistical updates, Administrative updates, addition of protocol revision history and change log	Incorporated FDA statistical considerations from IDE approval letter dated June 27, 2014

PROTOCOL CHANGE LOG

Version # Modified	Change Type	Section/Paragraph	Change Description
1.0	Initial Release	Entire document	IDE protocol submitted to FDA
1.1	Revision	Title Page	Revised date, version number
1.1	Revision	Synopsis	Revised Sponsor Contact, Sample Size
1.1	Revision	Table of Contents	Updated
1.1	Revision	6.2 Determination of Sample Size	Incorporated FDA statistical considerations from IDE approval letter dated June 27, 2014
1.1	Revision	6.3 Baseline and Demographics Characteristics	Clarified how "continuous variables" will be summarized. Added "95% confidence intervals will be utilized"
1.1	Revision	6.4.3 Safety Population	Added "lead-in patients are included in safety population"
1.1	Deletion	6.5.3.1 Primary Ablation…	Deleted "95% confidence interval" language
1.1	Deletion	6.5.3.5 Ulcer Healing	Deleted "95% confidence interval" language
1.1	Revision	6.6 Missing Data	Incorporated FDA statistical considerations from IDE approval letter dated June 27, 2014. Defined "sensitivity analysis of missing data" and methods of imputation
1.1	Revision	Protocol Revision History	Addition of Protocol Revision History
1.1	Revision	Protocol Change Log	Addition of Protocol Change Log
1.2	Revision	Synopsis, Sponsor Contact	Update Sponsor Contact