Medtronic

Cover page for Statistical Analysis Plan

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Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	VenaSeal Spectrum: Global, Post-Market, Prospective, Multi-Center, Randomized Controlled Trial of the VenaSeal™ Closure System vs. Surgical Stripping or Endothermal Ablation (ETA) for the Treatment of Early and Advanced Stage Superficial Venous Disease
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jia Guo, Principal Statistician
2.0	• Update to note that elimination of truncal reflux will be summarized without hypothesis testing for the VenaSeal vs. Surgical Stripping Study, due to halted enrollment in sections 4.1, 7.5 and 7.9. • Updated study design consistent with CIP changes in sections 5.1, 5.2, 6.2 and 7.9.3 (halting of Venaseal vs. Surgical Stripping study enrollment and reducing follow-up to 12 months and reduction in sample size of the VLU study) • Add note on handling of VenaSeal vs. Surgical Stripping study data collected beyond 12 months in section 7.1.1 • Added the scoring algorithm for the VenousTSQe and VenousTSQs in section 7.9.1.1.4 • Added test for superiority in non-inferiority is met in section 7.9.1.2.3 • Document updated using new template.	Nicholas Salkowski, Principal Statistician
3.0	• Re-organized the document so that each study endpoint is enumerated and the corresponding hypothesis, endpoint definition, analysis methods and analysis population are provided • Return-to-work endpoints, return-to-normal activities, anatomic closure endpoints all revised use a time-to-first-event analysis to allow for censoring and incorporation of unscheduled follow-up visits • Reintevention and healthcare utilization endpoints are revised to use a rate-based calculation to allow for potential recurrent events and differences in follow-up time • Updated scoring of the VenousTSQe and VenousTSQs based on the final recommendations	Tracy Bergemann, Distinguished Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event

Abbreviation	Definition
AVVQ	Aberdeen Varicose Vein Questionnaire
CEAP	Clinical, Etiological, Anatomical, and Pathophysiological Classification
CIP	Clinical Investigation Plan
CRF	Case Report Form
DUS	Duplex Ultrasound
DVT	Deep Vein Thrombosis
EGIT	Endovenous glue induced thrombosis
EHIT	Endovenous heat induced thrombosis
EQ-5D	EuroQoL 5 Dimensions Standardized Quality of Life Survey
EVLA	Endovenous Laser Ablation
ETA	Endovenous Thermal Ablation
GSV	Great Saphenous Vein
IFU	Instructions for Use
ITT	Intention-to-treat
PE	Pulmonary Embolism
PASS	Power Analysis and Sample Size
PP	Per-Protocol
PROM	Patient Reported Outcome Measure
QoL	Quality of Life
RFA	Radiofrequency Ablation
SAE	Serious Adverse Event
SAS	Statistical Analysis System software
SF-36	Short Form-36 Quality of Life Survey
SoC	Standard of Care
SSV	Small Saphenous Vein
US	United States
rVCSS	Revised Venous Clinical Severity Score
VenousTSQe	Venous Treatment Satisfaction Questionnaire- early
VenousTSQs	Venous Treatment Satisfaction Questionnaire- status
VLU	Venous Leg Ulcer
VRD	Venous Reflux Disease

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of VenaSeal Spectrum: Global, Post-Market, Prospective, Multi-Center, Randomized Controlled Trial of the VenaSeal™ Closure System vs. Surgical Stripping or Endothermal Ablation (ETA) for the Treatment of Early and Advanced Stage Superficial Venous Disease. The purpose of the VenaSeal Spectrum study is to evaluate the patient's experience and clinical improvement after treatment with the VenaSeal™ system compared to Standard of Care (SoC) treatments, surgical stripping or ETA, in the treatment of symptomatic superficial venous disease (CEAP 2-5). Patient-centered outcomes, vein closure, ability to return to work, and clinical improvement will be measured after treatment of

symptomatic venous reflux in the superficial truncal veins by the VenaSeal™ system or the comparator treatments. Additionally, in a separate single-arm study, CEAP 6 patients with at least one active venous leg ulcer will be enrolled, treated with the VenaSeal™ system and evaluated for wound healing. This study will complement the available clinical evidence for the VenaSeal™ system.

The purpose of this statistical analysis plan (SAP) is to document the analyses used for the analysis of study objectives and final reports for each study. Revisions to the SAP may be required if the protocol changes or updates to the analysis are needed. The study objectives are taken directly from the Clinical Investigation Plan (CIP). The SAP will further define the analyses of the safety and efficacy objectives.

4. Study Objectives

4.1 Primary Objectives

4.1.1 Primary Endpoints in the Randomized Studies

For the CEAP 2-5 Randomized Studies, there are three primary objectives that compare the VenaSeal™ system to surgical stripping and ETA.

Patient experience and satisfaction endpoints

Patient experience and satisfaction will be evaluated through a validated, patient-centered 2-part venous treatment satisfaction questionnaire (VenousTSQ-early [VenousTSQe] and VenousTSQ-status [VenousTSQs]). The difference between the two arms will be tested at 30 days.

Elimination of clinically relevant superficial truncal disease

The ability to achieve elimination of clinically relevant superficial truncal disease in the target veins will be evaluated at the index procedure. Elimination of clinically relevant superficial truncal disease is defined as the percentage of target vein length successfully treated. For the VenaSeal™ vs. ETA Study, the difference between the two arms will be tested. For the VenaSeal™ vs. Surgical Stripping Study, the ability to achieve elimination of clinically relevant superficial truncal disease in the target veins at the index procedure will be summarized without hypothesis testing, due to early discontinuation of enrollment.

4.1.2 Primary Endpoint in the Single Arm VLU Study

For the VLU Study, there is one primary objective to evaluate time to ulcer healing through 12 months.

Time to ulcer healing

The time to ulcer healing is defined as the probability of healing confirmation that is verified by an independent core laboratory through 12 months.

4.2 Secondary Objectives

4.2.1 Key Secondary Endpoints in the Randomized Studies

The key secondary objectives are to compare the VenaSeal™ system to surgical stripping and ETA in achieving the anatomical closure of superficial truncal veins at 6 months, and the ability to return to work post-index procedure.

Return to Work

Return to work is defined as the time in days patients need following a procedure to return to work.

Anatomical Closure

Anatomical closure is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm for subjects in the arms treated with the VenaSeal™ system or ETA. In the surgical stripping arm, it is defined as clinically significant refluxing truncal vein incompetency and no discrete segments of patency exceeding 5 cm.

4.2.2 Additional Secondary Endpoints in the Randomized Studies

The other secondary objectives of the study are to evaluate the VenaSeal™ system in the treatment of symptomatic venous reflux in the superficial truncal veins. Specific areas of analysis include effectiveness, safety, healthcare utilization, patient experience, and treating physician experience.

Effectiveness endpoints

1. Anatomic closure of the primary target vein at 30 days, and 12, 24, 36, 48 and 60 months
2. Anatomic closure of target vein at 30 days, and 6, 12, 24, 36, 48 and 60 months
3. Technical success of each target vein immediately post-index procedure
4. Reintervention of any target vein (including primary target vein) through 60 months
5. Time to reintervention of any target vein

Safety endpoints

1. Adverse events occurring in the target limb, evaluated from index procedure through 12 months
2. Serious adverse events evaluated through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study)

Healthcare utilization endpoints

1. Number and type of adjunctive treatments conducted through 12 months post-index procedure
2. Healthcare utilization related to the target limb Venous Reflux Disease through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study)
3. Procedures, tests, and treatment of AEs related to the treatment modality or index procedure through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study)

Patient experience endpoints

1. Time to return to normal activities
2. Intra-procedural and post-procedural pain at the index procedure, and 7 days and 30 days
3. Change in venous disease symptoms at 7 and 30 days, and at 6, 12, 24, 36, 48, and 60 months compared to baseline (7 and 30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study)
4. Change in AVVQ score at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline
5. Change in EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) at 30 days, and 6, 12, 24, 36, 48 and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline
6. Change in the 36-Item Short Form Health Survey (SF-36) reported by the patient at 30 days, and 6 and 12 months compared to baseline
7. Change in the Venous Dependent Quality of Life (VenousDQoL) reported by the patient at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline

Provider experience endpoint

1. Provider experience will be assessed post-index procedure for all treatment modalities, evaluating overall satisfaction with the procedure

4.2.3 Secondary Endpoints in the Single Arm VLU Study

In addition, secondary objectives in the VLU Study include effectiveness, healthcare utilization, and patient experience.

Effectiveness endpoints

1. Ulcer healing rate, as measured by the percentage of the ulcer area healed per given time period, according to an independent core laboratory through 24 months or until ulcer healing has been confirmed
2. Ulcer recurrence on the target limb following ulcer healing through 60 months
3. Ulcer-free time through 60 months

Healthcare utilization endpoints

4. Healthcare utilization and routine wound care treatments between study visits through 60 months

Patient experience endpoints

5. Peri-procedural patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days
6. Patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days

7. Elimination of clinically relevant superficial truncal disease in target vein at the time of index procedure as measured by the percentage of target veins successfully treated

5. Investigation Plan

5.1 Study Design

The study design is a global, post-market, prospective, multi-center, randomized-controlled study of patients with symptomatic superficial venous disease, with a single-arm embedded ulcer group. The study is designed with two Randomized Studies (VenaSeal vs. Surgical Stripping Study and VenaSeal vs. ETA Study) for CEAP 2-5 subjects and one single arm active VLU Study for CEAP 6 subjects. Each study will be individually assessed and analyzed for the overall study objectives.

There will be approximately 500 subjects enrolled in the VenaSeal Spectrum Study. Approximately 375 subjects will be enrolled in CEAP clinical classifications 2-5 in the Randomized Studies (108 subjects in VenaSeal vs. Surgical Stripping Study and about 264 subjects in VenaSeal vs. ETA Study), and up to 125 CEAP 6 subjects with VLUs will be treated with the VenaSeal™ system.

Enrollment of the VenaSeal vs. Surgical Stripping Study was closed on 22-Feb-2022. All subjects participating in the VenaSeal vs ETA Study or in the VLU Study (CEAP 2-6) will be followed up to 60 months post-index procedure, all subjects participating in the VenaSeal vs. Surgical Stripping Study will be followed up to 12 months post-index procedure.

Enrollment will take place at up to 40 sites globally.

To avoid introduction of bias to the study results due to disproportionate enrollment, enrollment at any individual site shall not exceed 20% of any single study (approximately 50 subjects for the Randomized Studies and 25 subjects for the VLU Study, excluding screen failures) of the total sample size. It is expected that sites enroll a minimum of 10 subjects per individual study the site is participating in. Enrollment was halted early for the VenaSeal vs. Surgical Stripping study, so control of each site's contribution to the overall total was not possible.

Randomization will be stratified by study site and CEAP classification 2/3 vs. 4/5. There is no blinding in this study. The detailed procedure of randomization information is described in the Randomization and Blinding Plan separately.

5.2 Duration

It is anticipated that enrollment will take approximately 36 months following enrollment of the first subject. The estimated study duration is approximately 8 years, including up to 60-month follow-up post-procedure and excluding the time required for preparing the final report. The expected duration of each subject's participation is up to 60 months after the index procedure, apart from subjects who were enrolled in the VenaSeal vs. Surgical Stripping Study. The latter will be followed through 12-months only.

Data will be recorded in the Case Report Form (CRF) at screening, baseline, index procedure (day 0), and during follow-up at 7 days (± 2 days), 30 days (± 7 days), 6 months (± 4 weeks), 12 months (± 8 weeks), 24 months (± 8 weeks), 36 months (± 8 weeks), 48 months (± 8 weeks) and 60 months (± 8 weeks).

Additional routine care visits can be conducted to accommodate adjunctive procedures 3 or more months following the index procedure (data for adjunctive procedures will be collected through 60 months), per the treating physician's discretion; these will not be considered study visits.

Data of subjects who were enrolled in the VenaSeal vs. Surgical Stripping Study will be recorded in the CRF at screening, baseline, index procedure (day 0), and during follow up at 7 days (± 2 days), 30 days (± 7 days), 6 months (± 4 weeks), and 12 months (± 8 weeks).

CEAP 6 subjects will have additional study visits until healing verification and data will be recorded in the CRFs at: 2 months (± 7 days), 3 months (± 7 days), 4 months (± 7 days), 5 months (± 7 days), 8 months (± 2 weeks), 10 months (± 2 weeks). If the healing has not occurred by 12 months, subjects will continue to follow standard wound care and remaining study visits. Subjects will come in for ulcer healing verification visits up to 24 months, after which no core laboratory ulcer assessment for wound healing will be required.

5.3 Inclusion Criteria

1. Patient is ⩾18 years of age.
2. Patient has venous reflux in superficial truncal vein(s) (e.g., GSV, SSV, accessory saphenous veins) with CEAP category 2 (symptomatic) or CEAP category 3, 4a, 4b, 5, 6 based on the American Venous Forum CEAP classification (2004), appropriate for treatment, as confirmed by DUS.
3. Eligibility for treatment:
    - VenaSeal vs ETA Study: Patient is eligible for treatment with the VenaSeal™ system and ETA.
    - VenaSeal vs Surgical Stripping Study: Patient is eligible for treatment with the VenaSeal™ system and surgical stripping.
    - VLU Study: patients should be eligible for treatment with the VenaSeal™ system.
4. Treatable refluxing segment of target vein(s) 10 cm in length or longer.
5. Patient has a target vein diameter of ⩾3 mm throughout the intended treatment segment of the target vein as measured by DUS while patient is standing.
6. Patient is willing and capable of complying with specified follow-up evaluations at the specified times.
7. Patient has an ability to understand the requirements of the study and to provide informed consent.

5.4 Exclusion Criteria

1. Patient has a known history of allergic sensitivities (including but not limited to cyanoacrylate adhesives), or any other condition, which in the opinion of the investigator may make the patient more susceptible to cyanoacrylate adhesive hypersensitivity.
2. Patient has known deep vein obstruction in the target limb, as identified by the site's standard of care.
3. Patient has abnormal pulse exam or ABI <0.8.
4. Patient has acute superficial thrombophlebitis.
5. Patient requires any non-target vein treatments in the contralateral or ipsilateral limb, or any other surgical procedure up to 30 days pre-procedure and through 3 months post-procedure.
6. Patient has any co-morbid conditions, which in the investigator's opinion may interfere with the patient's compliance with study visits and procedures, or may confound interpretation of study data

(e.g., congestive heart failure Class III and IV, non-ambulatory patients, severe hepatic dysfunction, life expectancy < 1 year).

7. IFU contraindications:
    - VenaSeal vs. ETA Study: Patient has VenaSeal™ system and/or ETA product's IFU contraindication(s).
    - VenaSeal vs. Surgical Stripping Study: Patient has surgical stripping and/or VenaSeal™ system IFU contraindication(s).
    - VLU Study: Patient has VenaSeal™ system IFU contraindication(s).
8. Patient is non-ambulatory.
9. Patient is a female of childbearing potential who may be pregnant or breastfeeding at the time of the index procedure. *
10. Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.
11. Patient is currently participating in an investigational drug or device study when the data collected could be conflicting or biased due to participation in another study.
12. Patient has documented COVID-19 infection currently or within the past 3 months. Patient is not completely recovered from past COVID-19 infection, per physician's discretion.
13. VLU Study: Patient has target ulceration identified to be of non-venous etiology, as confirmed by the independent core laboratory.
14. VLU Study: Patient has target circumferential ulceration that cannot be captured in a single photograph (any ulcer curvature around the leg that goes out of sight).

Note: CEAP 6 VLU patients are excluded at sites not identified as VLU Study sites.

*Pregnancy to be assessed per treating physician's routine practice; testing is not required if verbal confirmation is preferred. Breastfeeding patients may be included if mother's expressed milk is discarded surrounding the index procedure, per the treating physician's standard instructions. Sites must document routine methods utilized for such patients.

6. Determination of Sample Size

This evaluation has been designed as a global, post-market, prospective, multi-center, randomized controlled study of patients with symptomatic superficial venous disease, with a single arm embedded ulcer study. The study is designed with two randomized studies (VenaSeal vs. Surgical Stripping Study and VenaSeal vs. ETA Study) for CEAP 2-5 subjects and one single arm active VLU Study with CEAP 6 subjects. Each study will be individually assessed and analyzed for the overall study objectives.

The three primary endpoints in the Randomized Studies will be measured to compare VenaSeal™ vs. the treatment of ETA or surgical stripping on VenousTSQe and VenousTSQs (separately) at 30 days, and elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure. The primary endpoint of the VLU Study is time to ulcer healing and will be measured until healing has occurred.

Sample size evaluations are discussed separately for the randomized studies and the single-arm VLU Study below.

6.1 Randomized Studies

Analyses will be performed on all patients who pass the point of enrollment (randomization), as according to the intention-to-treat (ITT) principle. Patients will be analyzed in the arm they are randomized to regardless of the treatment received.

There are three primary endpoints and two key secondary endpoints with formal hypothesis testing for the Randomized Studies. Multiplicity adjustment needs to be considered to control the overall type I error. Each randomized study will have a family-wise type I error rate of 0.05. Within each study, Hochberg procedure will be used to control the family-wise type I error rate to 0.05 for the primary endpoints (Benjamini & Hochberg, 1995)[1]. Type I error preserved from the primary endpoints will be used for the key secondary endpoints.

A type I error of 0.0167 will be used in the following sample size calculations for this purpose.

In the two Randomized Studies, three primary endpoints will be assessed:

1) Peri-procedural patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at 30 days;

2) Patient satisfaction as measured by a validated patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days, and

3) elimination of clinically relevant superficial truncal disease in each target vein at index procedure. The two key secondary endpoints include achieving the anatomical closure of primary target superficial truncal veins at 6 months and the time to return to work post-index procedure.

For VenaSeal vs Surgical Stripping Study, 108 subjects randomized before 22-Feb- 2022 will be included in the analysis. These subjects will be followed for 12 months after index procedure. Since the enrollment was stopped for the VenaSeal vs. Surgical Stripping Study with up to 108 subjects, there is still reasonable power for the two TSQs and key secondary objectives. Therefore, the VenaSeal vs. Surgical Stripping Study will test two primary endpoints (Venous TSQe and TSQs at 30 days) and the key secondary endpoints. The elimination of truncal reflux at the index procedure will be summarized but not tested for hypothesis testing.

6.1.1 Sample Size Evaluation on Primary Endpoints

VenousTSQ

Subject experience and satisfaction will be measured through a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQ). The VenousTSQ is designed to have two components, the VenousTSQe and the VenousTSQs. As a result of the different content of both components of the VenousTSQ, the related endpoints are split into two separate primary endpoints, being:

1. *Peri-procedural patient satisfaction* as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at *30 days* post index procedure;
2. *Overall patient satisfaction* as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at *30 days* post index procedure.

While the VenousTSQ is a newly developed Patient Reported Outcome Measure (PROM), the questionnaire provides sufficient insight in the eventual scoring scales. Each of the two parts consists of

8-11 items in total. VenousTSQe consists of 8 items with items being able to be scored from 0 - 6. VenousTSQs consists of 11 items and items can similarly be scored from 0 - 6. Consequently, VenousTSQe and Venous TSQs have a potential scale that range runs from 0 - 48 and 0 – 66, respectively. Sample sizes are provided below for different scenarios with a varying number of potential items.

To determine the variance (SD), a comparison was made to other treatment satisfaction questionnaires (TSQs) that were developed by the same expert group. The Macular TSQ (MacTSQ) was designed as a measure of patient satisfaction with treatment for macular disease. The questionnaire consists of two subscales with each a maximum score of 36 (6 questions each) and a single scale with a maximum score of 72 (12 questions). The SD was reported as 3.56 for subscale 1, 5.04 for subscale 2, and 7.30 for the single scale. The Diabetes TSQ (DTSQ) was designed as a measure of patient satisfaction with treatment for diabetes. The questionnaire consists of a scale with a maximum score of 48 (8 questions) and a typical SD is around 5.0. To determine the SD for the two VenousTSQ endpoints, an overestimate was made in comparison with literature findings. The SD was selected to be equal to the number of included items in the score.

The null hypothesis on the primary endpoints of VenousTSQe and VenousTSQs at 30 days is that the VenaSeal™ system arm will have same PROM scale as that of the control (ETA or surgical stripping) arm. The alternative hypothesis is that the VenaSeal™ system arm will have a different PROM scale from that of the control arm. Rejection of the null hypothesis in favor of the VenaSeal™ system will signify that the treatment satisfaction with the VenaSeal™ system is superior to the treatment with ETA or surgical stripping. A minimum difference of 0.5 points per item, as a total score, is utilized as the minimum meaningful difference between comparison groups.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $p_A = p_C$
Ha: $p_A \neq p_C$

Where p_A and p_C are the true PROM scale for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively. The parameter assumptions are:

- $p_A - p_C = 0.5$ * [number of items]
- Common standard deviation of 1 * [number of items] points
- T test with two sided α 0.0167
- 1:1 randomization
- 7% attrition rate for VenousTSQ at 30 days

With these assumptions, a total of 237 subjects (220 evaluable, 110 in each arm) will yield 90% power to reject the null hypothesis in favor of the alternative hypothesis of superiority on VenousTSQe and VenousTSQs at 30 days in each study.

If a somewhat less conservative assumption is made for the standard deviation (0.75 * [number of items]), then there will still be reasonable power for the VenaSeal vs. Surgical Stripping study.

A 5 PROM point difference with a SD of 10 PROM points is assumed for 10 questions in either component of the VenousTSQ. Assuming the standard deviation increases with the number of questions and the minimum clinical difference of 0.5 points per question, the sample size calculations are not impacted by

the number of questions. Therefore, the sample size will not need to be adjusted based upon the number of items included in the score.

Number of Venous TSQ questions	Difference of PROM Points	SD of PROM points (assuming equal in both arms)	Sample size (1:1 evaluable)
6	3	6	110:110
8	4	8	110:110
10	5	10	110:110
12	6	12	110:110

Elimination of truncal reflux

The third primary endpoint is the elimination of clinically relevant superficial truncal disease in target veins at the index procedure. This endpoint will be measured as a percentage of treated vein vs. diseased vein for each target vein.

Based on clinical experience, the minimal clinically relevant difference in mean percentage of truncal disease elimination between treatment modalities is expected to be 10%. To calculate the sample size, a combination of the smallest minimal clinically relevant difference and the largest variance (SD) are justified being the conservative assumptions. A SD of 20% is used to calculate the sample sizes.

The null hypothesis on this primary endpoint is that the VenaSeal™ system arm will have the same percentage of reflux eliminated at the index procedure as that of the control (ETA or surgical stripping) arm. The alternative hypothesis is that the VenaSeal™ system arm will have the different percentage of reflux eliminated at the index procedure from the control arm. Rejection of the null hypothesis in favor of the VenaSeal™ system will signify that the treatment with the VenaSeal™ system is superior to the treatment with ETA or surgical stripping if the percentage of reflux treated for the VenaSeal™ system is greater than control.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $\mu_A = \mu_C$
Ha: $\mu_A \neq \mu_C$

Where μ_A and μ_C are the percentage of reflux treated at the index procedure for the VenaSeal™ system arm and ETA or surgical stripping arm.

The parameter assumptions are:

- $\mu_a - \mu_C = 10\%$
- Common standard deviation of 20%
- Two-sided t test with $\alpha = 0.0167$
- 1:1 randomization
- 3% attrition

With these assumptions, a total of 227 subjects (220 evaluable, 110 in each arm) will yield 90% power to reject the null hypothesis in favor of the alternative hypothesis of superiority in each study.

6.1.2 Sample size evaluation on key secondary endpoints

Return to work

Return to work is defined as the time in days patients need following a procedure to return to work. Return to work time can be influenced by factors that are independent of the type of work they are employed to do (e.g., including physical effort), the type of anesthesia that is used with or without hospitalization, and other regional/cultural differences.

To minimize the effects of independent factors that may influence the return-to-work time, several measures will be taken into account. Employment status will be captured for all patients. Only patients who have an active employment status (employed or independent worker, including stay at home parents) will be included in the analysis for return-to-work time. Information will be captured on the category of occupation to be able to distinguish between physical and sedentary work. A sensitivity analysis will be performed to investigate whether the day of the week of the procedure has an effect on the time to return to work. The sensitivity analysis will be a regression where the treatment arm and the day of the week of the procedure will be included as predictors.

A literature search on historical data for return-to-work time following treatment of venous reflux disease was conducted using the Pubmed database of clinical literature. Publications describing return to work times for treatment of venous reflux disease with the VenaSeal™ closure device, any type of endovenous laser ablation (EVLA) and radiofrequency ablation (RFA), or surgical stripping were considered. The resulting return to work times are summarized in Table 1, below. Where applicable, the return to normal activities time is included. The corresponding sample size (based on ITT) and measure of return time (mean vs. median) are included in the table. The results of the first five rows were used to estimate sample sizes for the return-to-work endpoint because these studies specifically report the mean and SD. Using a conservative approach, the resulting SDs for the three treatment groups (ETA, VenaSeal™ treatment, and surgical stripping) were compared against the median and IQR of the remaining findings to make sure the used estimation was justified compared to existing data. With this approach, the smallest differences between treatment with the VenaSeal™ device and the other treatments are utilized to calculate final sample size.

Table 1: Return to work/normal activity time post treatment of venous reflux disease (External Data)

Author	Treatment type	Sample size (# pts, ITT)	Measure	Time in days to return to normal activities	Time in days to return to work
Pronk	ETA: Laser	62	Mean (SD)	3.2 (4.3)	4.4 (5.4)
Lurie	ETA: RFA	45	Mean (95% CI)	1.15 (0.05-2.34)	4.7 (1.16-8.17)
Gibson	VenaSeal™	50	Mean (SD)	2.4 (+/- 4.1)	0.2 (+/- 1.1)
Lurie	Surgical stripping	40	Mean (95% CI)	3.89 (2.67-5.12)	12.4 (8.66-16.23)
Pronk	Surgical stripping	68	Mean (SD)	3.2 (4.0)	4.2 (3.7)
Samuel	ETA: Laser	38	Median (IQR)	4 (1-14)	4 (0-12)
	ETA: Laser	38	Median (IQR)	3 (1-14)	3 (1-8)
Rasmussen	ETA: Laser	125	Median (range)	2 (0–25)	3.6 (0–46)
Cotton	ETA: Laser	212	Median		7.7
Lattimer	ETA: Laser	56	Median (IQR)	7.5 (2-15)	

Carradice	ETA: Laser	140	Median (IQR)	3 (1-10)	4 (2-14)
Rasmussen	ETA: RFA	125	Median (range)	1 (0–30)	2.9 0–14)
Lane	ETA: RFA	83	Median (IQR)	2 (1-7)	2 (2-7)
Subramonia	ETA: RFA	48	Median (IQR)	3 (2-5)	10 (4-13)
Chan	VenaSeal™	29	Median (range)		1 (1-16)
Subramonia	Surgical stripping	45	Median (IQR)	12.5 (4-21)	18.5 (11-28)
Carradice	Surgical stripping	140	Median (IQR)	14 (7-25)	14 (13-28)
Cotton	Surgical stripping	294	Median		11.7
Rasmussen	Surgical stripping	125	Median (range)	4 (0–30)	4.3 (0–42)

The null hypothesis for the key secondary endpoint is that the VenaSeal™ system arm will have the same days to return to work as that of the control (ETA or surgical stripping) arm. The alternative hypothesis is that the VenaSeal™ system arm will have different days to return to work than that of the control arm. Rejection of the null hypothesis in favor of VenaSeal will signify that the ability to return to work after treatment with the VenaSeal™ system is superior to ETA or surgical stripping.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $r_A = r_C$

Ha: $r_A \neq r_C$

Where r_A and r_C are the true days of return to work for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively.

The parameter assumptions are:

- r_A = 0.2 in the VenaSeal™ system arm and r_C = 3 and 8 in ETA arm and surgical stripping arm, respectively
- standard deviation of 1.1 in the VenaSeal™ system arm, 2 in ETA arm and 3 in surgical stripping arm
- Two-sided t test with α = 0.0167
- 1:1 randomization

With these assumptions, a total of 22 subjects (evaluable; 11 in each arm) in the VenaSeal vs. ETA study and 10 subjects (evaluable; 5 in each arm) in VenaSeal vs. surgical stripping study will yield 90% power to reject the null hypothesis in favor of the alternative hypothesis of superiority in each study.

Closure rate

Closure rate is a generally used measure to determine the long-term success of venous reflux disease treatment. Literature may report on closure rate, occlusion rate, or recanalization rate at various moments in time. The endpoint used in this study focuses on the closure rate measured at 6 months.

To calculate the sample size based on historical data on closure rate, a literature search was conducted using the Pubmed database of clinical literature. Any literature older than 10 years was excluded from the analysis. Six-month closure rates for treatment of venous reflux disease with the VenaSeal™ closure device, any type of endovenous laser ablation and radiofrequency ablation, or surgical stripping were considered.

Closure rates were weighted within a treatment arm by multiplying the closure rate for that treatment with the sample size of the treatment arm. Table 2 below shows an overview of the literature that was used to calculate weighted closure rates that were used for sample size calculations.

Table 2: Closure Rates for Treatment of Venous Reflux Disease

Author	Year	Treatment	Follow-up	Sample size (# pts, ITT)	Closure/occlusion rate
Brittenden	2015	ETA: Laser	6M	212	83.0%
Bozoglan	2016	ETA: Laser	6M	60	100.0%
Eroglu	2018	ETA: Laser	6M	175	95.1%
Sydnor	2017	ETA: Laser	6M	100	100%
Wozniak	2016	ETA: Laser	6M	56	100%
Mese	XXXX	ETA: Laser	6M	60	100%
Atasoy	2015	ETA: Laser	6M	44	100%
Calik	2019	ETA: Laser	6M	200	95.6%
Lane	2016	ETA: RFA	6M	82	93.0%
Beteli	2017	ETA: RFA	6M	43	95.3%
Eroglu	2018	ETA: RFA	6M	175	94.1%
Sydnor	2017	ETA: RFA	6M	100	97.3%
Mendes	2016	ETA: RFA	6M	18	80.0%
Wozniak	2016	ETA: RFA	6M	54	100%
Mese	2015	ETA: RFA	6M	60	95.0%
Yang	2013	ETA: RFA	6M	100	99.0%
Morrison	2018	ETA: RFA	6M	114	96.2%
Creton	2010	ETA: RFA	6M	295	98.6%
Chan	2017	VenaSeal™	6M	57	90.3%
Almeida- FIH	2013	VenaSeal™	6M	38	92.1%
Gibson - WAVES	2016	Venaseal™	6M	70	98.0%
Proebstle- eSCOPE	2015	VenaSeal™	6M	70	91.4%
Morrison- VeClose	2018	VenaSeal™	6M	108	99.0%
Brittenden	2015	Surgical stripping	6M	294	84.4%
Jia	2010	Surgical stripping	6M	26	89.5%

Table 3 shows an overview of the weighted average closure rates at 6 months that were used to calculate the sample size for this endpoint.

Table 3: Weighted Average Closure Rate

Comparator	Total number of considered studies	Total sample size in considered studies	Weighted average closure rate at 6M
VenaSeal™	5	343	95.0%
ETA	18	1948	95.4%
Surgical stripping	2	320	84.8%

The null hypothesis on this key secondary endpoint is that the closure rate at 6 months in the VenaSeal™ system arm will have less than or equal to that in the control (ETA or surgical stripping) arm minus a clinically relevant difference of 10%. The alternative hypothesis is that the closure rate at 6 months in the VenaSeal™ system arm will be greater than that in the control arm minus a clinically relevant difference of 10%. Rejection of the null hypothesis will signify that the treatment with the VenaSeal™ system is not inferior to the treatment with ETA or surgical stripping.

Specifically, the null (Ho) and alternative (Ha) hypotheses are:

Ho: $\pi_A \leq \pi_C - 10\%$
Ha: $\pi_A > \pi_C - 10\%$

Where π_A and π_C are the closure rate at 6 months in the VenaSeal™ system arm and the ETA or surgical stripping arm.

The parameter assumptions are:

- π_A = 95% in the VenaSeal™ system arm and π_C = 95.4% and 84.8% in ETA and surgical stripping arm, respectively
- Likelihood Score (Farrington & Manning) test with one sided α 0.0167
- 1:1 randomization
- 10% attrition rate

With these assumptions, a total of 264 subjects (238 evaluable, 119 in each arm) will yield 80% power to reject the null hypothesis in favor of the alternative hypothesis of non-inferiority to the ETA arm. A total of 98 subjects (88 evaluable, 44 in each arm) will yield 80% power to reject the null hypothesis in favor of the alternative hypothesis of non-inferiority to the surgical stripping arm.

6.1.3 Overall Sample Size Evaluation

Power Analysis and Sample Size (PASS) was used to compute sample size. Based on the above fixed sample size calculations, the total sample size in the VenaSeal vs ETA study will be 264, to demonstrate the success on each primary endpoint with at least 90% power, as summarized in Table 4 below.

Table 4: Primary or Key Secondary Endpoint Sample Size for Randomized Studies

Primary or Key Secondary Endpoint	Total Sample Size: VenaSeal and ETA Arms	Total Sample Size: VenaSeal and Surgical Stripping Arms
VenousTSQe at 30 days	237	237
VenousTSQs at 30 days	237	237

Elimination of truncal reflux at index procedure	227	220
Return to work	22	10
Closure rate at 6 months	264	98
Overall Sample Size (Including Attrition)	**264**	**237**

The total sample size in the VenaSeal vs Surgical Stripping Study will be 108 subjects due to the enrollment closure on 22-Feb-2022.

6.1.4 Sample Size Re-estimation

No interim analysis sample size re-estimation is planned for the VenaSeal vs. ETA Study or the VenaSeal vs. Surgical Stripping Study.

6.2 VLU Study (Single-Arm Study)

6.2.1 Sample Size Consideration

The primary endpoint in the VLU Study is time to ulcer healing. For reference, the EVRA study evaluated clinical and cost effectiveness of early endovenous treatment and standard care vs. deferred intervention in patients with chronic venous ulceration. As there are no statistically powered hypotheses in the VLU Study, precision estimates (distance from point estimate to upper 95% two-sided confidence bound) were used to derive the sample size based on the outcomes of the EVRA study.

In comparison to the EVRA study, criteria for VLU Study inclusion are less restrictive, which may result in an ulcer population which is older and heals more slowly than the EVRA early-intervention group. Precision calculations utilized an assumed median time to healing of 70 days which is the approximate average of the median healing time between the EVRA early-intervention and deferred-intervention groups (56 and 82 days, respectively). Precision estimates for a range of sample sizes are provided in Table 5. A simulation was run 10,000 times on the assumption of exponential distribution of 70 days median time to healing. The simulation results show that a precision of less than 23 days can be obtained with a sample size of 125 subjects enrolled in the VLU Study.

Table 5: Sample Size for the VLU Study

Sample size	Evaluable Sample Size (10% attrition)	Precision
80	72	<30 days
90	81	<28 days
100	90	<26 days
110	99	<25 days
115	104	<24 days
120	108	<24 days
125	113	<23 days

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number and percentage of subjects screened, enrolled, received therapy and completed each scheduled clinical follow-up visit will be summarized. The number and percentage of subjects who complete the study and who exit early will be summarized by exit reason as documented on the case report form (CRF). The subject clinical follow-up compliance will be provided at each study visit by study arm via a flow diagram and/or table.

The VenaSeal vs. Surgical Stripping Study was originally planned to have 5 years of subject follow-up. However, in CIP version 4.0, the follow-up was reduced to 12 months and the endpoints were updated accordingly. It is likely that some subjects will collect data beyond 12 months during transition of the CIP change. Data collected beyond 12 months will be reported in listings. If there is a sufficient sample size for some endpoints, these endpoints may also be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

A deviation is any event in which the study is not conducted according to the CIP, applicable laws or regulations or the Investigator Agreement.

Protocol deviations will be reported descriptively by counts of type and be listed by identifying site. Counts of deviations, number and percentage of subjects who have CIP deviations will be summarized by associated visit and reason as documented in the CRF. Results will be summarized by study arm for the randomized studies.

7.1.3 Analysis Sets

CEAP 2-5 randomized studies

The primary analysis set for Randomized Studies will be the ITT analysis set. Per-protocol (PP) analyses may be performed as a sensitivity analysis. All analysis sets have been defined with the intent of minimizing bias in the data analysis.

Intent-to-Treat (ITT): All patients who are randomized in the arms in each study will be included in the analysis regardless of the treatment received or the outcome of the treatment.

Per-Protocol (PP): The ITT population excluding failed and no procedure treatment outcomes, subjects that are treated with the modality they were not randomized to and/or have not met the inclusion/exclusion criteria. A failed procedure with no procedure treatment outcomes is defined as a procedure where the procedure treatment was never attempted or a procedure that was aborted.

As treated (AT): Includes subjects in the arm they are treated with according to the treatment actually received, regardless of the arm they were randomized to.

VLU (single arm) Study

Intention-to-Treat (ITT): All patients with CEAP 6 who are enrolled in this study (either successful, incomplete or failed treatment outcome) will be counted in the ITT population, which will be the primary analysis set.

Per-Protocol (PP): The ITT population excluding failed treatment outcome and/or subjects that have not met the inclusion/exclusion criteria. A failed procedure with no procedure treatment outcomes is defined as a procedure where the procedure treatment was never attempted or a procedure that was aborted.

The primary analysis for this CEAP 6 single arm study will be on intention-to-treat (ITT) population. All analysis sets have been defined with the intent of minimizing bias in the data analysis.

7.2 General Methodology

Descriptive statistics of continuous characteristics/outcomes will be presented and include sample size, mean, median, standard deviation, minimum, and maximum. For categorical outcomes, the count and percentage of subjects in each category will be presented. Subject data listings and tabular and graphical presentations of results will be provided. All analyses will be based on ITT principle, unless otherwise specified. All statistical analyses will be performed using Statistical Analysis System (SAS) software (version 9.4 or higher) or other widely accepted statistical or graphical software.

7.3 Center Pooling

For each study, data will be pooled across sites for analysis. Results will be also summarized and presented for primary and key secondary endpoints by site for each study.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing data. A combination of sensitivity analysis and multiple imputation of the primary endpoints will be performed to assess the potential impact of missing data. The details will be described in the section 7.9.1.1.6 Missing Data Analysis below.

Unless otherwise specified, no statistical techniques will be used to impute missing data for the other objectives. The number of subjects included in each analysis will be reported. In time-to-event outcomes drop-outs will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach.

7.5 Adjustments for Multiple Comparisons

In the randomized studies, Hochberg procedure will be used in the adjustments for multiple comparisons on primary and key secondary endpoints (Benjamini & Hochberg, 1995)[1]. Familywise type I error 0.05 will be used for the primary endpoints and type I error preserved from the primary endpoints will be used for the key secondary endpoints.

VenaSeal vs. ETA Randomized Study

In each randomized study, p-values for the primary endpoints will be ordered from largest to smallest as $p_{p1} > p_{p2} > p_{p3}$ from the 3 hypothesis tests H_{p1}, H_{p2} and H_{p3}, and for the key secondary objectives in descending order as $p_{s1} > p_{s2}$ from the 2 hypothesis tests for key secondary endpoints H_{s1} and H_{s2}, the procedure is as follows:

Step 1. If $p_{p1} < \alpha$, then claim success on all 3 hypotheses for primary endpoints H_{p1}, H_{p2} and H_{p3}; and proceed to Step 1a, otherwise, go to step 2.	Step 1a. If $p_{s1} < \alpha$, then claim success on both hypotheses for key secondary endpoints H_{s1} and H_{s2}; otherwise, go to step 1b.
	Step 1b. If $p_{s2} < \alpha/2$, then claim success on hypothesis for key secondary endpoint H_{s2}; otherwise, both hypotheses for key secondary endpoints H_{s1} and H_{s2} are unsuccessful
Step 2. If $p_{p2} < \alpha/2$, then claim success on two hypotheses for primary endpoints H_{p2} and H_{p3}; and proceed to Step 2a, otherwise, go to step 3.	Step 2a. If $p_{s1} < \alpha/2$, then claim success on both hypotheses for key secondary endpoints H_{s1} and H_{s2}; otherwise, go to step 2b.
	Step 2b. If $p_{s2} < \alpha/4$, then claim success on hypothesis for key secondary endpoint H_{s2}; otherwise, both hypotheses for key secondary endpoints H_{s1} and H_{s2} are unsuccessful
Step 3. If $p_{p3} < \alpha/3$, then claim success on hypothesis for primary endpoint H_{p3}; and proceed to Step 3a, otherwise, no success on all 3 hypotheses for primary endpoints H_{p1}, H_{p2} and H_{p3}	Step 3a. If $p_{s1} < \alpha/3$, then claim success on both hypotheses for key secondary endpoints H_{s1} and H_{s2}; otherwise, go to step 3b.
	Step 3b. If $p_{s2} < \alpha/6$, then claim success on hypothesis for key secondary endpoint H_{s2}; otherwise, both hypotheses for key secondary endpoints H_{s1} and H_{s2} are unsuccessful
$\alpha = 0.05$ for Endothermal Ablation (ETA) study.	

VenaSeal vs. Surgical Stripping Randomized Study

In each randomized study, p-values for the primary endpoints will be ordered from largest to smallest as $p_{p1} > p_{p2}$ from the 2 hypothesis tests H_{p1}, and H_{p2}, and for the key secondary objectives in descending order as $p_{s1} > p_{s2}$ from the 2 hypothesis tests for key secondary endpoints H_{s1} and H_{s2}, the procedure is as follows:

Step 1. If $p_{p1} < \alpha$, then claim success on both hypotheses for primary endpoints H_{p1}, and H_{p2}; and proceed to Step 1a, otherwise, go to step 2.	Step 1a. If $p_{s1} < \alpha$, then claim success on both hypotheses for key secondary endpoints H_{s1} and H_{s2}; otherwise, go to step 1b.
	Step 1b. If $p_{s2} < \alpha/2$, then claim success on hypothesis for key secondary endpoint H_{s2}; otherwise, both hypotheses for key secondary endpoints H_{s1} and H_{s2} are unsuccessful
Step 2. If $p_{p2} < \alpha/2$, then claim success on endpoint H_{p2}, otherwise, no success	Step 2a. If $p_{s1} < \alpha/2$, then claim success on both hypotheses for key secondary endpoints H_{s1} and H_{s2}; otherwise, go to step 2b.

on both hypotheses for primary endpoints H_{p1}, and H_{p2}	Step 2b. If $p_{s2} < \alpha/4$, then claim success on hypothesis for key secondary endpoint H_{s2}; otherwise, both hypotheses for key secondary endpoints H_{s1} and H_{s2} are unsuccessful
$\alpha = 0.05$ for VenaSeal vs. Surgical Stripping Randomized Study.	

7.6 Demographic and Other Baseline Characteristics

Demographic, medical history and other clinically relevant baseline variables will be summarized by treatment using descriptive statistics (i.e., number of observations available, mean, standard deviation, minimum, and maximum for continuous variables and counts and percentages for qualitative variables).

7.7 Treatment Characteristics

Index procedure and post-procedural characteristics and results will be summarized using general methodology as described in Section 7.2.

7.8 Interim Analyses

No interim analysis is planned for the randomized studies or single arm VLU study.

7.9 Evaluation of Objectives

VenaSeal vs. Surgical Stripping

2 primary endpoints and 2 key secondary endpoints will be evaluated.

VenaSeal vs. ETA

3 primary endpoints and 2 key secondary endpoints will be evaluated.

VLU Single Arm Study

No hypothesis testing will be done.

7.9.1 Randomized Studies

7.9.1.1 Analysis of Primary Endpoints

7.9.1.1.1 Hypothesis

For Primary endpoints of VenousTSQe at 30 days and VenousTSQs at 30 days, the following hypothesis will be tested:

H_0: $p_A = p_C$
H_a: $p_A \neq p_C$

Where p_A and p_C are the true PROM scale for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively.

To compare the percentage of target vein length successfully treated between treatment and control, the following hypothesis will be tested:

H_0: $\mu_A = \mu_C$
H_a: $\mu_A \neq \mu_C$

Where μ_A and μ_C are the percentage of reflux treated at the index procedure for the VenaSeal™ system arm and ETA.

7.9.1.1.2 Endpoint Definition

The VenaSeal vs. ETA Randomized Study has three primary endpoints comparing the VenaSeal™ system to ETA.

1. *Peri-procedural patient satisfaction* as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at *30 days* post index-procedure.
2. *Overall patient satisfaction* as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at *30 days* post index-procedure.
3. Elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure as measured by the percentage of target vein length successfully treated.

The VenaSeal vs. Surgical Stripping Randomized Study has three primary endpoints comparing the VenaSeal™ system to Surgical Stripping.

1. *Peri-procedural patient satisfaction* as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at *30 days* post index-procedure.
2. *Overall patient satisfaction* as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at *30 days* post index-procedure.
3. Elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure as measured by the percentage of target vein length successfully treated will be summarized but no statistical hypothesis testing will be done.

7.9.1.1.3 Rationale for Performance Criteria

If the null hypothesis is rejected, it demonstrates that the treatment satisfaction or percentage of the target vein successfully treated with the VenaSeal™ system is significantly different from the treatment with ETA or surgical stripping.

When the two-sided P-value is less than the pre-specified critical value alpha per adjustment of multiple comparison (described in Section 7.5) and the mean of certain primary endpoint in treatment with VenaSeal™ is greater than that in control of ETA or Surgical Stripping, the superiority of treatment with VenaSeal™ on that primary endpoint can be declared.

7.9.1.1.4 Analysis Methods

VenousTSQe and VenousTSQs consist of 8 and 11 items, respectively, with each item having the possibility to be scored from 0-6. The scores will be collected from eCRFs at 30 days.

The VenousTSQe score is calculated as:

Item 1 (from the VenousTSQs) + Item 2 + Item 4 + Item 5b + Item 6b + Item 7

Items 1, 3, and 8 from the VenousTSQe are not used.

Since the VenousTSQe score is the sum of 6 items, it can range from 0 to 36.

The Venous TSQs score is calculated as:

Item 1 + Item 2 + Item 4b + Item 6 + Item 7b + Item 9

Items 3, 5, 8, 10 and 11 are not used.

Since the VenousTSQs is the sum of 6 items, it can range from 0 to 36.

Scoring Notes

Some items included in the scores are skipped when they are not applicable, based on a previous question. For example, consider 5a and 5b in the VenousTSQe

5a asks: "Immediately after the procedure, did you wear compression stockings or bandages?" If the response to 5a is "no", 5b is skipped. 5b asks "How bothered were you by wearing compression stockings / bandages?", so it doesn't apply if no stockings / bandages were worn. In these cases, when an item in the score is skipped because of a response to the prior, related question, it will be scored as 6. For item 5b, 6 indicates "not bothered at all", which is sensible, since a person cannot be bothered by stockings that are not worn.

If the follow-up question is supposed to be skipped, but is not, the follow-up response will be used only if it is consistent with the prior, related question. If 5a is marked "no" (indicating that stockings were not worn), and 5b is not skipped, then:

- If 5b = 5 or 5b = 6, 5b will be used to calculate the score.
- If 5b < 5, then the responses are inconsistent, and 5b will be considered missing.

If a prior question is marked "yes", but the follow-up question is left blank, then the item will be considered missing:

- If 5a is marked "yes", but 5b is missing, then 5b will be considered missing.

Calculating the Score When Items are Missing

The VenousTSQe and VenousTSQs scores are missing when any of the included items is missing.

Hypothesis Test of the TSQ

(Shapiro-Wilk test) Normality on the outcomes of primary endpoints of PROM scores and % of target vein length successfully treated will be checked in each treatment arm first.

If one of the treatment arms is not normal for a primary endpoint ($p < 0.05$), Wilcoxon rank-sum test will be used in the comparison between VenaSeal™ arm and control arm (ETA or Surgical Stripping). The test

statistic can be calculated by $Z = \frac{|R_1 - \mu_{R_1}| - 0.5}{\sigma_{R_1}}$ using normal approximation with 0.5 continuity correction, where R_1 is the summary of rank of PROM scores in treatment (VenaSeal) arm, μ_{R_1} is the expectation of R_1 and $\sigma^2_{R_1}$ is the variance of R_1. Null hypothesis can be rejected if $|Z| > Z_{\alpha/2}$ and P value can be calculated by $1 - \Phi(Z)$.

If both treatment arms are normal for a primary endpoint, Two-sample T test will be used in the comparison between VenaSeal™ arm and control arm (ETA or Surgical Stripping). Null hypothesis can be rejected if the test statistic t has $|t| > t_{\frac{\alpha}{2},N-1}$. If the Equality of Variances output has a p value ≥ 0.05, the "pooled" variance will be computed as the weighted average of the sample variances; if the Equality of Variances output has a p value < 0.05, the "Satterthwaite" will be computed as the weighted average of the sample variances.

7.9.1.1.5 Determination of Subjects' Data for Analysis

ITT population with available data will be used for the primary analysis on primary endpoints. For the sensitivity analyses, PP and AT populations will be used on primary endpoints.

7.9.1.1.6 Sensitivity and Missing Data Analysis

It is recommended to perform an additional scoring the of the TSQe that does not include Item 5, i.e. the Compression stockings question.

To account for missing data in the primary endpoint evaluation, two forms of imputation will be performed. For patients that have no baseline information collected, they will be assigned the average value of the TSQ in the control arm. For patients with a baseline visit and baseline information collected, multiple imputation will be performed as a sensitivity analysis. Subjects who do not obtain their VenousTSQe at 30 days, VenousTSQs at 30 days or the percentage of target vein treated at procedure will have these measurements imputed using PROC MI in SAS. The covariates to be used in the imputation model are age, gender, race, diabetes, CEAP classification, Historical Superficial and Deep Venous Treatment, Family History of Chronic Venous Disease, VCSS at baseline, 7 days and 30 days, Length of clinically relevant superficial truncal disease in target vein and treatment arms. Ten imputed data sets will be generated using regression method (REG option in PROC MI). The overall PROM scores for VenousTSQe and VenousTSQs and % target vein treated success and their standard errors will be generated for each of ten imputed data sets. PROC MIANALYZE in SAS will be used to summarize the overall treatment difference, standard error, and two-sided 95% confidence interval.

7.9.1.2 Analysis of Key Secondary Endpoints

7.9.1.2.1 Hypothesis

For key secondary endpoint of return to work, the following hypothesis will be tested:

H_0: $S_A(t) = S_C(t)$
H_a: $S_A(t) \neq S_C(t)$

Where $S_A(t)$ and $S_C(t)$ are the survival functions for freedom from return to work for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively.

For the other key secondary endpoint of primary target vein closure rate at 6 months, the following hypothesis will be tested:

H_0: $S_A(t) \leq S_C(t) - 10\%$
H_a: $S_A(t) > S_C(t) - 10\%$

Where t = 6 months, and $S_A(t)$ and $S_C(t)$ are the survival functions for freedom from vessel re-opening at 6 months in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively and -10% is the non-inferiority margin.

7.9.1.2.2 Endpoint Definition

Return to work is defined as the time in days patients need following a procedure to return to work. Employment status will be captured for all patients. Only patients who have an active employment status (employed or independent worker, including stay at home parents) will be included in the analysis for return-to-work time. Information will be captured on the category of occupation to be able to distinguish between physical and sedentary work. Patients will be censored at the time of study exit.

The other key secondary endpoint to be assessed is the primary target vein closure rate after index treatment. The primary target vein should be the saphenous vein (GSV, SSV, accessory saphenous veins) which at the investigator's discretion is most likely responsible for the greatest portion of the patient's symptoms or pathology. This vein will be treated first.

For subjects treated with the VenaSeal™ system or ETA, anatomic closure of the primary target vein is defined as Doppler ultrasound (DUS) showing primary target vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm. Any areas with >5 cm patency will be measured, and information will be collected on the location of the patency, length of the patency (cm), diameter of the patency (mm), the presence of flow (Y/N), the presence of reflux (Y/N), and the presence of thrombus (Y/N). For subjects treated with surgical stripping, anatomic closure of the primary target vein is defined as the absence of clinically significant refluxing truncal vein incompetency and no discrete segments of patency exceeding 5 cm in the primary target vein. Any areas with vein remnants will be measured and information will be collected on the location of the remnant, length of the remnant (cm), the presence of flow (Y/N), the presence of reflux (Y/N), and the presence of thrombus (Y/N). Lack of anatomic closure on the date of the index procedure will not be considered relevant to this endpoint, since some treatments may not achieve closure immediately.

7.9.1.2.3 Rationale for Performance Criteria

For return to work, if the null hypothesis is rejected, it demonstrates that the distribution of times to return to work with the VenaSeal™ system is significantly different from the treatment with ETA or surgical stripping. When the P-value is less than the pre-specified alpha per adjustment of multiple comparison (described in Section 7.5) and the mean/median time of return to work in treatment of VenaSeal™ is less than that in control of ETA or Surgical Stripping, the superiority of treatment of VenaSeal™ on return to work can be declared.

The closure rate hypothesis is a non-inferiority test. The null hypothesis H_0 will be rejected when the one-sided P-value is less than the pre-specified alpha per adjustment of multiple comparison (described in Section 7.5) and the non-inferiority of treatment with VenaSeal™ on closure rate at 6 months can be declared. Further, if non-inferiority is met a test for superiority will then be conducted.

7.9.1.2.4 Analysis Methods

For the return to work endpoint, a Kaplan-Meier survival estimator will be used to estimate the survival functions for both the VenaSeal™ and the control arm (i.e., ETA or Surgical Stripping). Day zero is the date of the index procedure. The censoring time is the time to study exit, the later of either the last contact date or the discontinuation date, or the time point for analysis, whichever comes first. A cumulative incidence figure will be produced to compare the two treatments. A log-rank test will be used to test whether the survival distributions differ between the treatment groups. If a patient is reported to have returned to work, but the date of return is unknown, the return date will be imputed from the date of the follow-up visit. For those who have returned to work, the median, Q1, Q3, minimum, and maximum will summarize the number of days to return to work, as well as the number who have not returned to work in each treatment arm.

The treatment effect for primary target vein closure at 6 months, one of the key secondary endpoints, is the difference in the survival curves at time t for each randomized study. A Kaplan-Meier survival estimator will be used to estimate each curve. Day zero is the date of the index procedure. The censoring time is the time to last study visit (scheduled or unscheduled), the time point for analysis, or time to exit, whichever comes first. The non-inferiority test for treatment (VenaSeal) versus control (ETA or Surgical Stripping) will be performed using the test statistic proposed in da Silva, Logan and Klein (2009)[3]. The Z test statistic will calculate $S_A(t) - S_C(t) + 0.10$ for the numerator where t is at 6 months and the square root of the sum of the Greenwood's variance estimators for each of $S_A(t)$ and $S_C(t)$ in the denominator.

7.9.1.2.5 Determination of Subjects' Data for Analysis

The return to work analysis will consist of patients in the ITT population who report having an occupation (employed or independent worker, including stay-at-home parent) at their baseline visit. The anatomic closure analysis will consist of the ITT population with available data will be used for the primary analysis on key secondary endpoints. For a sensitivity analysis, AT and PP populations will be used on key secondary endpoints.

7.9.1.3 Secondary Endpoints

Data supporting the following endpoints will be collected for both the CEAP 2-5 Randomized Studies. When appropriate, data will be evaluated for the CEAP 2-5 Randomized Studies to compare the VenaSeal™ system to surgical stripping or ETA. Data may also be pooled for all VenaSeal™ system subjects from the CEAP 2-5 randomized studies and VLU study as appropriate.

Data from VenaSeal vs. Surgical Stripping Study will be collected through the 12-month visit.

The secondary endpoints will provide additional clinical evidence related to effectiveness, safety, and patient and provider experience. The p-values from any pre-specified hypothesis tests of the remaining secondary objectives will not be adjusted for multiple comparisons. Reports or publications that contain these p-values will state that an appropriate multiple comparisons adjustment was not performed.

Descriptive statistics for the secondary endpoints will be provided. For categorical variables, the count and percentage of subjects with each outcome will be presented. For continuous variables, summary statistics (mean, standard deviation, median) will be presented. More analysis methodology details are provided below.

7.9.1.4 Effectiveness secondary endpoints

1. Anatomic closure of the primary target vein at 30 days, and 12, 24, 36, 48 and 60 months

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

- For subjects treated with the VenaSeal™ system or ETA it is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.
- For subjects treated with surgical stripping, anatomic closure of the target vein is defined as absence of clinically significant remnant refluxing truncal vein incompetency and no discrete segments of patency exceeding 5 cm at 30 days and 12 months only.

Lack of anatomic closure on the date of the index procedure will not be considered for this endpoint, since some treatments may not achieve closure immediately.

Analysis Methods

The probability of (primary) target vein closure of any primary target vein at each time point will be summarized by treatment arm in each study. The probability for each treatment arm will be estimated using the Kaplan-Meier method. Day zero is the date of the index procedure. The censoring time is the time to last study visit (scheduled or unscheduled), the time point for analysis, or time to exit, whichever comes first.

Determination of Subjects for Analysis

The anatomic closure analysis will consist of the ITT population.

2. Anatomic closure of target vein at 30 days, and 6, 12, 24, 36, 48 and 60 months

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

- For subjects treated with the VenaSeal™ system or ETA, anatomic closure of the target vein is defined as DUS showing target vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.
- For subjects treated with surgical stripping, anatomic closure of the target vein is defined as the absence of clinically significant remnant refluxing truncal vein incompetency and no discrete segments of patency exceeding 5 cm at 30 days, 6 and 12 months only.

Lack of anatomic closure on the date of the index procedure will not be considered for this endpoint, since some treatments may not achieve closure immediately.

Analysis Methods

The probability of target vein closures of any target vein at each time point will be summarized by treatment arm in each study. The probability for each treatment arm will be estimated using the Kaplan-Meier method. Day zero is the date of the index procedure. The censoring time is the time to last study visit (scheduled or unscheduled), the time point for analysis, or time to exit, whichever comes first.

Determination of Subjects for Analysis

The anatomic closure analysis will consist of the ITT population.

3. Technical success of each target vein immediately post-index procedure

Hypothesis

The following hypothesis will be tested:

$H_0: \pi_A = \pi_C$
$H_a: \pi_A \neq \pi_C$

Where π_A and π_C are the percentage of technical success post-index procedure in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively.

Endpoint Definition

- For subjects treated with VenaSeal™ system or ETA this is defined as DUS showing vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.
- For subjects treated with surgical stripping this is defined as the absence of clinically significant remnant refluxing truncal vein incompetency and no discrete segments of patency exceeding 5 cm.

Analysis Methods

The percentage of technical successes will be summarized by treatment arm in each study. The numerator is the number of technical successes, the denominator is the number of target veins treated at the index procedure. Fisher's Exact test will be used to compare arms for the endpoint.

Determination of Subjects for Analysis

The technical success analysis will consist of the AT population.

4. Reintervention of any target vein (including primary target vein) through 60 months, assessed at each follow-up visit. Subjects enrolled in the VenaSeal vs. Surgical Stripping Study will be followed through the 12 months visit only.

Hypothesis

The following hypothesis will be tested:

H_0: $r_A = r_C$
H_a: $r_A \neq r_C$

Where r_A and r_C are the rates of reintervention in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively.

Endpoint Definition

A reintervention is a retreatment of any segment of any target vein in the target limb previously treated as part of the study at the index procedure.

Analysis Methods

The rate of reintervention will be summarized by treatment arm in each study. The rate is calculated such that the numerator is the number of reinterventions and the denominator is the number of vein-years of follow-up. The amount of follow-up per person is defined as their date of exit or last known follow-up minus their date of index procedure. The vein-years is the amount of person-years times the number of target veins. A Poisson model will compare the rate of reintervention between treatment arms, using the number of reinterventions as the outcome and the person years of follow-up as an offset.

Determination of Subjects for Analysis

The reintervention analysis will consist of the ITT population.

5. Time to reintervention of any target vein (including primary target vein) through 60 months, as measured by the time between the index procedure and the first reintervention procedure. Subjects enrolled in the VenaSeal vs. Surgical Stripping Study will be followed through the 12 months visit only.

Hypothesis

The following hypothesis will be tested:

H_0: $S_A(t) = S_C(t)$
H_a: $S_A(t) \neq S_C(t)$

where $S_A(t)$ and $S_C(t)$ are the survival function estimates at time point t in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively. In the VenaSeal vs. Surgical Stripping Study, t=12 months and is otherwise t=60 months.

Endpoint Definition

A reintervention is a retreatment of any segment of any target vein in the target limb previously treated as part of the study at the index procedure.

Analysis Methods

The time to reintervention will be summarized by treatment arm in each study. Time to the first reintervention of any target vein by treatment will be presented with Kaplan-Meier estimation. Day zero is the date of the index procedure. The censoring time is the time to study exit, the later of either the last

contact date or the discontinuation date, or the time point for analysis, whichever comes first. A log-rank test will be used to compare arms.

Determination of Subjects for Analysis

The reintervention analysis will consist of the ITT population.

7.9.1.5 Safety secondary endpoints

1. Adverse events (AEs) occurring in the target limb, evaluated from index procedure through 12 months.

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

Adverse events occurring in the target limb defined as any of the following:

- Hypersensitivity to VenaSeal™ adhesive, defined as an allergic reaction to the VenaSeal™ adhesive. The presence of hypersensitivity is confirmed through adjudication. Relatedness to a study procedure and relatedness to the study device are defined.
- Phlebitis, defined as inflammatory reaction of a treated vein. The presence of phlebitis is confirmed through adjudication. Relatedness to a study procedure and relatedness to the study device are defined.
- Granuloma, defined as a grouping of macrophages. The presence of granuloma is confirmed through adjudication. Relatedness to a study procedure and relatedness to the study device are defined.
- Endovenous glue induced thrombosis (EGIT) or endovenous heat induced thrombosis (EHIT) for VenaSeal or Thermal Ablation, defined as extensions of a thrombus that extend from the treated vein into the deep venous system. The presence of a glue extension, thrombus extension, or combination glue/thrombus is confirmed through DUS visualization of the extension into the common femoral vein or popliteal vein from the target vein and extension length is specified.

CEC determination of the above events will be used for reporting.

Analysis Methods

Adverse events that are in any of the above enumerated categories will be characterized. Adverse events will be categorized per the specified definitions, and then summarized by study group.

Determination of Subjects for Analysis

The safety analysis will consist of the ITT population.

2. Additional events evaluated through 12 months:

    - Symptomatic deep vein thrombosis (DVT) events

- Symptomatic Pulmonary embolism (PE)
- Serious adverse events (SAEs)

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

CEC determination of serious adverse events will be used for reporting. The MedDRA codes for Deep vein thrombosis and Pulmonary embolism will be used for reporting of DVT and PE adverse events.

Analysis Methods

The probability of experiencing an SAE through 12 months will be summarized by treatment arm in each study. The probability for each treatment arm will be estimated using the Kaplan-Meier method. Day zero is the date of the index procedure. The censoring time is the time to study exit, the later of either the last contact date or the discontinuation date, or the time point for analysis, whichever comes first. The DVT and PE events will be summarized by reporting the number of events of each type and the number of patients in which they occurred, by treatment arm. Additionally, summary statistics will report the proportion of SAEs. Numerator is the number of target limbs (or subjects) with an SAE through 12 months, denominator is the number of target limbs (or subjects).

Determination of Subjects for Analysis

The safety analysis will consist of the ITT population.

7.9.1.6 Healthcare utilization secondary endpoints

The following healthcare utilization secondary endpoint data will be collected for both of the CEAP 2-5 Randomized Studies:

1. Rate of adjunctive treatments conducted through 12 months post-index procedure.

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

Rate of adjunctive procedures, phlebectomy or sclerotherapy, for varicosity on the target limb through 12 months post index procedure.

Analysis Methods

The number and rate of adjunctive procedures through 12 months will be estimated by study arm. To calculate the rate, the numerator is the count of adjunctive procedures. The denominator is the number of person-years of follow-up. The amount of follow-up per person is defined as their date of exit or last known follow-up or the date of their 12 month follow-up visit (whichever is first) minus their date of index procedure. A similar estimate will be constructed for the type of adjunctive procedure, phlebectomy or sclerotherapy.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

2. Healthcare utilization related to the target limb Venous Reflux Disease (VRD), as determined by the number of healthcare visits conducted, between study visits through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study).

Hypothesis

The following hypothesis will be tested:

$H_0: r_A = r_C$
$H_a: r_A \neq r_C$

Where r_A and r_C are the rates of healthcare utilization in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively.

Endpoint Definition

Rate of healthcare utilization visits related to venous reflux disease.

Analysis Methods

The number and rate of healthcare utilization visits will be estimated by study arm. To calculate the rate, the numerator is the count of HCU visits. The denominator is the number of person-years of follow-up. The amount of follow-up per person is defined as their date of exit or last known follow-up minus their date of index procedure. A similar estimate will be constructed within the HCU type of interest (Inpatient, Outpatient, Clinic, Outpatient ER visits).

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

3. Procedures, tests, and treatment of AEs related to the treatment modality or index procedure through 60 months (through 12 months for VenaSeal vs. Surgical Stripping Study).

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

Healthcare utilization measured by number of healthcare resources utilized for treatment of adverse events, including hospitalization, prolongation of hospitalization, actions taken or diagnostic tests performed.

Analysis Methods

A listing will be provided per adverse event of the actions taken.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

7.9.1.7 Patient Experience secondary endpoints

1. Time to return to normal activities as reported by the patients.

Hypothesis

For time to return to normal activities, the following hypothesis will be tested:

H_0: $S_A(t) = S_C(t)$
H_a: $S_A(t) \neq S_C(t)$

Where $S_A(t)$ and $S_C(t)$ are the survival functions for freedom from return to normal activities for the VenaSeal™ system arm and ETA or surgical stripping arm, respectively.

Endpoint Definition

Time to return to normal activities as reported by the patients.

Analysis Methods

For the return to normal activities endpoint, a Kaplan-Meier survival estimator will be used to estimate the survival functions for both the VenaSeal™ and the control arm (i.e., ETA or Surgical Stripping). A cumulative incidence figure will be produced to compare the two treatments. An event occurs when a patient indicates at a follow-up visit that they have returned to normal activities. The censoring time is the time to study exit, the later of either the last contact date or the discontinuation date, or the time point for analysis, whichever comes first. A log-rank test will be used to test whether the survival distributions differ between the treatment groups. If a patient is reported to have returned to normal activities, but the date of return is unknown, the return date will be imputed from the date of the follow-up visit. For those who have returned to normal activities, the median, Q1, Q3, minimum, and maximum will summarize the number of days to return to normal activities, as well as the number who have not returned to normal activities in each treatment arm.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

2. Intra-procedural and post-procedural pain at the index procedure, and 7 days and 30 days as reported by the patient using the numeric rating scale (NRS) with a scale of 0-10.

Hypothesis

There is no formal hypothesis test for this study objective.

Endpoint Definition

Pain is reported by the patient using a scale ranging from 0-10.

Analysis Methods

The total pain values at baseline, at each visit will be summarized within each treatment arm. In the VenaSeal vs. Surgical Stripping study, the pain information will further be summarized within types of anesthesia received during the procedure.

Determination of Subjects for Analysis

The analysis will consist of randomized subjects that underwent a procedure.

3. Change in venous disease symptoms at 7 and 30 days, and at 6, 12, 24, 36, 48, and 60 months compared to baseline (7 and 30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study), as measured by the revised Venous Clinical Severity Score (rVCSS) and subject self-reporting.

Hypothesis

The following hypothesis will be tested:

$H_0: \mu_A(t) - \mu_A(0) = \mu_C(t) - \mu_C(0)$

$H_a: \mu_A(t) - \mu_A(0) \neq \mu_C(t) - \mu_C(0)$

where $\mu_A(t)$ and $\mu_C(t)$ are the mean VCSS scores at time point t in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively. Time t is any of 7 days, 30 days, 6, 12, 24, 36, 48, or 60 months.

Endpoint Definition

The VCSS is a validated 10-question venous disease severity measurement intended to evaluate the responses to changes in disease severity over time and in response to treatment. Each signs / symptom can have a grade ranging from 0 (absent) to 3 (severe). The total VCSS score is the sum of all questions. The score ranges from 0 (no venous disease) to 30 (severe venous disease).

Analysis Methods

The total VCSS value at baseline, at each visit, and change from baseline will be summarized for ITT population. The comparison will be done between the VenaSeal and control (ETA or Surgical Stripping) arms. In order to test the above stated statistical hypothesis, a Wilcoxon two-sample test with t approximation will evaluate the change in the score index from baseline to time t. The analysis will be performed using SAS code similar to:

```
proc npar1way data= vcsschg Wilcoxon plots = none;
  title "Wilcoxon test of Change in VCSS scores";
  class trtGroup;
```

```
    var vcssdiff;
    where cpevent="XXX";
run;
```

Additionally, a linear mixed effects model will be fit on VCSS scores with an interaction variable fit for time and study group. Time points include baseline and scheduled follow-up visits. The model will account for the correlation of scores within each subject. Likelihood ratio tests will be used to test for the significance of the study group effect and the time effect. Partial t-tests will be used to compare scores between study groups at specific time points.

The analysis will be performed using SAS code similar to:

```
PROC MIXED;
 CLASS time trtGroup;
 MODEL VCSS = time trtGroup time*trtGroup;
 RANDOM INT / SUBJ=ptid corr=exch;
RUN;
```

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

4. Change in AVVQ score at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline.

Hypothesis

The following hypothesis will be tested:

H_0: $\mu_A(t) - \mu_A(0) = \mu_C(t) - \mu_C(0)$

H_a: $\mu_A(t) - \mu_A(0) \neq \mu_C(t) - \mu_C(0)$

where $\mu_A(t)$ and $\mu_C(t)$ are the mean AVVQ scores at time point t in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively. Time t is any of 7 days, 30 days, 6, 12, 24, 36, 48, or 60 months.

Endpoint Definition

The AVVQ (Aberdeen Varicose Vein Questionnaire) is a validated, venous-disease specific QoL measure including 13 questions that each correspond to one of four clinically recognizable aspects of health, being 1) pain and dysfunction, 2) cosmetic appearance, 3) extent of varicosity, 4) complications [Garratt AM et al 1993]. The total score of AVVQ is the sum of all questions and ranges from 0 to 100 for each leg.
Scores are computed if at least half the items are completed within the instrument, i.e., if 7 or more questions are missing, the overall score is also set to missing. If a question is omitted by a patient the total possible score for that question is subtracted from the maximum possible score for the questionnaire. This way a score out of 100 can still be calculated by dividing the total score by the new maximum possible and multiplying by 100. For patients suffering from varicose veins in both legs, but

missing responses for a question divided into left and right legs, the entire question is set to missing. For questions divided into left and right legs, some patients suffering from varicose veins in only one leg have a tendency to miss out boxes for the unaffected leg, rather than ticking the first box implying no symptoms. As a rule, if a patient misses any of the response set for one leg and having completed question 1 has not drawn in any varicose veins on the same leg, their missing responses for that one leg should be coded as zero i.e. no symptoms. Question 4 of the AVVQ was not asked in this study and therefore is excluded from the scoring. Because this question is missing, the maximum possible score is 97.783. Calculating the modified AVVQ to account for missing questions uses the following adjustment: Score = 100 * [Patient Score] / [Max Possible Score] where Patient Score is the sum of the answered questions. The scoring instructions for the AVVQ are located in the Statistical Appendices.

Analysis Methods

The total AVVQ value at baseline, at each visit, and change from baseline will be summarized for ITT population. The comparison will be done between the VenaSeal and control (ETA or Surgical Stripping) arms. In order to test the above stated statistical hypothesis, a Wilcoxon two-sample test with t approximation will evaluate the change in the score index from baseline to time t.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

5. Change in EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) at 30 days, and 6, 12, 24, 36, 48 and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline.

Hypothesis

The following hypothesis will be tested:

H_0: $\mu_A(t) - \mu_A(0) = \mu_C(t) - \mu_C(0)$

H_a: $\mu_A(t) - \mu_A(0) \neq \mu_C(t) - \mu_C(0)$

where $\mu_A(t)$ and $\mu_C(t)$ are the mean EQ-5D scores at time point t in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively. Time t is any of 7 days, 30 days, 6, 12, 24, 36, 48, or 60 months.

Endpoint Definition

The EQ-5D is a two-component tool consisting of a descriptive part that evaluates five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the EQ-VAS, a vertical, visual analog scale, used for self-reporting on health. The EQ-5D index can be calculated based on the EQ-5D-5L crosswalk from the US TTO value set. Guidance is on the EuroQol Group website (EQ-5D- 5L Value Sets): https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf.

Analysis Methods

The EQ-5D index and visual analog scale (VAS) values at baseline, at each visit, and change from baseline will be summarized for ITT population. The comparison will be done between the VenaSeal and control

(ETA or Surgical Stripping) arms. In order to test the above stated statistical hypothesis, a Wilcoxon two-sample test with t approximation will evaluate the change in the score index from baseline to time t.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

6. Change in the 36-Item Short Form Health Survey (SF-36) reported by the patient at 30 days, and 6 and 12 months compared to baseline.

Hypothesis

The following hypothesis will be tested:

H_0: $\mu_A(t) - \mu_A(0) = \mu_C(t) - \mu_C(0)$

H_a: $\mu_A(t) - \mu_A(0) \neq \mu_C(t) - \mu_C(0)$

where $\mu_A(t)$ and $\mu_C(t)$ are the mean SF-36 physical or mental health scores at time point t in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively. Time t is any of 7 days, 30 days, 6, or 12 months.

Endpoint Definition

The SF-36 is a 36-item generic QoL tool measuring health across three dimensions and including eight separate scales: 1) Functional status (including physical functioning, social functioning, role limitations attributed to physical problems, and role limitations attributed to emotional problems), 2) wellbeing (including mental health, energy and fatigue, and pain), and 3) overall evaluation of health (including general health perception). This study will report the results of the physical functioning and mental health scales.

Analysis Methods

The SF-36 physical functioning and mental health scales at baseline, at each visit, and change from baseline will be summarized for ITT population. The comparison will be done between the VenaSeal and control (ETA or Surgical Stripping) arms. In order to test the above stated statistical hypothesis, a Wilcoxon two-sample test with t approximation will evaluate the change in the scales from baseline to time t.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

7. Change in the Venous Dependent Quality of Life (VenousDQoL) reported by the patient at 30 days, and 6, 12, 24, 36, 48, and 60 months (30 days, 6 and 12 months only for VenaSeal vs. Surgical Stripping Study) compared to baseline.

Hypothesis

There is no hypothesis test for this endpoint.

Endpoint Definition

Subjects answer their general quality of life with potential responses on an ordinal scale as follows: excellent, very good, good, neither good nor bad, bad, very bad, or extremely bad. Subjects also answer what their quality of life would be without varicose veins with potential responses on an ordinal scale as follows: very much better, much better, a little better, the same, or worse.

Analysis Methods

For each treatment arm and time point, the count and percentage of subjects with each response will be presented.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

7.9.1.8 Provider Experience secondary endpoint

Hypothesis

The following hypothesis will be tested:

H_0: $p_A = p_C$
H_a: $p_A \neq p_C$
Where p_A and p_C are the probability of responding extremely satisfied or satisfied in the VenaSeal™ system arm and the ETA or surgical stripping arm, respectively.

Endpoint Definition

Provider experience will be assessed post-index procedure for all treatment modalities, evaluating overall satisfaction with the procedure. The physician will be asked to record his satisfaction with the procedure based on five-point scale ranging from ‘extremely satisfied’ to ‘extremely dissatisfied’. If the physician chooses ‘extremely dissatisfied’ or ‘dissatisfied’, options for reason of dissatisfaction include ‘patient adverse event’, ‘patient discomfort or dissatisfaction’, ‘device component issue’, ‘procedure time’, ‘procedure steps’, and ‘other’.

Analysis Methods

The percentage of providers responding either extremely satisfied or satisfied to the provider experience question per procedure. A Fisher's exact test will be used to compare the fraction of physicians reporting 'extremely satisfied' or 'satisfied' in each arm.

Determination of Subjects for Analysis

The analysis will consist of the ITT population.

7.9.2 VLU (Single Arm) Study

Analyses will be performed on all ITT subjects in the VLU Study.

Descriptive statistics will be presented for the study endpoints. For categorical variables, the count and percentage of subjects with each outcome will be presented. For continuous variables, summary statistics (mean, standard deviation, median) will be presented. Time to-event response variables may be displayed by using a Kaplan-Meier plot or cumulative incidence curve.

7.9.2.1 Analysis of Primary Endpoint

7.9.2.1.1 Hypothesis

There is no hypothesis testing for this primary endpoint.

7.9.2.1.2 Endpoint Definition

The primary endpoint of the VLU Study is time to ulcer healing and will be measured until healing has occurred, calculated through healing confirmation and verified by an independent core laboratory through 12 months. Once the site research team has been informed of all wounds healing on the target ulceration by the wound care center, the subject will undergo an ulcer healing verification visit within 2 weeks of ulcer healing to confirm healing and collect photographs of the ulcer. The ulcer assessment core laboratory will verify healing. If core laboratory does not confirm healing with the first set of photographs, the subject will return in 1 week for additional photographs to be collected and sent to the core laboratory. If the core laboratory does not confirm healing after the second set of photographs, but the treating physician believes the ulcer has healed, the ulcer will be classified as healed.

7.9.2.1.3 Rationale for Performance Criteria

There is no performance criteria and descriptive statistics will be presented for primary endpoint.

7.9.2.1.4 Analysis Methods

As a primary analysis, the Kaplan-Meier estimate on the time to ulcer healing will be provided. The subjects who are lost to follow up or exit but have no record on the time to ulcer healing will be censored at the time of last follow-up visit. Day 0 is the day of index procedure.

The median time to ulcer healing of the primary endpoint will be assessed from survival analysis when survival exceeds 50%. The two-sided 95% confidence interval of the median time to ulcer healing will be provided using the following formula to calculate the upper and lower bounds of a confidence interval for a median[2]:

j: $nq - z^*\sqrt{nq(1-q)}$

k: $nq + z^*\sqrt{nq(1-q)}$

where:

- **n:** The sample size
- **q:** The quantile of interest. For a median, we will use q = 0.5.
- **z:** The z-critical value

The j and k are rounded up to the next integer. The resulting confidence interval is between the jth and kth observations in the ordered sample data.

If any subjects do not have an observed ulcer healing time through 12 months, their ulcer healing times will be considered to be greater than 12 months for the purpose of calculating the confidence interval for the median.

Other summary statistics may be presented describing the distribution of time to ulcer healing.

7.9.2.1.5 Determination of Subjects' Data for Analysis

ITT population with data available will be used for the primary analysis on primary endpoint. For the secondary analysis, PP population will be used on the primary endpoint.

7.9.2.1.6 Missing Data Analysis

No statistical techniques will be used to impute missing data considering that time-to-event analysis will appropriately account for censoring.

7.9.2.2 Secondary Endpoints

The following are the analysis methods for the secondary endpoints in the VLU single-arm study. There There are no formal hypothesis tests for any of these endpoints.

7.9.2.3 Effectiveness secondary endpoints

The following ulcer-specific effectiveness endpoints will be evaluated:

1. Ulcer healing rate

Endpoint Definition

Ulcer healing rate is calculated by the percentage of the ulcer area healed, which is

$$100 * (1 - Area_k / Area_0)$$

for subject visit k. $Area_0$ indicates the wound area at baseline in cm^2. Measurements are taken by an independent core laboratory through 24 months or until ulcer healing has been confirmed. When the ulcer healing is confirmed, the ulcer healing percentage shall be set to 100. If $Area_k$ is larger than $Area_0$, then the percentage is set to 0.

Analysis Methods

Mean, standard deviation and sample size will be presented on Ulcer healing rate. Summary statistics will also be provided for area at baseline and area at each subject visit k.

Determination of Subjects for Analysis

ITT population with data available will be used.

2. Ulcer recurrence on the target limb through 60 months.

Endpoint Definition

Sites document the occurrence of an ulcer recurrence at subject visits along with the date of the recurrence.

Analysis Methods

The Kaplan-Meier estimates through 60 months on the time to ulcer recurrence will be provided. The subjects who are lost to follow up or exit without recurrence will be censored at the time of last contact. Day 0 is the day of ulcer healing.

Determination of Subjects for Analysis

Subjects from the ITT population with healed ulcers

3. Ulcer-free time

Endpoint Definition

Days between initial ulcer healing and first ulcer recurrence, as applicable, through 60 months.

Analysis Methods

Summary statistics including mean, standard deviation, median, minimum and maximum will be provided.

Determination of Subjects for Analysis

Subjects who have experienced a healed ulcer followed by an ulcer recurrence.

The following generic effectiveness endpoints will be evaluated:

4. Anatomic closure of the primary target vein at 30 days, and 12, 24, 36, 48 and 60 months:

Endpoint Definition

For subjects treated with the VenaSeal™ system it is defined as DUS showing vein closure, for the primary target vein, along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.

Analysis Methods

The probability of primary target vein closure of any primary target vein at each time point will be summarized. The probability will be estimated using the Kaplan-Meier method. Day zero is the date of the index procedure. The censoring time is the time to last study visit (scheduled or unscheduled), the time point for analysis, or time to exit, whichever comes first. Lack of anatomic closure on the date of the

index procedure will not be considered relevant to this endpoint, since some treatments may not achieve closure immediately.

Determination of Subjects for Analysis

ITT population

5. Anatomic closure of target vein at 30 days, and 6, 12, 24, 36, 48 and 60 months:

Endpoint Definition

Anatomic closure of the target vein is defined as DUS showing target vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.

Analysis Methods

The probability of target vein closures of any target vein at each time point will be summarized. The probability will be estimated using the Kaplan-Meier method. Day zero is the date of the index procedure. The censoring time is the time to last study visit (scheduled or unscheduled), the time point for analysis, or time to exit, whichever comes first. Lack of anatomic closure on the date of the index procedure will not be considered relevant to this endpoint because some treatments may not achieve closure immediately.

Determination of Subjects for Analysis

ITT population

6. Technical success of each target vein immediately post-index procedure

Endpoint Definition

Technical success of the target vein is defined as DUS taken immediately post-index procedure showing target vein closure along the entire treated vein segment with no discrete segments of patency exceeding 5 cm.

Analysis Methods

The percentage of technical successes will be summarized by treatment arm in each study. The numerator is the number of technical successes, the denominator is the number of target veins treated at the index procedure.

Determination of Subjects for Analysis

AT population

7. Reintervention of any target vein (including primary target vein) through 60 months.

Endpoint Definition

A reintervention is a retreatment of any segment of any target vein in the target limb previously treated as part of the study at the index procedure. Reinterventions are assessed at each follow-up visit.

Analysis Methods

The rate of reintervention will be summarized. The rate is calculated such that the numerator is the number of reinterventions and the denominator is the number of vein-years of follow-up. The amount of follow-up per person is defined as their date of exit or last known follow-up minus their date of index procedure. The vein-years is the amount of person-years times the number of target veins.

Determination of Subjects for Analysis

ITT population

7.9.2.4 Safety secondary endpoints

1. Adverse events (AEs) occurring in the target limb, evaluated from index procedure through 12 months.

Endpoint Definition

- Hypersensitivity to VenaSeal™ adhesive, defined as an allergic reaction to the VenaSeal™ adhesive. The presence of hypersensitivity is confirmed through adjudication. Relatedness to a study procedure and relatedness to the study device are defined.
- Phlebitis, defined as inflammatory reaction of a treated vein. The presence of phlebitis is confirmed through adjudication. Relatedness to a study procedure and relatedness to the study device are defined.
- Granuloma, defined as a grouping of macrophages. The presence of granuloma is confirmed through adjudication. Relatedness to a study procedure and relatedness to the study device are defined.
- Endovenous glue induced thrombosis (EGIT), defined as extensions of a thrombus that extend from the treated vein into the deep venous system. The presence of a glue extension, thrombus extension, or combination glue/thrombus is confirmed through DUS visualization of the extension into the common femoral vein or popliteal vein from the target vein and extension length is specified.

CEC determination of the above events will be used for reporting.

Analysis Methods

Adverse events that are in any of the above enumerated categories will be characterized. Adverse events will be categorized per the specified definitions, and then summarized.

Determination of Subjects for Analysis

The safety analysis will consist of the ITT population.

2. Additional events evaluated through 60 months:

- Symptomatic deep vein thrombosis (DVT) events
- Symptomatic Pulmonary embolism (PE)

- Serious adverse events (SAEs)

Endpoint Definition

CEC determination of serious adverse events will be used for reporting. The MedDRA codes for Deep vein thrombosis and Pulmonary embolism will be used for reporting of DVT and PE adverse events.

Analysis Methods

The probability of experiencing an SAE through 12 months will be estimated using the Kaplan-Meier method. Day zero is the date of the index procedure. The censoring time is the time to study exit, the later of either the last contact date or the discontinuation date, or the time point for analysis, whichever comes first. The DVT and PE events will be summarized by reporting the number of events of each type and the number of patients in which they occurred. Additionally, summary statistics will report the proportion of SAEs. Numerator is the number of target limbs (or subjects) with an SAE through 12 months, denominator is the number of target limbs (or subjects).

Determination of Subjects for Analysis

The safety analysis will consist of the ITT population.

7.9.2.5 Healthcare utilization secondary endpoints

The following healthcare utilization secondary endpoint data will be collected:

1. Number and type of adjunctive treatments conducted through 12 months post-index procedure.

Endpoint Definition

Rate of adjunctive procedures, phlebectomy or sclerotherapy, for varicosity on the target limb through 12 months post index procedure.

Analysis Methods

The number and rate of adjunctive procedures through 12 months will be estimated. To calculate the rate, the numerator is the count of adjunctive procedures. The denominator is the number of person-years of follow-up. The amount of follow-up per person is defined as their date of exit or last known follow-up or the date of their 12 month follow-up visit (whichever is first) minus their date of index procedure. A similar estimate will be constructed for the type of adjunctive procedure, phlebectomy or sclerotherapy.

Determination of Subjects for Analysis

ITT population.

2. Healthcare utilization related to the target limb Venous Reflux Disease (VRD), as determined by the number of healthcare visits conducted between study visits through 60 months.

Endpoint Definition

Rate of healthcare utilization visits related to venous reflux disease.

Analysis Methods

The number and rate of healthcare utilization visits will be estimated. To calculate the rate, the numerator is the count of HCU visits. The denominator is the number of person-years of follow-up. The amount of follow-up per person is defined as their date of exit or last known follow-up minus their date of index procedure. A similar estimate will be constructed within the HCU type of interest (Inpatient, Outpatient, Clinic, Outpatient ER visits).

Determination of Subjects for Analysis

ITT population

3. Procedures, tests, and treatment of AEs related to the treatment modality or index procedure through 60 months.

Endpoint Definition

Healthcare utilization measured by number of healthcare resources utilized for treatment of adverse events, including hospitalization, prolongation of hospitalization, actions taken or diagnostic tests performed.

Analysis Methods

A listing will be provided per adverse event of the actions taken.

Determination of Subjects for Analysis

ITT population

4. Healthcare utilization and routine wound care treatments between study visits through 60 months.

Endpoint Definition

Measurement of the type of wound care treatment (debridement, skin graft, dressing change, Unna boots, or other) and the quantity.

Analysis Methods

The counts of the type of wound care administered per study visit will be characterized.

Determination of Subjects for Analysis

ITT population

7.9.2.6 Patient Experience secondary endpoints

1. Time to return to work as reported by the patients.

Endpoint Definition

Return to work is defined as the time in days patients need following a procedure to return to work.

Analysis Methods

For the return to work endpoint, a Kaplan-Meier survival estimator will be used to estimate the survival function. A cumulative incidence figure will be produced. If a patient is reported to have returned to work, but the date of return is unknown, the return date will be imputed from the date of the follow-up visit date for the unknown date of return. Day zero is the date of the index procedure. The censoring time is the time to study exit, the later of either the last contact date or the discontinuation date, or the time point for analysis, whichever comes first. For those who have returned to work, the median, Q1, Q3, minimum, and maximum will summarize the number of days to return to work, as well as the number who have not returned to work.

Determination of Subjects for Analysis

The return to work analysis will consist of patients who report having an occupation (employed or independent worker, including stay-at-home parent) at their baseline visit.

2. Time to return to normal activities as reported by the patients.

Endpoint Definition

Time to return to normal activities as reported by the patients.

Analysis Methods

For the return to normal activities endpoint, a Kaplan-Meier survival estimator will be used to estimate the survival function. A cumulative incidence figure will be produced. Day zero is the date of the index procedure. The censoring time is the time to study exit, the later of either the last contact date or the discontinuation date, or the time point for analysis, whichever comes first. If a patient is reported to have returned to normal activities, but the date of return is unknown, the return date will be imputed from the date of the follow-up visit date for the unknown date of return. For those who have returned to normal activities, the median, Q1, Q3, minimum, and maximum will summarize the number of days to return to normal activities, as well as the number who have not returned to normal activities.

Determination of Subjects for Analysis

ITT population

3. Intra-procedural and post-procedural pain at the index procedure, and 7 days and 30 days as reported by the patient using the numeric rating scale (NRS) with a scale of 0-10.

Endpoint Definition

Pain is reported by the patient using a scale ranging from 0-10.

Analysis Methods

The total pain values at baseline, at each visit will be summarized.

Determination of Subjects for Analysis

ITT population

4. Change in venous disease symptoms at 7 and 30 days, and at 6, 12, 24, 36, 48, and 60 months compared to baseline, as measured by the revised Venous Clinical Severity Score (rVCSS) and subject self-reporting.

Endpoint Definition

The VCSS is a validated 10-question venous disease severity measurement intended to evaluate the responses to changes in disease severity over time and in response to treatment. Each signs / symptom can have a grade ranging from 0 (absent) to 3 (severe). The total VCSS score is the sum of all questions. The score ranges from 0 (no venous disease) to 30 (severe venous disease).

Analysis Methods

The total VCSS value at baseline, at each visit, and change from baseline will be summarized.

Determination of Subjects for Analysis

ITT population.

5. Change in AVVQ score at 30 days, and 6, 12, 24, 36, 48, and 60 months compared to baseline.

Endpoint Definition

The AVVQ (Aberdeen Varicose Vein Questionnaire) is a validated, venous-disease specific QoL measure including 13 questions that each correspond to one of four clinically recognizable aspects of health, being 1) pain and dysfunction, 2) cosmetic appearance, 3) extent of varicosity, 4) complications [Garratt AM et al 1993]. The total score of AVVQ is the sum of all questions and ranges from 0 to 100 for each leg.
Scores are computed if at least half the items are completed within the instrument, i.e., if 7 or more questions are missing, the overall score is also set to missing. If a question is omitted by a patient the total possible score for that question is subtracted from the maximum possible score for the questionnaire. This way a score out of 100 can still be calculated by dividing the total score by the new maximum possible and multiplying by 100. For patients suffering from varicose veins in both legs, but missing responses for a question divided into left and right legs, the entire question is set to missing. For questions divided into left and right legs, some patients suffering from varicose veins in only one leg have a tendency to miss out boxes for the unaffected leg, rather than ticking the first box implying no symptoms. As a rule, if a patient misses any of the response set for one leg and having completed question 1 has not drawn in any varicose veins on the same leg, their missing responses for that one leg should be coded as zero i.e. no symptoms. Question 4 of the AVVQ was not asked in this study and therefore is

excluded from the scoring. Because this question is missing, the maximum possible score is 97.783. Calculating the modified AVVQ to account for missing questions uses the following adjustment: Score = 100 * [Patient Score] / [Max Possible Score] where Patient Score is the sum of the answered questions. The scoring instructions for the AVVQ are located in the Statistical Appendices.

Analysis Methods
The total AVVQ value at baseline, at each visit, and change from baseline will be summarized for ITT population.

Determination of Subjects for Analysis
ITT population.

6. Change in EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D-5L) at 30 days, and 6, 12, 24, 36, 48 and 60 months compared to baseline.

Endpoint Definition

The EQ-5D is a two-component tool consisting of a descriptive part that evaluates five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the EQ-VAS, a vertical, visual analog scale, used for self-reporting on health. The EQ-5D index can be calculated based on the EQ-5D-5L crosswalk from the US TTO value set. Guidance is on the EuroQol Group website (EQ-5D- 5L Value Sets): https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf.

Analysis Methods

The EQ-5D index and visual analog scale (VAS) values at baseline, at each visit, and change from baseline will be summarized for ITT population.

Determination of Subjects for Analysis

ITT population

7. Change in the 36-Item Short Form Health Survey (SF-36) reported by the patient at 30 days, and 6 and 12 months compared to baseline.

Endpoint Definition
The SF-36 is a 36-item generic QoL tool measuring health across three dimensions and including eight separate scales: 1) Functional status (including physical functioning, social functioning, role limitations attributed to physical problems, and role limitations attributed to emotional problems), 2) wellbeing (including mental health, energy and fatigue, and pain), and 3) overall evaluation of health (including general health perception). This study will report the results of the physical functioning and mental health scales.

Analysis Methods
The SF-36 physical functioning and mental health scales at baseline, at each visit, and change from baseline will be summarized for ITT population. The comparison will be done between the VenaSeal and control (ETA or Surgical Stripping) arms. In order to test the above stated statistical hypothesis, a Wilcoxon two-sample test with t approximation will evaluate the change in the scales from baseline to time t.

Determination of Subjects for Analysis

ITT population

8. Change in the Venous Dependent Quality of Life (VenousDQoL) reported by the patient at 30 days, and 6, 12, 24, 36, 48, and 60 months compared to baseline.

Endpoint Definition
Subjects answer their general quality of life with potential responses on an ordinal scale as follows: excellent, very good, good, neither good nor bad, bad, very bad, or extremely bad. Subjects also answer what their quality of life would be without varicose veins with potential responses on an ordinal scale as follows: very much better, much better, a little better, the same, or worse.

Analysis Methods
For each time point, the count and percentage of subjects with each response will be presented.

Determination of Subjects for Analysis
ITT population

In addition, the primary endpoints of the Randomized Studies will also be assessed for the VLU Study:

9. Peri-procedural patient satisfaction from the VenousTSQe at 30 days

Endpoint Definition

Peri-procedural patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQe) at *30 days* post index-procedure. Scoring is as described in Section 7.9.1.1.2 above.

Analysis Methods

Summary statistics for the Venous TSQe at the 30 day visit will be presented.

Determination of Subjects for Analysis

ITT population

10. Patient satisfaction from the VenousTSQs at 30 days

Endpoint Definition

Overall patient satisfaction as measured by a validated, patient-centered venous treatment satisfaction questionnaire (VenousTSQs) at 30 days post index-procedure. Scoring is as described in Section 7.9.1.1.2 above.

Analysis Methods

Summary statistics for the Venous TSQs at the 30 day visit will be presented.

Determination of Subjects for Analysis

ITT population

11. Elimination of clinically relevant superficial truncal disease in target vein at the time of index procedure

Endpoint Definition

Elimination of clinically relevant superficial truncal disease in each target vein at the time of index procedure as measured by the percentage of target vein length successfully treated

Analysis Methods

Summary statistics will be presented.

Determination of Subjects for Analysis

ITT population

7.9.2.7 Provider Experience secondary endpoint

Endpoint Definition

Provider experience will be assessed post-index procedure for all treatment modalities, evaluating overall satisfaction with the procedure. The physician will be asked to record his satisfaction with the procedure based on five-point scale ranging from 'extremely satisfied' to 'extremely dissatisfied'. If the physician chooses 'extremely dissatisfied' or 'dissatisfied', options for reason of dissatisfaction include 'patient adverse event', 'patient discomfort or dissatisfaction', 'device component issue', 'procedure time', 'procedure steps', and 'other'.

Analysis Methods

The percentage of providers responding either extremely satisfied or satisfied to the provider experience question per procedure.

Determination of Subjects for Analysis

ITT population

7.10 Safety Evaluation

Descriptive statistics for the safety events will be provided. Quantitative variables will be presented with mean and standard deviation or median, minimum and maximum as appropriate. Qualitative variables will be presented with frequency and percentage. AEs will be tabulated and reported using the current version of MedDRA dictionary. SAEs will be tabulated and reported up to 60 months (up to 12 months for VenaSeal vs. Surgical Stripping study).

All observed device deficiencies that could have led to a serious adverse device effect and deaths with reason will be listed. Patient data listings and tabular and graphical presentations of results will be provided if needed.

Counts of Adverse Events through 60 months will be calculated for each study arm within each study, by event severity, by event type, by event relatedness to the study procedure, and by relatedness to the study device. Adverse events through 60 months will be summarized by treatment, System Organ Class (SOC) and Preferred Term (PT) terms on ITT. Similar counts will be provided up to 12 months in the VenaSeal vs. Surgical Stripping study.

A summary listing of all adverse events, including severity, treatment needed, resolution, relatedness to the study procedure, and relatedness to the study device will be produced.

A summary listing of all observed device deficiencies that could have led to a serious adverse event will be produced.

A summary listing of all deaths, including reasons for each death, will be produced.

7.11 Health Outcomes Analyses

This study will collect healthcare utilization data related to subject's venous reflux disease and care related to the VenaSeal™ closure system to demonstrate total costs over the follow-up period. Specifically, this study will collect:

1. Number and type of adjunctive treatments conducted through 60 months post-index procedure.
2. Subject's healthcare utilization related to their target limb VRD, as determined by medical record review and/or subject's report of healthcare visits conducted, and other health-related resources utilized (e.g., home healthcare services) between study visits
3. Procedures, tests, and treatment of AEs related to the VenaSeal™ system or the index procedure, as reported by sites in AE reporting
4. VLU Study: Subject's healthcare utilization and routine wound care treatments between follow-up visits through 60 months

US cost and global effectiveness data collected in the study will be used to validate and update VenaSeal™ system US cost-effectiveness model developed by Medtronic. The healthcare utilization data from non-US countries will then be transformed to identified regional costs which will then be used as model parameters for global regional cost-effectiveness and/or budget impact model adaptations.

Specific analysis will focus on additional VLU healthcare utilization for all ulcers on the target limb, including routine wound care treatment through ulcer healing. The additional VLU healthcare utilization will not be only limited to routine wound care treatments but also any other unscheduled healthcare utilizations including office visits and emergency room visits. The analysis in this section will be handled by healthcare economics team and an additional analysis plan will be created. The results of this analysis may not be included in the clinical study report.

Additional analyses to support country or payer-specific reimbursement needs will also be performed as necessary. Such analyses will be outlined in a separate Health Economics Analysis Plan developed and maintained by the Medtronic Reimbursement and Health Economics team. Analyses of this type may be outsourced to external vendors as necessary.

7.12 Changes to Planned Analysis

Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

8. Validation Requirements

Level I validation will be used for all the analysis on primary and key secondary endpoints. For all the other analysis, at least Level II validation will be used. Validation methods for each statistical output will be documented in the validation report (056-F288).

9. References

1. Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological)*, *57*(1), 289-300.
2. Conover W.J. Practical Nonparametric Statistics, 3rd Edition; New York, John Wiley & Sons, 1999.
3. da Silva, G.T., Logan, B.R., and Klein J.P. (2009) Methods for Equivalence and Noninferiority Testing. Biol Blood Marrow Transplant, 15, 120-127.

10. Statistical Appendices

Scoring instructions for the AVVQ:

AVVQ-scoring instructions Garratt.

The table below is guiding on how to input missing dates for AE onset:

Valid Portion	Missing Portion	Imputed Value for missing Portion
Month, Year	Day	Set Day = first day of that month and year, then set the day = later of (Imputed onset date, procedure date).
Year	Day, Month	Set date = later of (January 1st of that year, procedure date).
None	Day, Month, Year	Date of Procedure