Protocol Number:	S2473
Protocol Short Title:	Varithena versus Endothermal Ablation of the Great Saphenous Vein (VERITAS)
Protocol Name:	A Phase 4 Randomized Trial Comparing Varithena to Endothermal Ablation for the Treatment of the Great Saphenous Vein
Global Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752, United States
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Protocol Medical Safety Director:	Anna Chavez, MD Boston Scientific Anna.Chavez@bsci.com
Product:	Varithena (polidocanol injectable foam) 1%
Protocol ver.1.0 Approval Date:	23Feb2022
Protocol Amendment ver.1.2 Approval Date:	17Aug2023

NCT 05312970

Table 1: Protocol Revision History

VERSION NUMBER	AMENDMENT APPROVAL DATE	BRIEF DESCRIPTION OF CHANGES
1.0	23Feb2022	Original protocol
1.1	18Oct2022	Updated Table 2, clarified treatment groups-control arm, clarified Section 3.2 Description of Varithena, clarified Section 6.1.2 Retreatment Criteria, updated Section 7.3.15 Duplex Ultrasound reference, updated Section 11.8 End of Study now termed Trial Completion with expanded definitions, updated Varithena USPI references, clarified rVCSS assessment, updated Varithena complaint reporting mailbox address
1.2	17Aug2023	Revised Informed Consent Process to standard Boston Scientific Informed Consent language Section 7.3.1, Clarified Point of Enrollment Section 7.3.8, added Point of Treatment 7.3.10, and updated references to enrollment, randomization, and treatment throughout.

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Table 2: Terms, Acronyms, Abbreviations

The following abbreviations and specialist terms are used in this protocol.

AASV	Anterior Accessory Saphenous Vein
ABPI	Ankle-Brachial Pressure Index
ADR	Adverse Drug Reaction
AE	Adverse Event
CEAP	Clinical condition, etiological, anatomical location, and pathophysiological
CFR	Code of Federal Regulation
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CV	Curriculum Vitae
CVD	Chronic Venous Disease
CVI	Chronic Venous Insufficiency
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D	EuroQoL-5D
ETA	Endothermal Ablation
EVLA	Endovenous Laser Ablation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSV	Great Saphenous Vein
HASTI	Heaviness, Achiness, Swelling, Throbbing, and Itching
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instruction for Use
IPR-V3	Independent Photographic Review Visible Varicose Veins
IRB	Institutional Review Board

ISO	International Organization for Standardization
LOCF	Last non-missing post-baseline observation carried forward
mL	millilitre
PA-V3	Patient Assessment of Visible Varicose Veins
PCF	Physician-Compounded Foam
PI	Principal Investigator
QOL	Quality of Life
RFA	Radiofrequency Ablation
rVCSS	revised Venous Clinical Severity Score
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFJ	Saphenofemoral Junction
SoC	Standard of Care
SSV	Small Saphenous Vein
SUSAR	Suspected Unexpected Serious Adverse Reaction
USPI	United States Prescribing Information
VCSS	Venous Clinical Severity Score
VEINES-QOL/Sym	Venous insufficiency Epidemiological and Economic Study – Quality of Life/Symptoms
ver.	Version
VTU	Varithena Transfer Unit
VVSymQ	Varicose Veins Symptoms Questionnaire
WHO	World Health Organization
WOCP	Women of Child-bearing Potential

PROTOCOL SYNOPSIS

Protocol Number	S2473
Protocol Short Title	Varithena versus Endothermal Ablation of the Great Saphenous Vein (VERITAS)
Protocol Title	A Phase 4 Randomized Trial Comparing Varithena to Endothermal Ablation for the Treatment of the Great Saphenous Vein
Product	Varithena® (polidocanol injectable foam) 1%
Type of Protocol	Phase 4
Study Rationale	The purpose of this study is to observe insights into the benefits of Varithena compared to Endothermal Ablation (ETA) in the treatment of the great saphenous vein
Study Objectives	To collect comparative evidence on patient reported outcomes of Varithena compared to ETA when used to treat the incompetent great saphenous vein (GSV). ETA will include either radiofrequency ablation or endovenous laser ablation according to the site's standard practice. To provide long term (1-year, 2-year, and 3-year) outcomes.
Primary Endpoint	Change in Varicose Veins Symptoms Questionnaire (VVSymQ) between baseline and 3-month post treatment
Additional Assessments	• Change from baseline in revised Venous Clinical Severity Score (rVCSS) at 7-day, 3-month, 6-month, 12-month, 24-month, and 36-month post treatment • VEINES-QOL/Sym and EQ-5D at 7-day, 3-month, 6-month, 12-month, 24-month, and 36-month post treatment • Clinical condition, etiological, anatomical location, and pathophysiological (CEAP) clinical condition classification at 7-day, 3-month, 6-month, 12-month, 24-month, and 36-month post treatment • Varithena, ETA, and Procedure related serious adverse events (SAE) • Healthcare resource utilization for treated limb venous disease at 12-month, 24-month, and 36-month post treatment
Study Duration	Enrollment is estimated to take 9 months. The study will be considered complete with regard to the primary endpoint after all subjects have completed the 3-month follow-up. It is estimated that it will take approximately 4 years to complete this trial.
Study Design	Multicenter, randomized, controlled, open-label, parallel group trial.
Study Population	Patients with GSV incompetence, defined as reflux > 0.5 seconds on duplex ultrasound in a single limb.
Number of Patients	Approximately 100 randomized and treated subjects
Number & Location of Sites	Up to 15 sites located in the United States

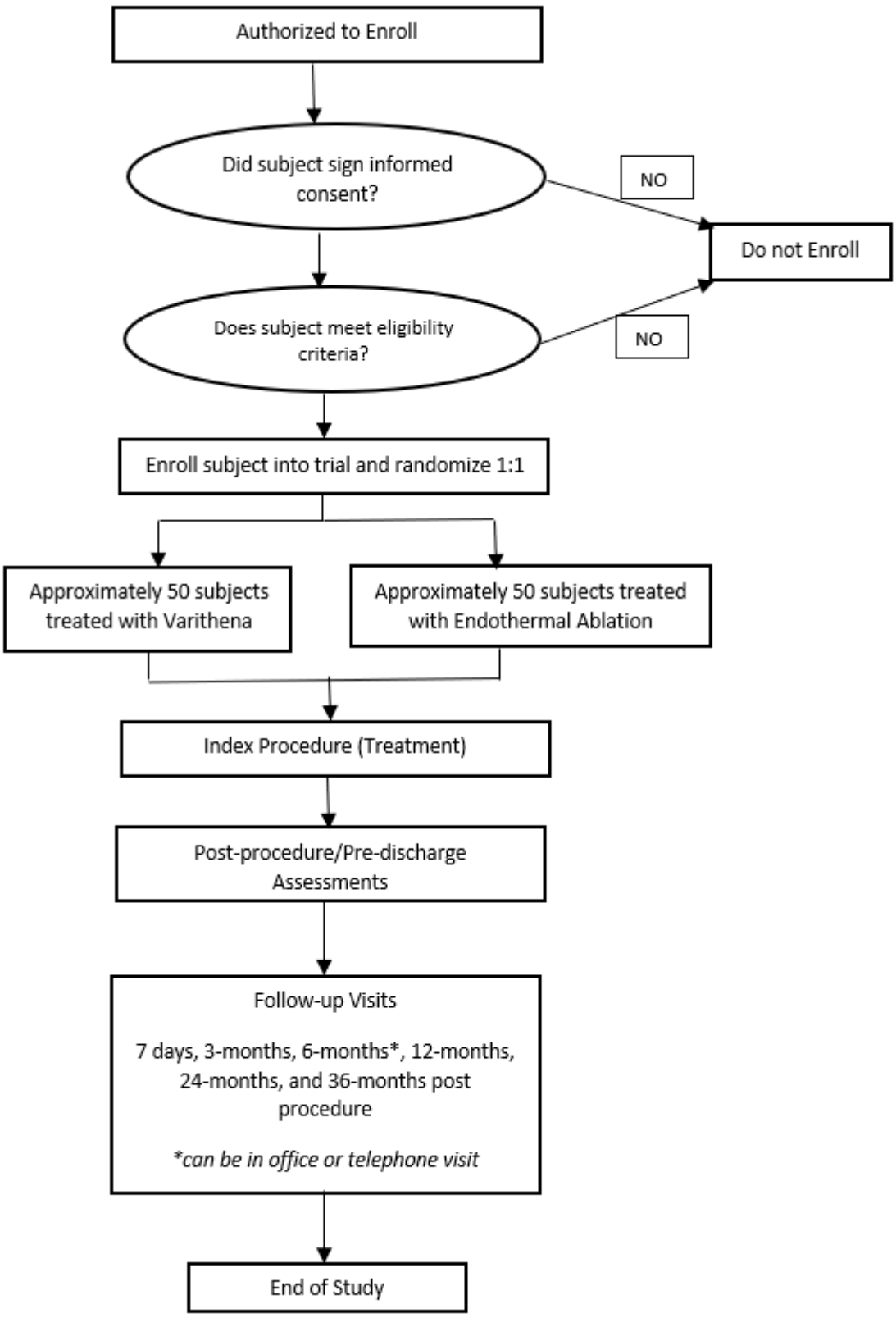
Treatment Groups – Control arm	FDA approved (PMA) or cleared (510k) ETA systems, including Radiofrequency ablation (RFA) systems or Endovenous laser ablation (EVLA) systems.
Treatment Groups – Investigational arm	Varithena® (polidocanol injectable foam) 1%
Multiple Interventions During Treatment	Additional interventions or treatments of the treated vein are not allowed during the index procedure or at any time until after the 3-month (primary endpoint) visit. Additional veins cannot be treated until after the 3-month timepoint.
Inclusion / Exclusion Criteria	Inclusion Criteria 1. Age ≥ 18 2. Primary GSV incompetence, defined as reflux > 0.5 seconds on Duplex ultrasound in a single limb (Note the contralateral limb can have varicosities or SVI if intervention is not required within 3 months i.e. asymptomatic) 3. Failed conservative therapy (compression, diet, exercise, leg elevation) 4. CEAP Clinical Condition Classification C2 - C6 5. Vein diameter 5-10mm, inclusive 6. GSV treatable length > 10cm 7. Superficial venous disease manifest by clinical symptoms (rVCSS ≥ 4) 8. Able to comprehend and sign an informed consent document and complete written study questionnaires 9. Willing and able to return for scheduled follow-up visits (7-days, 3-months, 6-months, 12-months, 24-months, and 36-months post-procedure) 10. Willingness to comply with post-treatment compression protocol Exclusion Criteria 11. Allergy to polidocanol, xylocaine, or epinephrine 12. Deep vein thrombosis or pulmonary embolism within 3 months prior to randomization or hypercoagulable disorder 13. Post thrombotic deep vein disease above the calf veins 14. Pregnancy or lactating (within 30 days of randomization) 15. Symptomatic peripheral arterial disease or ankle-brachial pressure index (ABPI) < 0.8 16. Previous treatment to targeted incompetent GSV or previous superficial thrombophlebitis in targeted GSV 17. Previous venous intervention in affected limb in past 3 months 18. Local aneurysmal GSV segments 19. Inability to walk unaided 20. Inability to wear post-procedure compression bandaging and stockings 21. Patients with clinically significant reflux of the small saphenous vein (SSV) or anterior accessory saphenous vein (AASV)

	22. In the clinical judgement of the investigator, patient who will require ipsilateral deep venous intervention within 3 months following randomized treatment 23. In the clinical judgement of the investigator, patient who will require contralateral venous intervention (superficial or deep) within 3 months following randomized treatment 24. Patient on therapeutic anticoagulants 25. Active malignancy 26. Life expectancy < 2 years 27. Documented COVID-19 infection currently or within 2 months prior to randomization 28. Enrollment in another clinical trial that could confound the endpoint within 3 months prior to screening or within 3 months following enrollment
Sample Size Justification	The objective of the study is to measure the change in VVSymQ score for both treatment groups within the same patient population in the same clinical setting, and the study is not powered to detect a difference between treatments. Whilst there is no pre-specified hypothesis relating to the comparison between treatment groups, a sample size of approximately 100 patients would allow a minimally detectable absolute difference of 2.0 points in a t-test with 2-sided alpha level of 0.05, assuming a standard deviation of 5.0 points in both arms. The assumption for the standard deviation is based on baseline standard deviation values observed in the Vanish 1 and Vanish 2 studies (4.96 and 4.55, respectively).
Statistical Methods	The absolute change in VVSymQ score between baseline and 3-month follow-up will be evaluated for each subject. Changes in scores will be summarized by treatment group (n, mean, standard deviation, min, max, and 95% confidence interval) and compared using a two-sample t-test.
Procedures in Screening/Baseline Period	The following assessments are collected or obtained during the screening and baseline period: • Informed consent • Demographics and medical history • Duplex ultrasound • Mapping of superficial and deep veins • VVSymQ • VEINES-QOL/sym • rVCSS • CEAP Clinical Classification • EQ-5D
Randomization	After written informed consent has been obtained, patients will be randomized 1:1 to either Varithena or ETA. Randomization will be performed by a computer-generated block randomization scheme. The EDC system will be used to randomize patients by site into the trial.

Study Visits and Follow-up	Subject visits will occur at baseline and at the treatment procedure, with follow-up visits at 7-days, 3-months, 6-months, 12-months, 24-months, and 36-months post-procedure. Assessment of the primary endpoint will occur at 3-months post-procedure. All follow-up visits will be conducted in the office/clinic with the exception of the 6-months post-procedure which may be conducted either in the office/clinic or via telephone contact.

The study will be conducted and documented in accordance with the current Declaration of Helsinki, the protocol, standards of Good Clinical, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical study agreement.

1 SCHEMA



2 SCHEDULE OF VISITS

Procedure/Assessment	Screening	Index procedure (Treatment)	Follow-up Visits					
			7 days post procedure (± 3 days) office visit	3 months post procedure (± 14 days) office visit	6 months post procedure (± 14 days) office visit or telephone	12 months post procedure (± 30 days) office visit	24 months post procedure (± 30 days) office visit	36 months post procedure (± 30 days) office visit
Informed consent process	X							
Demographics	X							
Medical history	X							
Physical examination	X							
Duplex ultrasound	X		X	X		X	X	X
Mapping of superficial and deep veins	X							
Randomization	X							
Varithena or ETA procedure		X						
VVSymQ	X		X	X	X	X	X	X
VEINES-QOL/sym	X		X	X	X	X	X	X
rVCSS	X		X	X	X	X	X	X
EQ-5D	X		X	X	X	X	X	X
CEAP Clinical Classification	X		X	X	X[1]	X	X	X
Adverse event assessment		X	X	X	X	X	X	X

[1]Performed only if patient returns for office visit

3 BACKGROUND

3.1 Disease background

The exact etiology and pathophysiology of varicose veins remains elusive, however, valvular dysfunction leading to valvular reflux is thought to be the underlying cause.[1] Varicose veins due to failure of the terminal (proximal) valve of the great saphenous vein (GSV) at the saphenofemoral junction (SFJ) is commonly seen, affecting up to 25% of the adult population in the United States with the prevalence and severity increasing with age.[2] More than 30 million adults in the United States aged 18 to 70 have varicose veins, with women twice as likely as men to develop varicosities. Varicose veins often require treatment for symptoms, including leg pain, aching, heaviness, restless legs, cramps, throbbing, fatigue, itchiness, tingling, and edema. These symptoms are frequently the cause of absenteeism from work, disability, and decreased quality of life.[3] Symptoms motivate patients to seek treatment, with >400,000 patients treated in the US each year.[4]

Current therapeutic approaches for the treatment of chronic venous insufficiency (CVI) and varicose veins include compression treatment, open venous surgery, endovenous thermal ablation (ETA; which includes both endovenous laser ablation using a laser or radiofrequency ablation using radio waves), ambulatory phlebectomy, liquid sclerotherapy, and foam sclerotherapy, with treatment strategy largely dependent on clinical class, etiology, anatomy, and pathophysiology of the chronic venous disease (CVD).[3] Historically, open venous surgery comprised of ligation and stripping was the standard treatment, however, given that these procedures were found to be invasive, painful, cause an increased complication rate, lead to long recovery times, and result in high rates of recurrence, minimally invasive procedures replaced surgical stripping as the standard of care for varicose veins and CVI. Endovenous thermal ablation is one such minimally invasive treatment method that has demonstrated benefits over conventional open venous surgery. These catheter-based procedures require threading a relatively inflexible catheter through long segments of incompetent vein and are better suited to the larger diameter saphenous veins above the knee and less suitable in areas with significant venous tortuosity. Thermal ablation requires the use of tumescent anesthesia to be injected around the vein as a heat sink, therefore, it is not used for visible varicosities (subcutaneous veins) due to the risk of skin burn and inability to cannulate these veins. Furthermore, thermal ablation below the knee is thought to be associated with thermal injury to the saphenous nerve; thus, thermal ablation is generally more effective when confined to above the knee.

In 2016, The American College of Phlebology Guidelines Committee identified ETA as one of the preferred methods for treatment of symptomatic incompetence of the accessory GSVs.[5] However, for harder to treat varicose veins (i.e., most located below the knee and visible varicosities), supplemental treatments such as ambulatory phlebectomy (invasive) and liquid sclerotherapy (minimally invasive), or foam sclerotherapy (minimally invasive), have been utilized.[3] Sclerotherapy involves destruction of the vein using a chemical sclerosant under ultrasound guidance. While the solution can be delivered in either a foam or liquid form, foam allows for prolonged contact time increasing the effectiveness of the procedure and therefore is used more frequently. However, physician-compounded foam (PCF) uses liquid sclerosants that are not FDA-approved and because there is no standard formulation, this can result in inconsistencies in the stability, bubble size, and density that can lead to rare but serious adverse events. Varithena (Polidocanol Injectable Foam) attempts to address this issue using a standardized low-nitrogen foam for consistent performance.

3.2 General Description of Varithena

Varithena (polidocanol injectable foam) is indicated for the treatment of incompetent great saphenous vein, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee. Varithena has been shown to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system. Varithena product is available in four configurations, each containing two sterile, connected, 303-mL aluminium alloy cylinders, one containing polidocanol solution (10 mg/mL) under carbon dioxide, and the other containing pressurized oxygen. The injectable foam is generated after activation of the polidocanol canister with oxygen from a second aluminium canister, resulting in a final gas mixture of oxygen:carbon dioxide in a ratio of 65:35 with low (<0.8%) nitrogen content. At the time of use, Varithena is generated as an injectable foam of controlled density and bubble size. The foam is then transferred to a syringe through the Varithena transfer unit.. The mechanism of action of polidocanol is chemical. As a non-ionic surfactant, the hydrophobic pole of the polidocanol molecule attaches to the lipid membrane of venous endothelial cells and disrupts the osmotic barrier. The resulting cell destruction creates a thrombogenic exposed endothelial surface to which platelets attach followed by thrombus formation, occluding the vein lumen which is later replaced by fibrous tissue. Varithena treatment is non-surgical and minimally invasive.

The purpose of this multi-center, randomized, controlled, open-label, parallel-group study is to collect comparative long-term (1-,2-, and 3-year) evidence on patient reported outcomes of Varithena compared to ETA when used to treat the incompetent GSV. The primary endpoint of the study is change in Varicose Veins Symptoms Questionnaire (VVSymQ) between baseline and 3-months post-treatment. Additional endpoints that will be collected include changes from baseline in revised Venous Clinical Severity Score (rVCSS), Venous Insufficiency Epidemiological and Economic Study- Quality of Life/ Symptoms (VEINES-QOL/Sym), Clinical condition, etiological, anatomical location, and pathophysiological (CEAP) clinical condition classification, and EuroQol-5D (EQ-5D) at 7-days, 3-months, 6-months, 12-months, 24-months, and 36-months post-treatment, adverse events, and healthcare resource utilization for treated limb venous disease at 12-, 24-, and 36-months.

3.3 Clinical Summary of Varithena

There is a large set of clinical data available that comprises hundreds of procedures supporting the safety and efficacy of Varithena for the treatment of incompetent GSV, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee.[6-14] Notably, three multicenter, randomized control trials provide robust data suggesting that Varithena is able to provide clinically meaningful improvements of key varicose vein symptoms[7,9,10], enhance quality of life[7,10], and improve the appearance of veins.[7,9,10]

The two pivotal studies supporting approval of Varithena were randomized, blinded, multicenter clinical trials designed to assess the efficacy and safety of Varithena 0.5%, 1.0%, and 2.0% (VANISH-1) and Varithena 0.5% and 1.0% (VANISH-2) compared with placebo in the treatment of both symptoms and appearance of varicose veins in patients with SFJ incompetence as evidence by reflux of the GSV or major accessory veins.[7,9] In both studies, a Varithena 0.125% treatment group was included as a control for blinding of the duplex ultrasound assessment. The primary efficacy endpoint for both studies was change in VVSymQ Electronic Daily Diary Score from baseline to week 8 post-treatment. Secondary endpoints included Patient Assessment of Visible Varicose Veins (PA-V3) score and Independent Photographic Review Visible Varicose Veins (IPR-V3) score. Tertiary endpoints that were not powered included duplex response, rVCSS, and VEINES-QOL/Sym. Varithena significantly improved symptoms, as measured by change in VVSymQ score from baseline, at week 8 at all concentrations of Varithena tested in both

VANISH-1 [Placebo (-2.13) vs. Varithena 0.5% (-5.68) vs. Varithena 1.0% (-4.87) vs. Varithena 2% (-5.78); all p<0.0001 vs. placebo][7] and VANISH-2 [Placebo (-2.00) vs. Varithena 0.5% (-6.01) vs. Varithena 1.0% (-5.06); all p<0.0001 vs. placebo].[9] Treatment with Varithena also led to significant improvements in varicose vein appearance as measured by IPR-V3 (clinician assessment) and PA-V3 (patient self-assessment). In VANISH-1, baseline IPR-V3 scores decreased by 0.01, 0.77, 0.76, and 0.91 for patients in the placebo, Varithena 0.5%, Varithena 1%, and Varithena 2% groups, respectively from baseline to 8 weeks (all p<0.0001 vs. placebo). In patients treated with Varithena, PA-V3 scores also showed significant improvement from baseline to 8 weeks with decreases 1.40, 1.60, and 1.75 for patients in the Varithena 0.5%, Varithena 1%, and Varithena 2% groups, respectively, compared to just 0.15 in the placebo group (all p<0.0001 vs. placebo). A similar trend was observed in VANISH-2 with both Varithena groups having significantly greater improvement from baseline to 8-week follow-up in appearance of varicose using both a clinician and patient assessment compared to placebo (p's<0.0001). Safety outcomes were comparable between groups in both studies.

The physiological response to treatment as measured by duplex ultrasound (duplex response) was defined as elimination of reflux through the SFJ and/or complete occlusion of all incompetent GSV and major accessory veins at baseline. The primary comparison for duplex response in both studies was the pooled Varithena groups vs. the Varithena 0.125% (control) group. For both studies, the pooled Varithena groups were statistically superior to the control group. In VANISH-1 and VANISH-2, in the pooled groups, 75% and 85% of patients respectively, compared with 42% of patients and 60% of patients, respectively, in the control groups, met the criteria for response to treatment. These differences were statistically significant (p≤0.0002).

rVCSS is a clinician rating of severity of chronic venous insufficiency ranging from 0 to 30, where higher scores indicate more severe venous disease. In VANISH-1 and VANISH-2, the adjusted mean changes from baseline in rVCSS in the 1% Varithena treatment groups were 3.70 and 5.05, respectively, at Week 8 compared with 0.75 and 1.52 points in the placebo groups, respectively. For both studies, the differences between these improvements were statistically significant (p<0.0001).

VEINES-QOL/Sym is a disease-specific quality of life instrument, ranging from 0 (worst possible quality of life) to 100 (best possible quality of life). In VANISH-1 and VANISH-2, the adjusted mean changes from baseline in VEINES-QOL/Sym in the pooled Varithena treatment groups were 21.2 and 21.6, respectively, at Week 8 compared with 7.7 and 7.4 points in the placebo groups, respectively. For both studies, the differences between these improvements are statistically significant (p<0.0001).

To assess long-term safety and durability of treatment with Varithena, patients treated with the currently approved dose concentration (1%; n=58) from the VANISH-2 study were followed through 1 year.[8] Results from the study illustrate that treatment with Varithena leads to durable, clinically meaningful, and ongoing improvements at 1 year in symptoms (as measured by the VVSymQ score) and appearance (as measure by IPR-V3 and PA-V3 scores). Severe adverse events were those that would be expected during long-term follow-up of the patient population studies and were classified as being unrelated to treatment. Importantly, there were no new venous thrombus adverse events (AEs), no recurrence or extension of previously diagnosed venous thrombi, and no clinically relevant sequelae in patients previously diagnosed with venous thrombus AEs. Overall, results from these studies demonstrate that Varithena can improve symptoms and appearance of varicose veins with reasonable safety.

In the third randomized trial, outcomes of patients treated with 1% Varithena (n=39) were compared to those treated with placebo (n=38).[10] The primary efficacy endpoint, change in patient-reported symptoms

[HASTI score (heaviness, achiness, swelling, throbbing, and itching)] from baseline to week 8, was significantly greater in Varithena treated patients (30.7 points) compared to those treated with placebo (16.7 points; p=0.0009). Treatment with Varithena led to improvements in m-VEINES-Sym, m-VEINES-QOL, CIVIQ-2, PGIC-Symptoms, PGIC-Day-to-Day, PGIC-Appearance, and physician-assessed appearance scores from baseline to week 8 compared to treatment with placebo. A patient from each group experienced a serious adverse event, both considered unrelated to the study drug (placebo-transient ischemic attack; Varithena- sick sinus syndrome). There were no reports of pulmonary emboli or neurological events in the Varithena-treated patients.

The remaining clinical literature, comprised of single-arm observational and retrospective studies offer additional support for the use of Varithena in the treatment of incompetent great saphenous vein, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee in terms of closure rate success[14], improvements in symptoms and disease severity[12,13], and benefits of combination treatment with endovenous thermal ablation (ETA).[11]

Taken together, the clinical literature supports the safety and efficacy of Varithena for the treatment of incompetent GSV, accessory saphenous veins, and visible varicosities of the GSV system above and below the knee. All randomized trials have demonstrated a clear benefit of Varithena over placebo as measured by improvements in both symptoms and appearance. Further, the AEs most commonly observed in the clinical studies of Varithena® are manageable events that would be expected in patients undergoing a minimally invasive medical procedure for the treatment of GSV incompetence including infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, and superficial thrombophlebitis. Importantly, unlike with physician-compounded foam sclerosants, no patients in the Varithena trials experienced clinically important neurological or visual adverse events suggestive of cerebral gas embolism. Considering all previous trials have compared Varithena to placebo, this study is designed to provide insights into the benefits of Varithena over ETA.

4 STUDY OBJECTIVE and PURPOSE

4.1 Study Objective

This study will collect comparative evidence on patient reported outcomes of Varithena compared to ETA when used to treat the incompetent Great Saphenous Vein (GSV). ETA will include either Radiofrequency ablation or endovenous laser ablation according to the site's standard practice. This study will provide long term (1-year, 2-year, and 3-year) outcomes.

4.2 Study Design

This is a multicenter, randomized, controlled, open-label, parallel group study.

4.3 Randomization

After written informed consent has been obtained, patients will be randomized 1:1 to either Varithena or ETA. Randomization will be performed by a computer-generated block randomization scheme. The EDC system will be used to randomize patients by site into the trial.

4.4 Primary Endpoint

The primary endpoint will assess the change in Varicose Veins Symptoms Questionnaire (VVSymQ) between baseline and 3-month post treatment.

4.5 Additional Assessments

- Change from baseline in revised Venous Clinical Severity Score (rVCSS) at 7-day, 3-month, 6-month, 12-month, 24-month, and 36-month post treatment
- Venous insufficiency Epidemiological and Economic Study – Quality of Life/Symptoms (VEINES-QOL/Sym) and EuroQoL-5D (EQ-5D) at 7-day, 3-month, 6-month, 12-month, 24-month, and 36-month post treatment
- Clinical condition, etiological, anatomical location, and pathophysiological (CEAP) clinical condition classification at 7-day, 3-month, 6-month, 12-month, 24-month, and 36-month post treatment
- Varithena, ETA, and Procedure related serious adverse events (SAE)
- Healthcare resource utilization for treated limb venous disease at 12-month, 24-month, and 36-month post treatment

5 PATIENT SELECTION

5.1 Patient Population

This study is designed to collect comparative evidence on patient reported outcomes of Varithena compared to ETA when used to treat patients experiencing symptoms of superficial venous incompetence of the Great Saphenous Vein (GSV), defined as reflux > 0.5 seconds on duplex ultrasound in a single limb. Data will be collected on approximately 100 randomized and treated patients at up to 15 investigational sites in the United States.

See Section 7 Informed Consent Process on requirements to assess the patient's capacity to participate in the study and Section 11.3 Institutional Review Board (IRB)/Independent Ethics Committees (IEC) on regulatory and ethical oversight of the patient's protection during the study.

5.2 Patient Selection

5.2.1 Inclusion Criteria

A patient must meet all the following inclusion criteria to be enrolled in this study:

1. Age ≥ 18
2. Primary GSV incompetence, defined as reflux > 0.5 seconds on Duplex ultrasound in a single limb (Note the contralateral limb can have varicosities or SVI if intervention is not required within 3 months)
3. Failed conservative therapy (compression, diet, exercise, leg elevation)
4. CEAP Clinical Condition Classification C2 - C6
5. Vein diameter 5-10mm, inclusive
6. GSV treatable length > 10cm
7. Superficial venous disease manifest by clinical symptoms (rVCSS ≥ 4)
8. Able to comprehend and sign an informed consent document and complete written study questionnaires

9. Willing and able to return for scheduled follow-up visits (7-days, 3-months, 6-months, 12-months, 24-months, and 36-months post-procedure)
10. Willingness to comply with post-treatment compression protocol

5.2.2 Exclusion Criteria

A patient must not meet any of the following exclusion criteria to be enrolled in this study:

11. Allergy to polidocanol, xylocaine, or epinephrine
12. Deep vein thrombosis or pulmonary embolism within 3 months prior to randomization or hypercoagulable disorder
13. Post thrombotic deep vein disease above the calf veins
14. Pregnancy or lactating (within 30 days of randomization)
15. Symptomatic peripheral arterial disease or ankle-brachial pressure index (ABPI) < 0.8
16. Previous treatment to targeted incompetent GSV or previous superficial thrombophlebitis in targeted GSV
17. Previous venous intervention in affected limb in past 3 months
18. Local aneurysmal GSV segments
19. Inability to walk unaided
20. Inability to wear post-procedure compression bandaging and stockings
21. Patients with clinically significant reflux of the small saphenous vein (SSV) or anterior accessory saphenous vein (AASV)
22. In the clinical judgement of the investigator, patient who will require ipsilateral deep venous intervention within 3 months following randomized treatment
23. In the clinical judgement of the investigator, patient who will require contralateral venous intervention (superficial or deep) within 3 months following randomized treatment
24. Patient on therapeutic anticoagulants
25. Active malignancy
26. Life expectancy < 2 years
27. Documented COVID-19 infection currently or within 2 months prior to randomization
28. Enrollment in another clinical trial that could confound the endpoint within 3 months prior to screening or within 3 months following enrollment

5.3 Patient Completion

Study patient participation is considered to complete upon completing the 36-month follow up visit.

5.4 Patient Withdrawal

Patients may choose to withdraw from the study (treatments and assessments) at any time for any reason without prejudice to their future medical care by the physician or at the institution. A patient who withdraws

consent will always be asked about the reason(s) for withdrawal and the presence of any AE. If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to all further participation in the study including any further follow-up. The reason for patient withdrawal must be documented in the patient's medical record.

The Investigator or Sponsor may withdraw the patient at any time (e.g., in the interest of patient safety). The withdrawal of a patient from the study by the Investigator should be discussed where possible with the Sponsor. The reason for withdrawal will be recorded (if given) in all cases of withdrawal.

- For patients who withdraw before the end of the study, all End of Study assessments should be completed, if possible, prior to withdrawal.
- If a patient withdraws from the study for any reason, all efforts should be made to follow AEs unless the patient withdraws consent.

Withdrawn patients will not be replaced.

5.5 Patients "Lost to Follow-Up" prior to the Last Scheduled Visit

A subject can be considered lost to follow-up after the subject misses 2 consecutive annual follow-up visits without due cause. No subject will be considered lost to follow-up prior to the 3-month follow-up visit in order to make every effort to collect evaluable data for the primary endpoint. A minimum of 3 attempts (i.e., 2 phone calls followed by a certified letter, or other traceable letter, if necessary) should be made to contact the subject or subject's next of kin for each missed follow-up visit and this information should be documented in the source. Missed or late visits will be recorded as Protocol Deviations.

6 TREATMENT OF PATIENTS

6.1 Varithena Product Description

Varithena (polidocanol injectable foam) 1% is a low-nitrogen, microfoam with uniform density, size, and stability, dispensed from a proprietary canister device. It is formulated with a gas mixture (carbon dioxide/oxygen) designed to maintain physical foam characteristics while allowing rapid bubble absorption following injection. The foam remains coherent, displacing the blood in the vein and efficiently delivering the sclerosant to the venous endothelium. It is echogenic and therefore can be directed to the intended segments of incompetent vein using duplex ultrasound. The net effect is that with a small total dose of active sclerosant, a large vein can be emptied of blood. The sclerosant, neither diluted nor de-activated, acts on the endothelium and in combination with adequate post-treatment compression can successfully sclerose large veins.

Varithena is indicated for the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the GSV system above and below the knee. Varithena improves the symptoms of superficial venous incompetence and the appearance of visible varicosities.

6.1.1 Dosage & Administration

Commercially distributed Varithena (polidocanol injectable foam) 1% (Approved 25 Nov 2013 NDA 205098) will be administered by intravenous injection using ultrasound guidance, administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities as described in the United States Prescribing Information (USPI). Use up to 5mL per injection and no more than 15mL per session.

6.1.2 Retreatment Criteria

Additional interventions or treatments of the treated vein are not allowed during the index procedure or at any time until after the 3-month visit. Additional veins, including contralateral superficial or deep veins, cannot be treated during the procedure and until the 3-month timepoint. After the 3-month timepoint, additional veins may be treated according to the investigator desired modality. Following the initial treatment with Varithena, each subject is followed for 36 months and retreatment data of the index target vein will be collected.

6.1.3 Safety Criteria for Adjusting or Stopping Treatment(s)

A patient who discontinues treatment is normally expected to continue to participate in the study (e.g. for safety, efficacy and survival follow-up) unless they specifically withdraw consent to all further participation in any study procedures and assessments.

6.1.4 Post-treatment Management

Following treatment, patients should be treated with compression bandaging and stockings per the USPI for Varithena or ETA Instruction for Use (IFU). Other post-treatment management for Varithena or ETA will follow standard of care (SoC).

6.1.5 Duration of Treatment and Follow up

Enrollment is estimated to take 9 months. The study will be considered complete with regard to the primary endpoint after all subjects have completed the 3-month follow-up. It is estimated that it will take approximately 4 years to complete this trial.

6.1.6 Concomitant Therapies or Interventions

Patients should not be enrolled in the study if they were previously treated in the target incompetent GSV or superficial thrombophlebitis in targeted GSV. Additionally, patients should not be enrolled in the study if they received venous intervention in the affected limb within three months prior to enrollment.

6.2 Product Labelling / Packaging / Storage / Handling

6.2.1 Labelling and Packaging

Varithena and ETA are indicated for the treatment of incompetent great saphenous veins. The products, labelling, and packaging in the study remain as commercially distributed.

6.2.2 Storage and Handling

Product storage and handling will follow the Varithena USPI and ETA IFU.

7 MEASUREMENTS AND EVALUATIONS

7.1 Study Blinding and Treatment Group Assignment

This study is open label. There is no study blinding to either the investigator or patient.

Patients presenting with incompetent GSV, defined as reflux > 0.5 seconds on duplex ultrasound in a single limb will be considered for this study. After consenting and meeting inclusion criteria and none of the exclusion criteria, patients will be randomized to either Varithena (test) or ETA (control). The EDC system will be used to assign subjects to the test or control treatment group.

7.2 Time and Event Schedule

7.2.1 Screening Visit

The screening phase begins when the informed consent is fully signed and dated and ends at point of treatment.

The following evaluations will be performed:

- Informed consent must be signed, as described in section 7.3.1
- Patient demographic information will be collected, as described in section 7.3.2
- Medical history information will be collected, as described in section 7.3.3
- Mapping of Superficial and Deep Veins, as described in section 7.3.4
- Physical examination will be conducted, as described in section 7.3.5
- A urine/serum pregnancy test will be conducted for all women of child-bearing potential (WOCP), as described in section 7.3.6
- Eligibility to participate in the study will be assessed, as described in section 7.3.7
- VVSymQ, as described in section 7.3.133
- VEINES-QOL/sym, as described in section 7.3.144
- rVCSS, as described in section 7.3.155
- EQ-5D-5L, as described in section 7.3.166
- CEAP Clinical Condition Classification, as described in section 7.3.188

If a patient is determined to be eligible to participate in the study, the site will follow the process as described in section 7.3.9

7.2.2 Index Procedure Visit

The index procedure visit may be performed on the same day as the screening visit if the patient successfully completes the screening visit and is confirmed eligible for the study.

The patient will undergo the Varithena or ETA procedure as assigned per randomization. Varithena or ETA procedure will be administered per SoC and the USPI/IFU relevant to the product for the treatment of the GSV. Specific procedure data will be collected as described in section 7.3.11.

In addition, the following evaluations will be performed:

- Adverse events will be recorded and assessed as described in section 7.3.12

7.2.3 7 Days (±3 Days), 3 Months (±14 Days), 12 Months (±30 Days), 24 Months (±30 Days), and 36 Months (±30 Days) Follow Up Visit

These follow up visits will be conducted in-person.

The following evaluations will be performed for a patient treated with either Varithena or ETA:

- Adverse events will be recorded and assessed as described in section 7.3.12

- VVSymQ, as described in section 7.3.133
- VEINES-QOL/sym, as described in section 7.3.144
- rVCSS, as described in section 7.3.155
- EQ-5D-5L, as described in section 7.3.166
- Duplex ultrasound, as described in section 7.3.177
- CEAP Clinical Condition Classification, as described in section 7.3.188

7.2.4 6 Months (±14 Days) Follow Up Visit

This follow up visit may be conducted in-person or by telephone.

The following evaluations will be performed for a patient treated with either Varithena or ETA:

- Adverse events will be recorded and assessed as described in section 7.3.12
- VVSymQ, as described in section 7.3.133
- VEINES-QOL/sym, as described in section 7.3.14
- rVCSS, as described in section 7.3.15
- EQ-5D-5L, as described in section 7.3.16

If the follow up visit is conducted in-person, the following evaluation will also be performed:

- CEAP Clinical Condition Classification, as described in section 7.3.18

7.2.5 Early Discontinuation

The patient completes the study upon completing the 36-month follow up visit.

For patients who discontinue prior to study completion, the following evaluations will be performed. In the event of a continuing adverse event determined to be related to Varithena in the opinion of the investigator, the patient will be asked to return for follow-up assessments for their continued safety unless they have withdrawn their consent to do so, until the AE has resolved or is deemed to be continuing indefinitely.

- Record the date and reason for study completion as listed in section 5.3
- Record the date and reason for study withdrawal as listed in section 5.4
- Record any adverse events, as described in section 7.3.12

7.3 Study Evaluations and Procedures

7.3.1 Informed Consent Process

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any product, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ICH GCP, any applicable national regulations, and local Ethics Committee and/or

Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have IRB approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

7.3.2 Demographics

The following demographic data will be obtained: age at time of consent, gender, race, and ethnicity.

7.3.3 Medical History

Medical history deemed clinically significant, relevant to the clinical trial objectives and design will be collected per body system: allergy/immunology, blood, dermatology/skin, endocrine metabolic, infection, neurologic, vascular.

Diagnosis and medical history for incompetent great saphenous vein will be recorded separately from medical history.

All ongoing medical conditions and adverse events arising from treatment of those conditions present for 30 days or more are generally considered a part of the patient's baseline medical history and must be recorded where indicated.

7.3.4 Mapping of Superficial and Deep Veins

The Investigator or delegate will map the superficial and deep veins through duplex ultrasound with the patient standing of the extremities to identify the target vessel prior to the start procedure and will record the maximum vein diameter. The course of the vein mapping will be performed according to SoC.

7.3.5 Physical Examination

A physical examination, including actual measured height and actual scale measured weight (required at screening only), will be performed by a qualified licensed individual. A review of body systems will include the following:

- General appearance, overall well-being and functional capacity
- Musculoskeletal, extremities and mobility

Any abnormalities or changes in intensity, duration or frequency not noted during the initial review of body systems should be documented in the source documentation and reported appropriately in the CRF. If a new change to baseline finding occurs at a subsequent visit, the new finding must be assessed for adverse event criteria, adverse event reporting, and will be documented. Resolution of any abnormal findings reported during the study will be noted in the source documentation.

7.3.6 Pregnancy Test

A urine or serum beta hCG pregnancy test will be performed on all females of child-bearing potential.

7.3.7 Eligibility Review

Data documenting demographic information, medical history, physical examination, prior treatment, and pregnancy test (if applicable) will be reviewed against the eligibility criteria to determine eligibility. The determination will be recorded on the relevant eCRF.

7.3.8 Point of Enrollment

Subjects will be considered enrolled once the patient is determined to be eligible to participate in the study and informed consent has been obtained.

7.3.9 Randomization Event

If a patient is determined to be eligible to participate in the study, the site will proceed with randomization.

Randomization will be determined using assignment by a computer-generated randomization scheme. Each patient will be assigned a unique numeric patient identity code.

Randomization will be in a 1:1 ratio of Varithena to ETA treatment arms.

7.3.10 Point of Treatment

Subjects will be considered treated once randomized treatment commences. Only treated subjects will be followed per study protocol safety event reporting and follow-up visit tests/assessments schedule.

7.3.11 Treatment Record

The index treatment record of the target GSV, including doses and start/stop time, will be recorded in the relevant eCRF.

If the target GSV was retreated, as described in Section 6.1.2, the detail of treatment(s) will be separately recorded.

7.3.12 Observation and Recording of Adverse Events

If the patient is unable to attend a study visit, AEs can be collected by telephone contact.

At any time during the study, the patient may volunteer information that resembles an AE. The Investigator should obtain all the information required to complete the AE form. Where possible, a diagnosis, rather than a list of signs or symptoms, should be recorded. Any medical management of an event and the resolution of an event must be recorded in source documentation and on the appropriate eCRF using medical terminology according to Sponsor instructions.

The Investigator will assess all AEs for grading, severity and relationship to study treatment(s). Definitions and procedures for assessment can be found in Section 8.

7.3.13 Varicose Veins Symptoms Questionnaire (VVSymQ)

VVSymQ is a patient-reported outcome measure based on daily patient assessment of the varicose vein symptoms determined to be most important to patients: heaviness, achiness, swelling, throbbing, and itching. VVSymQ scores range from 0 to 25, where 0 represents no symptoms and 25 represents all 5 symptoms experienced all of the time.

7.3.14 Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL/sym)

VEINES-QOL/sym is a disease-specific quality of life instrument, ranging from 0 (worst possible quality of life) to 100 (best possible quality of life). This assessment is scored with 26 responses and include questions about symptoms, daily activity, one year change in disease, and time of day leg pain in most intense.

7.3.15 Revised Venous Clinical Severity Score (rVCSS)

rVCSS is a clinician rating of severity of chronic venous insufficiency ranging from 0 to 30 where higher scores indicate more severe venous disease. rVCSS assesses nine common signs/symptoms of venous disease: skin changes and pigmentation, inflammation and induration, and ulcers (including number, size, and duration). A tenth item assesses compression compliance. Each item is scored individually on a 0-3 point scale.

7.3.16 5-level EQ-5D version (EQ-5D-5L)

EQ-5D-5L is a patient reported outcome measure that provides a simple descriptive profile and single index value for health status. The questionnaire consists of 5 questions pertaining to specific health dimensions, including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and overall health status rating scale.

7.3.17 Duplex Ultrasound

The Investigator or delegate will perform a duplex ultrasound according to the VasCore Core Lab protocol with the patient standing of visualizing the target vessel at the timepoints described in Section 7.2.3. The duplex ultrasound will be uploaded onto an image transfer platform as described in Section 10.

7.3.18 CEAP Clinical Condition Classification

Clinical condition, etiological, anatomical location, and pathophysiological (CEAP) is a descriptive classification for chronic venous disorders. The Investigator or delegate will determine the appropriate clinical condition classification upon physician examination. The clinical condition classification is reported as one of the following:

C_0 = no visible or palpable signs of venous disease
C_1 = telangiectasies or reticular veins
C_2 = varicose veins
C_3 = edema
C_{4a} = pigmentation or eczema
C_{4b} = lipodermatosclerosis or strophie blanche
C_5 = healed venous ulcer
C_6 = active venous ulcer

8 ADVERSE EVENTS

8.1 Adverse Event Definitions

Adverse experience will be considered synonymous with the term adverse event and vice versa.

8.1.1 Definitions of AE/ADR for Drugs (Reference: ICH E2A)

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Drug Reaction (ADR)

A response to a drug which is noxious and unintended and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational medicinal product or package insert/summary of product characteristics for an approved product).

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR)

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening ("life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or prolongation of existing hospitalization;
    - Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- results in a persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect
- is an important medical event that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above,
    - Medical and scientific judgment should be exercised in deciding whether medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SADR, the nature or severity of which is not consistent with the applicable product information (e.g., USPI for an approved product).

8.1.2 Recording Adverse Events

ADR/SADR related to Varithena will be documented from the start of the index procedure through 36-month follow up. In addition, only SAE related to ETA or to the procedure will be documented from the start of index procedure through 36-month follow up. ADR/SADR/SAE should be managed as discussed in Section 8.3.

At any time during the study, the patient may volunteer information that resembles an ADR/AE. In this study, patients should be encouraged to report spontaneously or in response to general, non-directed questions. Once it is determined that an ADR/AE has occurred, the Investigator or physician sub-Investigator should determine if the ADR/AE meets seriousness criteria and is related to Varithena, to the ETA device, or to the procedure according to Section 8.1.1. Any medical management of an event and the date of resolution of the event must be recorded in the source document and on the appropriate eCRF using medical terminology according to Sponsor instructions.

For each related ADR/SADR/SAE, the following information will be recorded:

- ADR/AE term
- Serious criteria
- Severity
- Action taken

- Relevant concomitant medications
- Relevant laboratory/test data
- Relationship to study treatment
- Expected/Unexpected
- Date of onset
- Outcome and type of resolution (with/without sequelae)
- Date of resolution

Once the patient has been discharged from the study, the Investigator has no obligation to seek further follow-up with the patient in order to identify new ADRs/SADRs/SAEs. However, if the Investigator becomes aware of an ADR/SADR/SAE that has occurred following the patient's discharge from the study and the Investigator considers the ADR/SADR/SAE has reasonable possible relationship to Varithena or is possibly, probably, or definitely related to the ETA device, then the Investigator should report the SADR/SAE as described in the protocol.

8.2 Causality Assessment

The Investigator or physician sub-Investigator will assess the causal relationship between Varithena and each ADR/SADR, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may be been caused by Varithena?” Only events with a reasonable possibility of relationship to Varithena will be reported as described in Section 8.5. All other events documented in the study will be addressed through periodic clinical study reporting.

For SAEs, causal relationship will be also assessed for relationship to the procedure and ETA.

The Investigator should pay careful attention to the attribution of relation to the SADR/SAE as there may be similar events reported for both Varithena and ETA. Judgment of relation by time of administration and patient assignment to treatment or control group should be considered.

8.2.1 Criteria for Assessing the Relationship of Varithena, ETA Device, or Procedure to an Adverse Event

Not Related

Relationship to Varithena, to ETA device, or to the procedure can be excluded when:

- the event has no temporal relationship with the use of Varithena, ETA device, or the procedure;
- the serious event does not follow a known response pattern to Varithena or ETA device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of ETA device or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ that cannot be affected by Varithena, ETA device, or procedure;

- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by ETA device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Possibly Related

The relationship with the use of Varithena, the ETA device, or with the procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probably Related

The relationship with the use of Varithena, the ETA device, or with the procedure seems relevant and/or the event cannot be reasonably explained by another cause.

Definitely (Casual) Related

The event is associated with Varithena, the ETA device, or the procedure beyond reasonable doubt when:

- the event is a known side effect of the product category Varithena or the ETA device belongs to or of similar drugs/devices and procedures;
- the event has a temporal relationship with Varithena, the ETA device, or the procedure;
- the event involves a body-site or organ that
    - Varithena, the ETA device, or the procedure are applied to;
    - Varithena, the ETA device, or the procedure have an effect on;
- the serious event follows a known response pattern to Varithena or the ETA device (if the response pattern is previously known);
- the discontinuation of ETA device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use of Varithena or the ETA device;
- the event depends on a false result given by the ETA treatment
- used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

8.3 Submitting Safety Reports

ADR, SAE, SADR, or SUSAR related to Varithena, the ETA device, or procedure must be reported to the Sponsor or its designate by completing the Adverse Event form in the eCRF. SAE, SADR, SUSAR related

to Varithena, the ETA device, or procedure must be reported within 24 hours of becoming aware of the event. If the EDC is not available, the Investigator or other study site staff reports the event to the appropriate Sponsor representative by email to the study-specific mailbox. The Sponsor representative will advise the Investigator/study site staff how to proceed.

The Adverse Event form provided in the eCRF should be completed and signed by the Investigator or physician sub-Investigator. The entire Adverse Event form needs to be completed, if possible, to keep requests for additional information to a minimum. Patients experiencing ADR, SAE, SADR or SUSAR should be followed clinically and with laboratory studies, if appropriate, until medical treatment and/or medical monitoring of the event is no longer required because the event resolves or stabilizes, returns to baseline if a baseline value is available, can be attributed to agents other than the study treatments or a referral for appropriate follow-up care has been made.

The Investigator must promptly inform the IRB of all SUSARs needed per IRB requirements. These events will be reported by the Sponsor as appropriate to the regulatory authorities. The Investigator will receive notification of these events across all study centers from the Sponsor.

ETA safety reporting must follow the direction for use and the commercial complaint reporting process as appropriate for each specific device.

AE/SAE unrelated to Varithena or the procedure should be directly reported to pharmacovigilance@bsci.com as according to the Varithena commercial complaint reporting process.

8.4 Periodic Safety Reporting

ADRs/SADRs/SAEs will be recorded on the AE form and the severity graded using NCI CTCAE version 5.0. The Investigator or physician sub-Investigator will judge the seriousness of each AE and whether it is Varithena, ETA, or procedure related.

Periodic safety reports prepared by the Sponsor will be distributed across all study centers. The Investigator will be responsible for informing the IRB.

8.5 Expected Adverse Events

The study is based on the evaluation of an FDA-approved injectable foam that has been shown to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities. As reported in the Highlights of Prescribing Information, “in clinical trials, the most common related adverse events (occurring in ≥3% of patients treated with Varithena) were pain/discomfort in extremity, infusion site thrombosis (retained coagulum), injection site hematoma or pain, thrombophlebitis superficial, and extravasation.”

8.6 Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical interest specific to the understanding of the study treatments and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allow ongoing surveillance of these events in order to characterize and understand them in association with the use of Varithena.

AESI for Varithena include proximal deep vein thrombosis, common femoral vein thrombus extension, pulmonary embolism, hypersensitivity and anaphylaxis, gas embolism with neurological abnormalities, accidental intra-arterial administration, pregnancy, lactation, use in paediatrics.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be a separate document and will be updated as required, in association with any protocol amendments. The plan will include descriptions of tables, listings and figures and will describe statistical programming considerations.

9.1 Study Design and Determination of Sample Size

This is a multicenter, randomized, controlled, open-label, parallel group study.

The objective of the study is to measure the change in in VVSymQ score for both treatment groups within the same patient population in the same clinical setting, and the study is not powered to detect a difference between treatments.

Whilst there is no pre-specified hypothesis relating to the comparison between treatment groups, a sample size of approximately 100 patients would allow a minimally detectable absolute difference of 2.0 points in a t-test with 2-sided alpha level of 0.05, assuming a standard deviation of 5.0 points in both arms. The assumption for the standard deviation is based on baseline standard deviation values observed in the Vanish 1 and Vanish 2 studies (4.96 and 4.55, respectively).

A target of approximately 100 patients will be randomized and treated in a 1:1 ratio between treatment groups.

9.2 Statistical Populations and Sub-Groups

The **Safety (As Treated) Population** consists of all patients who receive treatment with either Varithena or ETA and will be analyzed according to the actual treatment they received. All safety and healthcare resource endpoints will be analyzed in the safety population.

9.3 Baseline and Demographic Characteristics

Demographics, medical history and ongoing conditions, baseline disease assessments and disease diagnosis will be summarised descriptively.

Baseline results for efficacy assessments (VVSymQ, VEINES-QOL/sym, rVCSS and EQ-5D-5L) will be presented in summaries along with post baseline results (see Section 9.4).

9.4 Efficacy Analyses

9.4.1 Handling of Missing Data

Handling of missing data will be described in the statistical analysis plan.

9.4.2 Primary Efficacy Endpoint Analysis

The absolute change in VVSymQ score between baseline and 3-month follow-up will be evaluated for each subject. Changes in scores will be summarized by treatment group (n, mean, standard deviation, min, max, and 95% confidence interval (CI)). The study is not powered to test formal statistical hypotheses, however results of a t-test comparing mean absolute change between treatment groups will be presented.

9.4.3 Secondary Efficacy Endpoint Analysis

For each of VVSymQ, VEINES-QOL/sym, rVCSS and EQ-5D-5L, summary tables of scores and change from baseline at each timepoint (7-days, 3-months, 6-months, 12-months, 24-months and 36-months post treatment) will be presented for each treatment group. No formal statistical hypotheses are to be tested.

Results of paired t-tests comparing change from baseline to each timepoint as well as t-tests comparing mean absolute change between groups at each timepoint will be presented.

9.5 Safety Analyses

Procedure and treated leg related AEs and SAEs will be coded and summarized for each of the treatment groups. Number of patients and number of events will be displayed for each body system and event term.

9.6 Other Analyses

Healthcare resource utilization may be summarized descriptively at the 12, 24 and 36 months timepoints.

Results of closure rates, defined as the rate of occluded treated target veins with no patent segments exceeding 5 cm in length, measured by duplex ultrasound may be summarized for each treatment group at the 7-day, 3-month, 12-month, 24-month, and 36-month timepoints.

9.7 Interim Analyses

No interim analyses are planned for the study.

10 DATA MANAGEMENT

Patient data from the study will be collected via a limited access secure electronic data capture (EDC) system. Data will be entered in the electronic case report forms (eCRFs) at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the eCRF system and according to the eCRF Classic Rave eCRF Completion Guidelines. The eCRF instructions will also provide the study site with data entry instructions. All changes made to collected data will be documented in an electric audit trail and available to review by the Sponsor or its representative. The associated Rave database has been designed to meet regulatory compliance for deployment as part of a validated system compliance with the laws and regulations pertaining to the use of electronic records and signature applicable to the conduct of clinical studies.

Data verification and data validation checks will be routinely performed using electronic edit checks and manual data review. Any data discrepancies will be referred back to the Investigator and site staff. When data have been entered, reviewed, edited the Investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing.

A clean database will be declared after consistency checks have been run, all SAE reconciliations have been resolved, all the data in the database has been accounted for, all edit checks have been run and data discrepancies have been resolved or accepted and a Quality Check on a sample of the data has been performed. After the database has been declared clean it will be locked and editing in the database will only be allowed with the proper documentation. A final copy of the eCRF will be archived at the study site.

AEs will be coded according to the version of MedDRA agreed with Boston Scientific. Concomitant medications will be coded using the version of the WHO Drug dictionary agreed with Boston Scientific.

After database lock, data will be extracted to SAS® (SAS Institute, Inc., Cary, NC, USA) for analysis as defined in the SAP. SAEs related to Varithena or the Varithena procedure will be entered into the Varithena safety database.

10.1 Image Management System

Duplex ultrasounds collected at 7-day, 3-month, 12-month, 24-month and 36-month post procedure will be deidentified and uploaded into an image management system. Further instructions for deidentifying and uploading duplex ultrasounds will be provided by the image management system vendor in the VasCore Core Lab protocol.

11 LEGAL/ETHICS and ADMINISTRATIVE PROCEDURES

11.1 Good Clinical Practice/Regulatory Compliance

The procedures set out in the this study protocol, pertaining the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by the current version of 21 CFR Parts 11, 50, 54, 56, 312, 812; International Council for Harmonisation (ICH) Harmonised Tripartite Guideline E6 (R2): Good Clinical Practice: Consolidated Guideline, and International Standard ISO 14155:2020 Clinical investigation of medical devices for human patients – Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the Sponsor. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate the potential for recruiting the required number of suitable patients within the agreed recruitment period. The Investigator will maintain a list of appropriately qualified person to whom the Investigator has delegated significant study-related tasks.

11.2 Study Site and Investigator Qualification

This study will be performed by qualified and licensed Investigators at approximately 15 sites located in the United States. Information on the principal investigator at each investigational site, the address details for each investigational site and the emergency contact details for the principal investigator at each site, as well as the roles, responsibilities and qualifications of the investigators will be maintained in the TMF throughout the study.

The investigator is responsible to ensure that all site staff are appropriately qualified by education, training, and experience to perform the delegated study related duties he/she has allocated to them, which must be recorded on the site delegation of authority log.

When specific tasks are delegated by an Investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, ensuring personnel are competent to perform the tasks they have been delegated and providing adequate supervision of those to whom tasks are delegated. Where there is a Sub-Investigator at a site, the Sub-Investigator should not be delegated the primary supervisory responsibility for the site. The Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

Institutional practices and local requirements for qualifying study staff members and teams, including but not limited to GCP training, is required for all staff responsible for study activities. The frequency of repeat

training may be dictated by the requirements of their employing institution, and as required when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

All participating study sites will be reviewed by the study Sponsor or designee to verify that they are able to conduct the study.

11.2.1 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ICH GCP, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the patient.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign Protocol Signature page documenting their agreement to conduct the study in accordance with the protocol.
- Provide their qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes to or deviate from this protocol, except to protect the life and physical well-being of a patient in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the Varithena, ETA device, and procedure) every AE as applicable per the protocol.
- Report to the IRB/EC and regulatory authorities any SUSARs, if required by applicable laws or regulations or this protocol or by the IRB/EC and supply the Sponsor with any additional requested information related to the safety reporting of a particular event.
- Allow the Sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a patient during and after a patient's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).

- Inform the patient of the nature and possible cause of any adverse events experienced.
- Inform the patient of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the patient with well-defined procedures for possible emergency situations related to the clinical study and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the patient is enrolled in this clinical study.
- Ensure that, if appropriate, patients enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the patient's approval or when required by national regulations, the patient's personal physician about the patient's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a patient's premature withdrawal from clinical investigation while fully respecting the patient's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

11.2.2 Investigator CV

The Investigator will provide the Sponsor or designee with his/her, as well as those of any sub-Investigator or staff personnel with significant study responsibilities, current curriculum vitae (CV) and any revisions/updates.

11.2.3 Investigator Agreement Form (Form FDA 1572)

The Investigator will be required to sign and date an Investigator Agreement form provided by the Sponsor for the original and each subsequent change in Investigator at the site and return the original signed document to the Sponsor. A copy of the signed form will be given to the Investigator for their files.

11.2.4 Financial Agreements and Financial Disclosure

Financial agreements with each site are described separately.

Financial disclosure statements will be completed for the Investigator and all sub-investigators to disclose potential conflicts of interest (per 21 CF Part 54 and ISO 14155). The Investigator is responsible for ensuring completed and signed financial disclosure forms are submitted to the Sponsor or designee. A copy of the form(s) will be given to the Investigator for their files. Financial disclosure information will be collected by the Sponsor before the start of the study and maintained for one year after study completion.

11.2.5 Site Qualifications

The Institution must have appropriately qualified Investigators, and clinical and administrative support staff in place to adequately conduct the trials according to GCP in general and must have the adequate expertise and staff to conduct this study in compliance with the relevant guidelines and regulations (see section 11.1) and to treat incompetent great saphenous vein with the study treatments.

11.3 Institutional Review Board (IRB)/Independent Ethics Committees (IEC)

11.3.1 Institutional Approval of the Protocol

It is the responsibility of the Investigator to submit this protocol, the ICF (approved by the Sponsor or designee), relevant supporting information and all types of patient recruitment information to the IEC/IRB for review and approval prior to site initiation. A copy of the written approval of the protocol and ICF must be received by the Sponsor or designee prior to recruitment of patients. Prior to implementing changes in the study, the Sponsor and IEC/IRB must also approve any revised informed consent documents and amendments to the protocol with documentation of the approvals submitted to the Sponsor or designee. The approval document should clearly state the study reference, date of review and actions taken.

The Investigator will be responsible for keeping the IEC/IRB apprised of the progress of the study, any changes to the protocol, deviations from the protocol and serious/unexpected adverse events.

11.3.2 Ethics/IRB Committee Membership Roster

The Investigator must submit a complete and current roster of the IEC/IRB to the Sponsor or designee. Some institutions, due to reasons of confidentiality, may not release their roster. Where such instance occurs, an Institutional signed and dated Statement of Compliance identifying the institution's Federal Wide Assurance Number, assigned by the Office of Human Research Protection within the Department of Health and Human Services, is an acceptable substitute.

11.4 Patient Privacy and Confidentiality

The confidentiality of records that may be able to identify patients and/or the Sites and Investigators will be protected in accordance with applicable laws, regulations and guidelines and HIPAA requirements.

The Sponsor and Investigator affirm and uphold the principle for the patient's right to protection against invasion of privacy. Throughout this study, all data collected and analysed by the Sponsor (data controller) or designee (data processor) will be treated confidentially and identified by an identification number.

To verify compliance with the protocol, the Sponsor will require the Investigator to permit its designee access to the patient's primary medical record to review those portions that directly concern this study (including but not limited to laboratory test results, radiology images, and hospital and outpatient records).

As part of required content of the informed consent, the patient must be informed that his/her records will be reviewed by the Sponsor, Sponsor representative and/or a representative of the appropriate regulatory agency, if applicable. The informed consent or related document will also state that patient privacy will be maintained pursuant to the Health Insurance Portability and Accountability Act (HIPAA), 21 CRF 21. Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the patient before the patient is entered in the study.

Data collected during this study may be used to support the development, registration or marketing of Varithena. Collected data may be reviewed by the Sponsor and/or its representatives, independent auditors who validate the data on behalf of the Sponsor, third parties with whom the Sponsor may develop, register or market Varithena, national or local regulatory authorities and the IRB/EC which granted approval for this study to proceed. Data may be transferred to and used for the purpose (s) for which it was originally collected in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The Sponsor, as the data controller, will ensure that, prior any

transfer, appropriate safeguards are in place to protect the data as required under the General Data Protection Regulation (EU) 2016/679 and other applicable data protection legislation.

11.5 Study Monitoring

Monitoring type (Remote, Onsite) and frequency during the conduct of the study will be detailed in the study monitoring plan and will be performed by qualified personnel from the Sponsor or Sponsor designee. During the monitoring visit, the progress of the study will be discussed with the Investigator or his/her representative. The ICF will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Patient source data must be available for review. The Investigator and his/her staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

The study monitor will record the date of each visit together with a summary report outlining the status and progress of the study. Proposed actions will be discussed with the Investigator or delegate study team members and confirmed in writing.

Telephone and electronic mail contact will be made with the Investigator and study staff as necessary during the data collection and report writing periods. All relevant study communications will be filed in the investigator site file.

11.6 Modification of the Protocol

All amendments to the protocol must be documented in writing, reviewed, and approved by the Investigator and Sponsor and submitted to the IEC/IRB for approval/positive vote prior to initiation. If the protocol amendment substantially alters the study design or potential risk to the patient, new written informed consent must be obtained from each patient for continued participation in the study.

11.7 Suspension or Termination of Study

If conditions arise requiring further clarification before the decision can be reached to proceed with or terminate the study, the study will be suspended until the situation has been resolved.

The Sponsor has the right to terminate this study and remove all study material from the site at any time. Examples of situations where this might occur include:

- It becomes apparent that patient enrollment is unsatisfactory with respect to quality and/or quantity or data recording is chronically inaccurate and/or incomplete.
- The incidence and/or severity of adverse events in the study indicate a potential health hazard caused by the study treatment.

11.8 Trial Completion

The study will be considered complete with regard to the primary endpoint after all patients have completed the 3-month follow up visit, were discontinued prior to the 3-month follow up visit, have died, or the follow up visit window is closed.

For regulatory purposes the end of the study with regard to all follow up after all patients have completed the 36-month follow up visit, were discontinued prior to the 36-month follow up visit, have died, or the follow up visit window is closed at which point the declaration of the end of study will be submitted to the IEC/IRB, as required.

Following this, the Sponsor or delegate will advise the sites on the procedure for closing the study.

Once the end of the study has been declared, no more prospective patient data will be collected and sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

11.9 Clinical Study Report

Irrespective of the outcome of the study the Sponsor will prepare a Clinical Study Report (CSR) within one year of completion of the study or within three months of early suspension or termination of the study.

11.10 Departure from Protocol

No departure may be made from the protocol unless an amendment has been agreed to in writing by both the Investigator and the Sponsor and approved by the IEC/IRB.

No waivers will be granted for inclusion and exclusion criteria to this protocol.

11.10.1 Protocol Deviations

All protocol deviations will be listed and will be assessed as major or minor throughout the clinical study and finalised prior to database lock.

Criteria for protocol deviations will be defined and reviewed prior to database lock and described in the Protocol Deviation Management Plan. The following protocol deviations will be considered:

- Violation of exclusion or inclusion criteria
- Non-compliance to treatment (major deviations from the planned schedule of administration)
- Continuously missed evaluations of efficacy variables or major deviations in the timing of efficacy related assessments

11.11 Recording, Access to and Retention of Source Data

Investigators are required to prepare and maintain adequate source documentation which includes:

- Documents relative to the patient medical history that verify eligibility criteria
- Records covering patient participation in the study including basic identification information, results of physical examinations and diagnostic tests, original laboratory results (initialled and dated by Investigator), therapy, study treatment administration, concurrent medication information, pathology reports, and visit/consult notes.

All key data must be recorded in the patient's source documents including the informed consent acquisition.

The Investigator must permit authorized representatives of the Sponsor, the regulatory authorities, the IEC/IRB, and auditors to inspect facilities and records relevant to the study.

The monitor (auditors, IEC/IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form will include a statement by which the patients allow the above-named access to source data that substantiate information recorded in the eCRFs. These personnel, bound by professional secrecy, will not disclose any personal information or personal medical information.

As described in the ICH GCP Guidelines, 'essential documents', including eCRFs, source documents, consent forms, laboratory test results, etc., should be retained by the Investigator until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of a clinical development of the IP. These documents may be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the

Sponsor. The Investigator must obtain written permission from the Sponsor prior to destruction of any study documents.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of FDA in accordance with 21 CFR 312, 21 CFR 812, or other regulatory authorities in accordance with regulatory requirements.

11.12 Electronic Case Report Forms

The Investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed in to eCRFs that have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the Investigator or delegate as stated on the Delegation of Authority Log. Overwriting of information or use of liquid correcting fluid is not allowed in source documentation.

Once the study monitor has verified the contents of the completed eCRF against the source data, queries may be raised if the data are unclear or contradictory. The eCRFs must be reviewed and electronically signed and dated by the Investigator once all data has been entered and all queries resolved.

11.13 Publications

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, in advance of submission. The review is intended to protect Sponsor proprietary information existing either at the date of commencement of the study or generated during the study. No individual Investigator may publish results from his/her site until after publication of the primary manuscript describing the full study population.

The detailed obligations regarding the publication of any data, material results or other information that is generated or created in relation to the study shall be set out in the agreement between the Investigator and Sponsor.

In accordance with recommendations from the International Committee of Medical Journal Editors, the study will be listed in a publicly accessible registry of clinical trials such as clinicaltrials.gov.

11.14 Audit/Inspections

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of the FDA, the Sponsor and its representatives, and the IEC/IRB for each study site.

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13 SUPPLEMENTS/APPENDICES

Supplements and appendices follow on the next page.

Protocol Approval & Release Signature Page

Protocol Number:	S2473
Protocol Short Title:	Varithena versus Endothermal Ablation of the Great Saphenous Vein (VERITAS)
Protocol Name:	A Phase 4 Randomized Trial Comparing Varithena to Endothermal Ablation for the Treatment of the Great Saphenous Vein
Protocol Version:	1.2
Protocol Approval Date:	17Aug2023

The above-referenced protocol was reviewed and approved for release by the following:

Approver	Signature	Date
Steven Elias, MD Global Co-Principal Investigator		
Antonios Gasparis, MD Global Co-Principal Investigator		
Jennifer Hansen Senior Director, PI Clinical		
Timothy Keo Clinical Trial Manager		
Anna Chavez, MD Director, Medical Safety		
Cathy Zeng Fellow, Biostatistics		

Principal Investigator Protocol Review Statement

Protocol Number:	S2473
Protocol Short Title:	Varithena versus Endothermal Ablation of the Great Saphenous Vein (VERITAS)
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Protocol Version:	1.2
Protocol Approval Date:	17Aug2023

The Principal Investigator (undersigned) hereby declares that they have read this protocol and agrees to its contents.

The undersigned confirms that the study will be conducted and documented in accordance with the current version of the Declaration of Helsinki, the protocol, standards of Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the clinical study agreement.

By written consent to this protocol, the Investigator agrees to the above and to fully co-operate with all monitoring and audits in relation to this study by allowing direct access to all documentation, including source data, by authorized individuals representing Boston Scientific, IEC/IRBs and/or by regulatory authorities.

Principal Investigator Name (please print): _____

Principal Investigator Signature: _____

Date (DD/MMM/YYYY): _____

VVSymQ

The VVSymQ is a 5-item PRO that includes the following five symptoms: heaviness, achiness, swelling, throbbing, and itching. Two versions of the VVSymQ were created to reflect pre-treatment and post-treatment. Table 1 shows the Pre-Treatment VVSymQ items, response options, and response option scores. Table 2 shows the Post-Treatment VVSymQ items, response options, and response option scores. The only difference between the versions is that the reference to the "leg to be treated" in the pre-treatment version is replaced with "treated leg" in the post-treatment version. Response options and scores remain the same in both versions.

Table 3: Pre-Treatment VVSymQ

Item	Response Scale	Response Option Scores
Please answer the following for the time since waking up today…	N/A	N/A
Since waking up today, how often had you had the following problem in your leg to be treated? **Heaviness**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your leg to be treated? **Achiness**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your leg to be treated? **Swelling**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your leg to be treated? **Throbbing**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your leg to be treated? **Itching**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5

Table 4: Post-Treatment VVSymQ

Item	Response Scale	Response Option Scores
Please answer the following for the time since waking up today…	N/A	N/A
Since waking up today, how often had you had the following problem in your treated leg? **Heaviness**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your treated leg? **Achiness**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your treated leg? **Swelling**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your treated leg? **Throbbing**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5
Since waking up today, how often had you had the following problem in your treated leg? **Itching**	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	0 1 2 3 4 5