Protocol Number:	BTG-001652-01
Protocol Short Title:	VIEW-VLU
Protocol Name:	Observational Study of the Effect of **V**ar**I**th**E**na® on **W**ound Healing in the Treatment of **V**enous **L**eg **U**lcers Resulting from Chronic Venous Insufficiency
Sponsor:	Provensis Ltd A BTG International group company 5 Fleet Place London EC4M 7RD
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Investigational Product (IP)	Commercially distributed Varithena® (polidocanol injectable foam) 1%

VERSION NUMBER	APPROVAL DATE	BRIEF DESCRIPTION OF CHANGES
1.0	18May2017	Original protocol
1.1	14Aug2017	Protocol amended to include Canadian sites

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PROTOCOL APPROVAL & RELEASE SIGNATURE PAGE

Protocol Number:	BTG-001652-01
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Protocol Version:	1.1
Protocol Approval Date:	14Aug2017

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

Approver	Signature	Date (DD/MMM/YYYY)
Coordinating Principal Investigator	Michael Shu	8/15/17
Sponsor: Senior ~~Manager~~ VP Clinical Development	[signature]	17 August 2017
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Sponsor: Statistician	[signature]	10AUG2017

INVESTIGATOR PROTOCOL REVIEW STATEMENT

Protocol Number:	BTG-001652-01
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Protocol Version:	1.1
Protocol Approval Date:	14Aug2017

The investigational site Principal Investigator (undersigned) hereby declares that he/she has read this protocol and agrees to its contents.

The undersigned confirms that the registry will be conducted and documented in accordance with the Declaration of Helsinki, this protocol, standards of Good Clinical Practice, applicable laws and regulatory requirements specified in the protocol, and the stipulations of the Clinical Trial Agreement (CTA).

By written consent to this protocol, the Principal Investigator agrees to the above and to fully co-operate with all monitoring and audits in relation to this registry by allowing direct access to all documentation, including source data, by authorized individuals representing Provensis Ltd, BTG International, the institutional review board (IRB) and/or by regulatory authorities.

Investigator Name (please print): _____

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

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1. TERMS, ACRONYMS, ABREVIATIONS

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 Etiologic Anatomic Pathophysiologic
CFR	Code of Federal Regulation
CI	Confidence Interval
CRA	Clinical Research Associate
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
CVD	Chronic Venous Disorders
DCF	Data Clarification Form
DCT	Data Capture Tool
DMP	Data Management Plan
DM	Data Management
DVT	Deep Vein Thrombosis
EQ-5D-5L	EuroQol five dimension five level questionnaire
FDA	Food and Drug Administration
FPI	Full Prescribing Information
GCP	Good Clinical Practice
GSV	Great Saphenous Vein
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iDCT	Investigator Data Capture Tool
IFU	Instructions for Use
IRB	Institutional Review Board
IP	Investigational Product
NPRS	Numeric Pain Rating Scale
PE	Pulmonary Embolism
RCT	Randomized-Controlled Trial
QOL	Quality of Life
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sDCT	Subject Data Capture Tool
SEPS	Sub-fascial Endoscopic Perforator Vein Surgery
SIC	Subject Identification Code
SFJ	Saphenofemoral Junction
SoC	Standard of Care
SPJ	Saphenopopliteal Junction
SSV	Small Saphenous Vein
SW	Source Worksheet
USWR	United States Wound Registry

VAS	Visual Analogue Scale
VCSS	Venous Clinical Severity Score
VLU	Venous Leg Ulcer
WCC	Wound Care Center
WHI	Wound Healing Index

2. PROTOCOL SYNOPSIS

Protocol Number	BTG-001652-01
Protocol Short Title	VIEW-VLU
Protocol Title	Observational Study of the Effect of **V**ar**I**th**E**na® on **W**ound Healing in the Treatment of **V**enous **L**eg **U**lcers Resulting from Chronic Venous Insufficiency
Investigational Product	Commercially distributed Varithena® (polidocanol injectable foam) 1% (Approved 25 Nov 2013 NDA 205098)
Type of Protocol	Phase 4 Registry
Rationale	The purpose of this registry is to observe the effects of Varithena® on venous leg ulcer (VLU) healing in patients who have symptoms of chronic venous insufficiency. The impact of treatment on rate of healing, rate of recurrence, subject's pain and quality of life will be observed.
Objective(s)	To evaluate VLU healing rate, recurrence rate, and patient reported outcomes for Varithena® in C6 disease per Clinical Etiologic Anatomic Pathophysiologic (CEAP) classification
Primary Endpoint (s)	• Rate of epithelial migration (mm/week) measured by wound perimeter on photograph taken using the data capture tool (DCT) and submitted to Tissue Analytics® for analysis • Wound closure at 12 weeks (±1wk) post-treatment • Time from initial treatment with Varithena® to wound closure
Secondary Endpoint (s)	• Percent of wounds remaining closed at 3 months post-wound closure • VLU recurrence (at same site) at 6 months and 12 months post-treatment • Change in pain at ulcer location on numeric pain rating scale (NPRS) compared to baseline at 12 weeks, 6 months, and 12 months post-treatment • Change on EuroQol five dimension five level questionnaire (EQ-5D-5L) quality of life assessment compared to baseline at 12 weeks and 12 months post-treatment • Change in Venous Clinical Severity Score (VCSS) of treated leg from Screening/Baseline to 12 weeks and 12 months post-treatment • Number of ulcer free weeks defined as weeks from closure

	(complete epithelialization is recorded) to date of recurrence (at same site) or last contact if no recurrence
Duration	Enrollment will take place over approximately a 12 month period. For each subject, the registry lasts about 12 months.
Design	Multicenter, open-label, 12-month registry. Enrollment is performed by Investigator who plans to treat subject's great saphenous vein (GSV) system and/or anterior accessory saphenous vein (AASV) incompetence and resulting VLU using Varithena®. VLU recurrence information is collected for those with healed wounds during the 12 month follow-up period. Note: In cases of cluster wounds, Investigator collects data for a single, primary wound. If more than one wound meets eligibility criteria, Investigator determines which wound to evaluate as the primary. All endpoint measurements are collected for the primary wound.
Population	Patients classified C6 on CEAP classification with active VLU resulting from venous insufficiency of the GSV system and/or AASV
Subject Sample and Investigational Sites	Up to 200 subjects scheduled to receive Varithena® for active VLU (C6) resulting from venous insufficiency of the GSV system and/or AASV will be enrolled at up to 40 investigational sites in the United States and Canada.
Treatment	Subjects scheduled for treatment with Varithena® are treated in accordance with the Investigator's standard of care (SoC), including treatment of varicose tributaries in the proximity of the ulcer bed. Administration procedures and volume are per SoC, full prescribing information (FPI) and instructions for use (IFU). Additional treatment(s) with Varithena® can be administered at Investigator's discretion and according to FPI. Post-procedure care, including compression dressing, should be used and prescribed in accordance with Investigator's SoC.

Eligibility Criteria	Inclusion Criteria 1. Men and women; age ≥18 2. Investigator has selected Varithena® to treat patients classified C6 with chronic (≥ 3 months) VLU resulting from GSV and/or AASV incompetence 3. Wound can be visualized in one plane to allow for image collection of the entire wound in one photograph, or if wound is circumferential, subject must be able to capture the entire wound using multiple photographs taken from directly above the wound (straight on) 4. Reflux >500ms on duplex ultrasound 5. Willing and able to collect wound photographs and data using an application installed on a tablet 6. Willing and able to return for scheduled follow-up and wound care visits 7. Ability to comprehend and sign informed consent form (ICF) and complete questionnaires Exclusion Criteria 8. Contraindications to Varithena® 1% in accordance with the FPI 9. Any serious concomitant disease, per physician's discretion, that confounds wound healing, including malignant changes of wound 10. Concomitant heat ablation, or heat ablation of index leg within 6 weeks prior to treatment with Varithena® 11. Significant arterial disease or ankle-brachial pressure index (ABPI) ≤ 0.8 12. In the opinion of Investigator, wound would close within 12 weeks without additional treatment
Statistical Power and Sample Size	No formal statistical hypotheses are being tested and no formal sample size calculation has been performed. The aim of the registry is to collect additional data on treatment effects of a specific indication for which Varithena® is approved but has not been examined in detail. Previous feasibility metrics indicate approximately 200 subjects can be enrolled within one year.

Statistical Methods	Wound area and perimeter will be measured at baseline and each week up to 12 weeks in order to assess rate of epithelial migration, wound closure at 12 weeks and time to wound closure. Secondary endpoints, VCSS, NPRS, and EQ-5D-5L will be calculated as difference from baseline at each visit. Recurrence will be defined as wounds that were reported to have closed, but did not remain so. Summary statistics of the primary and secondary endpoints will be reported with 95% confidence intervals (CI). CIs will be estimated using the Kaplan-Meier method for time to event analyses and the exact (e.g., Clopper-Pearson) method for binomial proportion analyses. Additionally, distribution of continuous endpoints will be evaluated for skewness. Missing data will not be imputed.
Registry Procedures	See Table 1: Schedule of Registry Assessments below
Data Collection	All Investigator and subject data is collected via a DCT. There are two versions of the DCT: physician-facing, referred to as Investigator data capture tool (iDCT), and subject-facing, referred to as subject data capture tool (sDCT). Investigator data can be entered into the iDCT through an application downloaded on a Sponsor-provided tablet or by using the web portal. Subjects collect wound photographs and answer an NPRS question on a Sponsor-provided tablet via the sDCT at designated time points. This allows for photograph and data collection between clinic visits. Data is maintained in a Health Insurance Portability and Accountability Act (HIPAA) compliant database. Subject data is linked to Investigator data by the subject identification code (SIC).
Central Imaging	All wound photographs collected for this registry are submitted via the iDCT and sDCT. Tissue Analytics® analyzes each photograph, or set of photographs for circumferential wounds, and provides wound color and size data for statistical analyses.

3. SCHEDULE OF REGISTRY ASSESSMENTS

Table 1

Registry Visit	Screening/ Baseline	Enrollment/ Treatment[a] (Day 0)	Week 1 Follow-Up Visit[b]	Week 2 through Wound Closure (at WCC) Weekly	Week 12 (±1wk) Follow-Up Visit	3 Months (±1wk) Post-Closure (phone call)	6 Month (±1wk) Follow-Up (phone call)	Month 12 (±1wk) Follow-Up Visit
Informed consent	X							
Duplex ultrasound of superficial and deep veins	X		X (as necessary)					
Screening: eligibility criteria	X							
Demographics, comorbidities, wound history	X							
Wound Characteristics		X[c]						
Varithena® treatment		X	X (as necessary)[d]					
Hospitalizations for wound?		X	X		X	X	X	X
Subject training to use sDCT			X					
Review of VLU recurrence (if applicable)						X	X	X
Photograph(s) of wound (or closed wound area)	X	X[c]	X[e]	X[e]	X	X[e,f]	X[e,f]	X
Numeric Pain Rating Scale		X[c]	X[e]	X[e]	X	X[e,f]	X[e,f]	X
VCSS		X[c]			X			X
EQ-5D-5L quality of life assessment		X[c]			X			X

[a]completed within 14 days of Screening/Baseline visit. Screening/Baseline and Enrollment/Treatment visit measurements and evaluations may occur at the same visit if subject is provided adequate time to consider and have all questions answered.
[b]not required within first week; should be scheduled per SoC for first follow-up
[c]should be completed prior to treatment with Varithena®
[d]additional treatment with Varithena® cannot occur sooner than 5 days after index treatment
[e]collected/completed by subject using sDCT
[f]Investigator or designee to request during phone follow- up

4. BACKGROUND

4.1 Venous Leg Ulcers from Chronic Venous Insufficiency

VLUs are the most common chronic wounds in ambulatory elderly population accounting for 60-70% of all lower extremity wounds. There is higher prevalence of VLUs in individuals with fewer economic resources and years of education. VLUs also result in reduced quality of life and social isolation.[1] VLUs are also known to have high recurrence rates ranging from 54-78%.[2] Symptomatic venous disease prevalence is estimated to be 5% of the population.[3] Prevalence of VLUs in the population older than 60 years of age is 1-3%[4,5] with annual treatment costs reaching $14.9 billion.[6]

It is well known that compression therapy results in healing of VLUs, but there is a challenging subset of the ulcer population that does not respond to standard compression therapy alone. The landmark ESCHAR trial by Gohel et al compared compression therapy (multilayered compression bandage wraps) to superficial venous surgery plus compression therapy. There was no significant improvement in the ulcer healing between both the groups (89% versus 93%) at 48 months.[7,8] The ESCHAR trial also reported a reduction in 12-month ulcer recurrence rates in the surgery plus compression group versus those with compression therapy alone (12% versus 28%; CI 1.78-4.27; $p < 0.0001$). This difference in ulcer recurrence rates persisted at 4 years. The recurrence rates with surgery were similar to the results reported earlier by Barwell et al.[9] A weakness of the trial was that there was no surgical arm without compression. It is also important to note that this study did not include treatment of pathologic perforators. Conversely, Scriven et. al. studied patients with normal deep venous system and demonstrated improvement in venous ulcer healing with saphenous vein stripping, even without compression bandaging.[10]

The association of incompetent perforators and venous ulcers is well-known. In the 1990s and mid-2000s, sub-fascial endoscopic perforator vein surgery (SEPS) was widely used for the treatment of perforator reflux.[11] However, minimally invasive thermal ablations and ultrasound guided sclerotherapy have made SEPS obsolete in the western hemisphere. The North

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American SEPS registry (17 U.S. centers, 155 limbs, 85% with class C5 and C6 disease) included SEPS procedure along saphenous vein ablation in severe venous disease. Ulcer healing at one year was 88%, with the median time to ulcer healing of 54 days.[12] Other studies demonstrated similar results.[13,14,15] A systematic review of one randomized-controlled trial (RCT) and 19 case series' reported results of the SEPS procedure performed with or without superficial ablation on 1140 limbs. Ulcer healing was noted in 88% of limbs with a recurrence rate of 13%, at a mean time of 21 months.[16] Although minimally invasive percutaneous ablation of perforators has replaced SEPS in the management of perforator reflux, most studies unfortunately reported occlusion rates of the perforators as opposed to ulcer healing.[17]

Ultrasound-guided sclerotherapy is the least invasive of the available treatments for perforating reflux. Ultrasound-guided injection of morrhuate sodium in 80 limbs with perforator incompetence was shown to result in significant improvement in VCSS, and rapid healing in 86.5% of the VLUs, with a mean time to heal of 36 days. The ulcer recurrence rate was 32% at a mean of 20 months, despite poor compliance (15%) with compression therapy recommendations.[18] Rojas et al compared ultrasound-guided polidocanol foam with compression therapy. One group received conservative treatment (37 patients) with layered compression therapy and the other group received ultrasound-guided polidocanol foam (33 patients). In a follow-up period of 21 weeks, 72.8% of all ulcers closed. There was a statistically significant higher healing rate of 84.8% in polidocanol group compared to 62.1% in the compression therapy group.[19]

Harlander-Locke et. al. evaluated the impact of radiofrequency ablation of incompetent GSV, small saphenous vein (SSV) and posterior tibial perforator vein on the healing rates of venous leg ulcers. One-hundred forty radiofrequency ablations were performed on 110 venous ulcers in 88 limbs (74 on superficial veins and 66 on perforator veins). The mean ulcer duration prior to ablation was 71 months. After at least 6 months follow-up, 76 of 110 ulcers (69 %) had healed. The mean time-to-healing was 142 days (± 14 days). The healing rate improved from 1.0 cm^2/month (standard error 0.1 cm^2/month) prior to ablation to -4.4 cm^2/month (standard error 0.1 cm^2/month; $p < 0.05$) after ablation. Six of the healed ulcers (7.1%) recurred within 1 year.[20]

O'Hare et.al. attempted to assess the value of adding foam sclerotherapy to four layer bandage system in speeding venous ulcer healing. This trial failed to recruit sufficient patients for formal comparison. However, at 12 weeks, 13/21 (62%) in the control group and 12/13 (92%) who had additional foam sclerotherapy healed. At 24 weeks, healing rates were 17/ 20 (85%, 1 died) in

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[20] Harlander-Locke M, Lawrence PF, Alktaifi A, Jimenez JC, Rigberg D, DeRubertis B. The impact of ablation of incompetent superficial and perforator veins on ulcer healing rates. Vasc Surg 2012;55:458-64.

the control group and 12/13 (92%) who received foam sclerotherapy. There were no significant thrombotic complications of deep vein thrombosis (DVT) or pulmonary embolism (PE) in either group. This study suggests that addition of early foam sclerotherapy to compression bandaging may be safe and effective in occlusion of the saphenous vein.[21]

4.2 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.

A complete description of Varithena® may be found in the FPI (Appendix C) and IFU (Appendix D).

4.3 Varithena® Clinical Summary

Varithena® (polidocanol injectable foam) has been evaluated in 12 clinical studies. 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 saphenofemoral junction (SFJ) incompetence as evidenced by reflux of the GSV or major accessory veins. In both studies, a Varithena® 0.125% treatment group was included as a control for blinding of the duplex ultrasound assessment. Patients with a history of deep vein thrombosis or pulmonary embolism, inability to comply with post-treatment compression due to severe peripheral arterial disease or leg obesity, incompetence of the small saphenous vein or deep venous reflux as a major source of reflux, reduced mobility, major surgery, pregnancy, or prolonged hospitalization within three months were excluded. In these clinical trials, the maximum volume of injectable foam or placebo to be administered per treatment session was 15mL.

In VANISH-1, patients received one blinded treatment and in VANISH-2, patients received one blinded treatment with an option for a second blinded treatment 1 week later. In VANISH-2, patients in the Varithena® 1.0% treatment group received an average of 1.4 blinded treatments. All patients received post-procedure compression therapy for 14 days following treatment.

Of the 519 patients randomized into VANISH-1 and VANISH-2, a total of 511 were treated with either Varithena® 0.5% (n=111), 1.0% (n=110), or 2.0% (n=63), Varithena® 0.125% as control (n=114), or placebo (n=113).

[21] O'Hare JL, Earnshaw JJ. Randomised clinical trial of foam sclerotherapy for patients with a venous leg ulcer. Eur J Vasc Endovasc Surg (2010) 39, 495e499.

For both VANISH-1 and VANISH-2, treatment with 1.0% was superior to placebo in improving symptoms as measured by VVSymQ® (Varicose Vein Symptom Questionnaire), when either a duration or an intensity scale was used to measure patients' symptoms.

VCSS 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 VCSS 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).

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 0.125% (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 0.125% (control) groups, met the criteria for response to treatment. These differences were statistically significant (P≤0.0002).

VEINES-QOL (Venous Insufficiency Epidemiological and Economic Study Quality of Life) 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 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).

For efficacy endpoints, Varithena® treatment effects were consistent across subgroups of age, sex, BMI (up to 48 kg/m2), CEAP clinical class, GSV diameter (up to 25.9 mm) and VCSS.

A total of 1333 patients in 12 clinical trials were evaluated for safety when treated with Varithena® at dose concentrations of 0.125%, 0.5%, 1.0% or 2.0%, including 437 patients treated with Varithena® in placebo-controlled clinical trials.

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. These include infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, and superficial thrombophlebitis. Post-procedural pain resolved within 1 week in 80% of the cases reported, and very few Varithena®-treated patients were treated with opioid analgesics within 10 days of the study treatment procedure.

In the 1333 patients treated with Varithena® in the clinical studies, there were no anaphylaxis or major hypersensitivity reactions, no deaths or non-fatal SAEs attributed to the study treatment, and only a small number of patients with severe AEs or withdrawals due to AE. The following venous thrombus AEs occurred: common femoral vein thrombus extension (2.9%), proximal DVT (1.7%), distal DVT (1.1%), isolated gastrocnemius and soleal vein thrombosis (1.4%). Proximal symptomatic venous thrombi occurred in <1% of patients treated with Varithena®. Approximately half (49%) of patients with thrombi received treatment with anticoagulants.

Neurologic adverse events (e.g., cerebrovascular accident, migraines) have been reported in patients following administration of physician-compounded foam sclerosants. None of the 1333 patients in the Varithena® trials experienced clinically important neurological or visual adverse

events suggestive of cerebral gas embolism. The incidence of neurologic and visual adverse events within one day of treatment in the placebo-controlled studies was 2.7% in the pooled Varithena® group and 4.0% in the placebo groups.

Skin discoloration adverse events were reported in 1.1% of the pooled Varithena® group and 0.7% of the placebo group in the placebo-controlled studies.

The VANISH-2 trial (22) compared 0.5% and 1% Varithena® concentration to placebo in 232 patients (placebo n=57; 0.125% control n=57; 0.5% Varithena® n=60; 1% Varithena® n=58). 94.8% of the patients enrolled were in the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) clinical class C2 through C4 [C2 (varicose veins) 31.9%; C3 (edema) 40.1%; C4 (skin changes) 22.8%], while C5 (healed venous ulcer) and C6 (active venous ulcer) class accounted only to 5.2%. The primary and secondary endpoints included improvement in the varicose vein related symptoms and appearance. These parameters were tested with 3 newly validated clinical outcome assessments and patient reported outcome measures; the Varicose Vein Symptoms Questionnaire (VVSymQ), a patient self-assessment score of 5 most important symptoms of varicose veins; the Patient Self-Assessment of Visible Varicose Veins (PA-V3); and, the Independent Photography Review of Visible Varicose Veins (IPR-V3) by experts in venous disease. At 8 weeks, Varithena® in concentrations of 0.5% and 1% demonstrated statistically significant superior results when compared to placebo with larger improvements of symptoms and greater improvements in physician and patient assessments of the appearance as compared to placebo. 60% of the Varithena® patients demonstrated at least one adverse event compared with 39% of placebo. However, 95% of these were mild or moderate. No pulmonary emboli were detected and no clinically significant neurologic or visual adverse events were reported. The most common adverse events with Varithena® were retained coagulum, limb pain, and superficial thrombophlebitis most of which resolved at end of study. Of the 232 patients that were treated at baseline visit, 230 patients completed the eighth week follow-up visit. These 230 patients then entered the one-year extension study. Of these, 87.9% received additional open label Varithena®, within 2 to 3 weeks after the 8-week follow-up visit. These results were reported in a subsequent study (23). At 1 year, there was improvement in symptoms as measured by reductions in mean VVSymQ score, IPR-V3 and PA-V3. There were also reductions in disease severity, as measured by the Venous Clinical Severity Score (VCSS) and quality of life measures. There were no new venous thrombotic events. There were no clinically important long term adverse sequelae in patients who had thrombophlebitis at the 8-week visit, including recurrence of thrombosis or evidence of post-thrombotic syndrome at 1 year. The proportion of patients with a duplex ultrasound response was 89% at 8 weeks and 73% at 1 year.

In a separate study (VANISH-1), Varithena® was tested in patients with patients with moderate to severe symptoms of superficial venous incompetence and visible varicosities of the GSV system (24). 279 were randomized to either placebo (n=56), 0.125% Varithena® (n=57), 0.5% Varithena® (n=51), 1% Varithena® (n=52), or 2% Varithena® (n=63). The primary endpoint was similar to the VANISH-2 trial. Patient-reported venous symptom improvement was measured as a change from baseline to week 8 in the VVSymQ score. Secondary endpoints included appearance measures tested with IPR-V3 and PA-V3 scores. Tertiary endpoints measured included duplex ultrasound response, changes in VCSS, and the modified Venous Insufficiency Epidemiological and Economic Study. At week 8, VVSymQ scores for the pooled Varithena® group (0.5% + 1% + 2%; $p < 0.0001$) and individual dose concentrations ($p < 0.001$) were significantly superior to placebo. Mean changes from baseline to week 8 in IPR- V3 and PA-V3 scores were also significantly greater for pooled Varithena® than for placebo ($p < 0.0001$). The tertiary end point of duplex ultrasound response was defined as the elimination of sapheno-femoral junction (SFJ) reflux and/or complete occlusion of the incompetent GSV and/or major

saphenous accessory vein. This Duplex ultrasound response rates for patients treated with Varithena® 0.5%, 1%, and 2% foam (pooled and individually) ranged from 59% to 83%. There were no pulmonary emboli noted. No patient discontinued the study due to an adverse event. 15 patients (5.5%) had a common femoral vein thrombus extension. 5 patients had proximal DVTs (popliteal vein or above), 4 had distal DVTs, and 3 had isolated gastrocnemius and soleal DVTs. The total of 27 patients with DVTs accounted for a DVT rate of 9.8% with this technique. In summary, Varithena® has been studied in more than 1300 patients and has demonstrated consistent improvement in patient-reported clinical outcomes and in clinical appearance. Varithena® has a distinct advantage over other non-thermal techniques in the treatment of patients with severe venous disease, as the foam can reach the veins under the diseased and lipodermatosclerotic skin as well as the feeder veins in close proximity to the venous ulcers, without any concern for nerve injury. Neovascularized veins, tortuous veins, and post-thrombotic (scarred) veins are extremely difficult to navigate with thermal technologies and other non-thermal technologies. Varithena® is again advantageous in these settings as foam can traverse through these areas.

Varithena® treatment has been shown to result in both hemodynamic and symptomatic benefit for patients. The Varithena® studies have had equivalent pooled benefit to alternative therapies (surgery and sclerotherapy) so it can be anticipated that, as with other studies, there will be improved ulcer healing following Varithena® treatment. Varithena® can uniquely extend therapy to the most distal varicose tributaries, close or even under the ulcer bed. It is possible the treatment may confer greater advantage, as it did with a few C5 and C6 patients. It is therefore appropriate to investigate the benefit Varithena® may provide in accelerating ulcer healing and reduction of ulcer recurrence. Given the paucity of treatment availability for this patient population, there is great value in better understanding the effects of Varithena® on healing, recurrence rates and quality of life for patients with venous insufficiency resulting in VLUs. This registry is designed to provide insights into treating this difficult indication.

5. REGISTRY OBJECTIVE AND PURPOSE

5.1 Objective(s)

The purpose of this registry is to observe the effects of Varithena® on VLU healing in patients who have the symptoms of chronic venous insufficiency. The objective of the registry is to evaluate VLU healing rate, recurrence rate, and patient reported outcomes for Varithena® in C6 disease per Clinical Etiologic Anatomic Pathophysiologic (CEAP) classification

5.2 Design

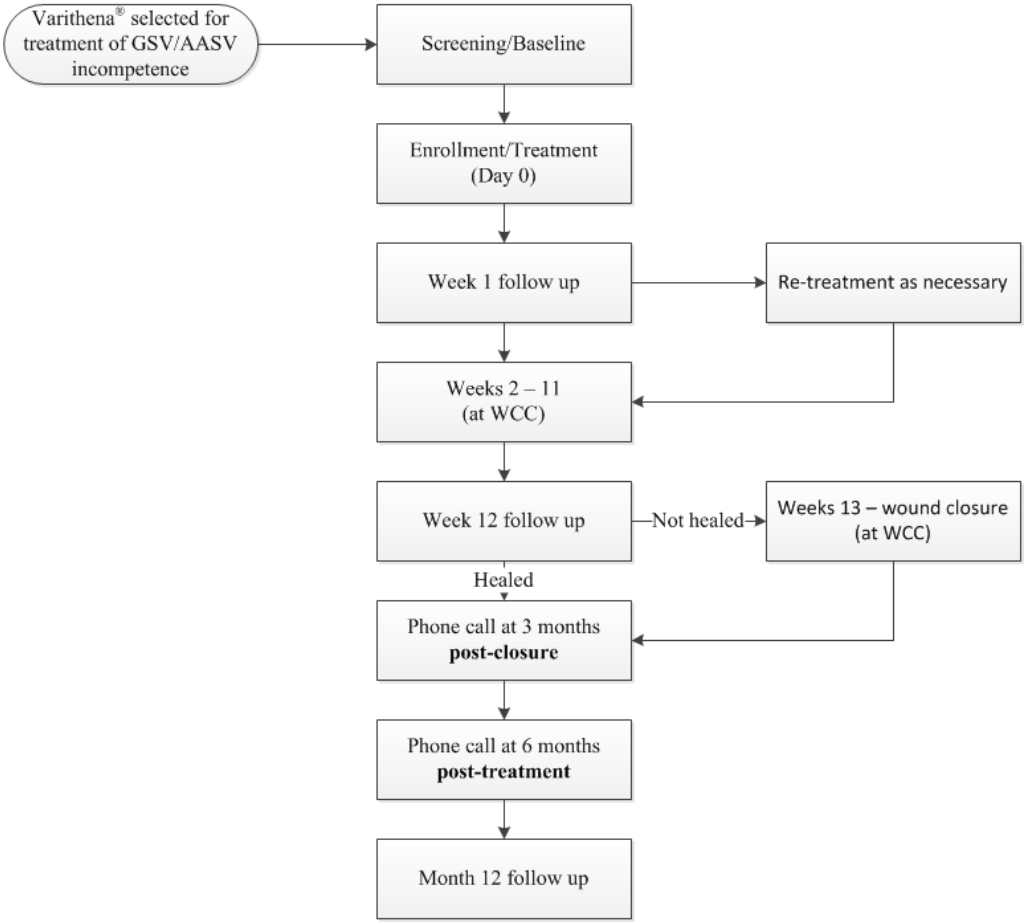
This 12 month, multicenter, open-label registry is designed to collect treatment and outcome data related to subjects treated with Varithena® for GSV system and/or AASV incompetence resulting in VLU. Subjects are treated per Investigator's SoC and in accordance with the FPI and IFU. For subjects with healed ulcers during the 12 month follow-up period, VLU recurrence information is collected. Wound recurrence is defined as the reopening of a wound that was previously closed; recurrence must occur at same location.

Note: In cases of cluster wounds, Investigator collects data for a single, primary wound. If more than one wound meets eligibility criteria, Investigator determines which wound to evaluate as the primary. All endpoint measurements are collected for the primary wound.

For each subject, participation in the registry lasts approximately 12 months. Subjects are seen at the investigational site for initial treatment, about one week after treatment for initial follow-up visit (and retreatment if necessary), 12 weeks (±1wk) and 12 months (±1wk) after initial treatment. Between follow-up visits, and until wound closure, subjects are asked to collect weekly photographs of the wound via the sDCT during dressing changes at the wound care center (WCC).

Additionally, follow-up phone calls are placed at 3 months (±1wk) post-closure and 6 months (±1 week) post-treatment. At that time, subjects are asked to take a picture of the wound area and complete the NPRS using the sDCT. (Figure 1)

Figure 1. Study Schematic



5.3 Primary Endpoint(s)

- Rate of epithelial migration (mm/week) measured by wound perimeter on photograph taken using the DCT and submitted to Tissue Analytics® for analysis
- Wound closure at 12 weeks (±1wk) post-treatment
- Time from initial treatment with Varithena® to wound closure

5.4 Secondary Endpoint(s)

- Percent of wounds remaining closed at 3 months (±1wk) post-wound closure date, determined via photograph assessed by Tissue Analytics®; non-healed wounds are not included in percent calculation
- For healed wounds, rate of VLU recurrence collected via phone calls and subject-collected photographs at 6 months (±1wk) and 12 months (±1wk) post-treatment
- Change in pain on NPRS compared to baseline at 12 weeks (±1wk), 6 months (±1wk), 12 months (±1wk) post-treatment
- Change on EQ-5D-5L quality of life assessment compared to baseline at 12 weeks (±1wk) and 12 months (±1wk) post-treatment
- Change in VCSS from Baseline to 12 week (±1wk) and 12 month (±1wk) follow-up
- Number of ulcer free weeks defined as weeks from time of closure (complete epithelialization is recorded) to date of recurrence or last contact if no recurrence (at study completion or withdrawal)

6. SUBJECT SELECTION

6.1 Registry Population

This registry is designed to collect data related to treatment with Varithena® in patients experiencing symptoms of chronic venous insufficiency of the GSV or AASV system who are classified C6 on the CEAP with active VLU.

Data is collected for up to 200 subjects selected by their physician to receive Varithena®. Enrollment is to occur at up to 40 investigational sites in the United States and Canada.

6.2 Subject Selection

6.2.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1 Men and women; age ≥18
2 Investigator has selected Varithena® to treat patients classified C6 with chronic (≥ 3 months) VLU resulting from GSV and/or AASV incompetence
3 Wound can be visualized in one plane to allow for image collection of the entire wound in one photograph, or if wound is circumferential, subject must be able to capture the entire wound using multiple photographs taken from directly above the wound (straight on)
4 Reflux >500ms on duplex ultrasound
5 Willing and able to collect wound photographs and data using an application downloaded on a tablet
6 Willing and able to return for scheduled follow-up and wound care visits
7 Ability to comprehend and sign ICF and complete questionnaires

6.2.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

8 Contraindications to Varithena® in accordance with the FPI
9 Any serious concomitant disease, per physician's discretion, that confounds wound healing, including malignant changes of wound
10 Concomitant heat ablation, or heat ablation of index leg within 6 weeks prior to treatment with Varithena®
11 Significant arterial disease or ABPI ≤ 0.8
12 In the opinion of Investigator, wound would close within 12 weeks without additional treatment

6.3 Subject Completion

A subject is considered to have successfully finished the registry upon completion of the 12 month follow-up phone call.

6.4 Withdrawal

For cases in which the subject does not complete all assessments and follow-up visits, the subjects are classified as follows:

- Investigator withdrawal – Investigator can withdraw a subject from the registry for a safety concern, non-compliance, or for any other concern warranting withdrawal of the subject in the judgment of Investigator. Reason for Investigator withdrawal of a subject and last date of contact for the registry are documented on the Completion Log.
- Subject withdrawal – Subjects may withdraw from participation at any time during the registry. All data collected prior to withdrawal shall remain part of the registry data. Reasonable effort should be made to encourage the subject to remain in the registry. If the subject declines, determine and document the reason for withdrawal on the Completion Log.
- Lost to follow-up – A subject is considered lost to follow-up if there have been at least three documented attempts to contact the subject for follow-up without success. Last date of contact is documented on the Completion Log.

7. TREATMENT OF SUBJECTS

7.1 Varithena® (polidocanol injectable foam) 1%

Treatment with Varithena® is selected and administered per SoC and the FPI. Varithena® is commercially available. As such, investigational product (IP) accountability and tracking is not necessary.

7.1.1 Dosage & Administration

Subject is treated on Day 0 with up to 15mL of Varithena®, above and below the knee as needed, per Investigator's clinical judgement and the FPI. Each injection should not exceed 5mL. Date of treatment, number of injection sites, and volume above and below the knee is recorded in the iDCT. Appendix E: Use of Varithena® to manage patients with GSV-derived venous hypertension and chronic venous leg ulcer is provided as a guide to best practices in treating this indication.

7.1.2 Additional Treatment

Additional treatment(s) of Varithena® can be administered at Investigator's discretion and according to FPI. Note that additional treatment should not be administered sooner than 5 days after previous treatment. Date of additional treatment, number of injection sites, and volume above and below the knee is recorded in the iDCT.

7.1.3 Post-treatment Management

Following treatment with Varithena®, subjects should be treated with compression dressing per Investigator's SoC. Subjects are referred to a local WCC. The WCC does not need to be affiliated with the investigational site. Subjects' compression dressing is checked and changed at the WCC. Subjects are asked to continue to visit the WCC weekly for continuing care until the wound is healed. At each WCC when the wound area is exposed, the patient should make every effort to take a photograph of the wound, or the wound area if the wound has healed, using the sDCT. The pain rating should also be recorded in the sDCT by response to the NPRS. The staff at the WCC are not delegated under the investigational site, so the subject should understand that they are responsible for collecting the photograph and answering the NPRS question independently.

If the wound is not healed at the 12 Week Follow-up visit, the subject continues to visit the WCC for continuing care until wound closure, collecting a wound photograph and answering the NPRS question at each appointment.

7.1.4 Duration of Treatment and Follow-up

Following the initial treatment with Varithena®, each subject is followed for 12 months. Additional treatment can be administered following the initial treatment; however, it is recommended that re-treatment occur as close to the time of the initial treatment as is possible, but not sooner than 5 days, according to FPI and IFU. Date of re-treatment, number of injection sites, and volume above and below the knee is recorded in the iDCT.

During the follow-up period, subjects are followed for VLU-related hospitalizations, wound recurrence, and other clinical outcomes. Subjects are assessed at the investigational site at Week 1 Follow-up visit (about one week after treatment), 12 weeks (±1wk) post-treatmentand 12 months (±1wk) post-treatment. Subjects are contacted by telephone for follow-up 3 months (±1wk) post wound-closure, and 6 months (±1wk) post-treatment. Subjects collect wound photographs between follow-up visits when the wound dressing is being changed at the WCC.

7.1.5 Concomitant Therapies or Interventions

Subjects should not be enrolled in the registry if they were treated for venous insufficiency in the index leg with heat ablation above the knee within the 6 week period prior to enrollment. Treatment with heat ablation could confound the outcome of treatment with Varithena®. For subjects who have had recent heat ablation treatment (greater than 6 weeks but less than 6 months), it should be clear to Investigator that ulcer is not healing or would not heal were subject not to receive additional treatment.

It is suggested that heat ablation not be used after treatment until the primary endpoint data have been collected at Week 12 Follow-up visit. This allows for assessment of the effects of Varithena® without heat ablation as a confounding factor.

8. MEASUREMENTS AND EVALUATIONS

8.1 Time and Event Schedule

8.1.1 Screening/Baseline Visit (can occur up to 14 days prior to treatment) *(Clinic)*

The screening phase begins when the ICF is fully signed and dated and ends at the initiation of initial treatment with Varithena® (Day 0).

The following evaluations are performed at Screening/Baseline:

- Review and signing of the ICF
- Review and confirmation of eligibility to participate in the registry
- Collection of demographic information, wound history (including prior treatments), and physical examination to assess venous and wound characteristics
- Collection of photograph (photographs if wound is circumferential) in iDCT

8.1.2 Enrollment/Treatment Visit (Day 0) *(Clinic)*

Screening/Baseline and Enrollment/Treatment visit measurements and evaluations may occur at the same visit if subject is provided adequate time to consider and have all questions answered.

The following are performed at this visit:

- Collection of data prior to treatment:
  - Photograph(s) of wound in iDCT
  - VCSS
  - NPRS
  - EQ-5D-5L quality of life assessment
- Varithena® Treatment – treatment procedure and collection of treatment details

8.1.3 Week 1 Visit (1st Follow-up Visit Per SoC) *(Clinic)*

This visit is not required to occur within first week after initial treatment but should be the first follow-up visit per SoC. If retreatment is expected, this visit should occur no sooner than 5 days after initial treatment. Date of visit is documented in the iDCT.

The following are performed at the Week 1 visit:

- Subject is trained to use sDCT
  - Subject collects photograph(s) of wound using sDCT (additional training required for circumferential wounds)
  - Subject enters NPRS response into sDCT
- Assessment of medical compression therapy compliance
- Documentation of re-treatment details, if applicable

8.1.4 Week 2 through Wound Closure *(at WCC)*

The subject does not return to the investigational site at this time. The subject presents to a WCC for wound care and dressing changes on about a weekly basis. During each visit to the WCC, subject is asked to take a photograph (multiple photographs for circumferential wounds) of the wound and answer the NPRS question using the sDCT. It is important that the subject understands that the WCC staff may not be aware of the registry, so collection of the photograph(s) and answering the NPRS question should be completed independently. The subject should refer questions about the sDCT and data collection to the investigational site, or contact Tissue Analytics® for technical support.

If the wound is not healed at the Week 12 Follow-up visit, subject continues to collect photograph(s) and answer NPRS questions at weekly WCC visits until wound closure.

8.1.5 Week 12 Visit (±1wk) *(Clinic)*

The following are performed and entered into the iDCT at this visit:

- Collection of wound photograph(s) or photograph of wound area if wound is healed
- VCSS
- NPRS
- EQ-5D-5L quality of life assessment
- Assessment of medical compression therapy compliance

8.1.6 3 Months (±1wk) Post-Wound-Closure *(Telephone)*

Once the subject's wound is determined to be healed, Tissue Analytics® schedules a reminder for Investigator or delegate to contact the subject by phone at 3 months (±1 week) to perform the following:

- Assessment for VLU recurrence
- Assessment of medical compression therapy compliance
- Request that subject collects the following using the sDCT:
    - Photograph of wound area, or wound if reccurred
    - NPRS

8.1.7 6 Months (±1wk) Post-Treatment *(Telephone)*

Investigator or delegate contacts the subject by phone to perform the following:

- Assessment for VLU recurrence
- Assessment of medical compression therapy compliance
- Request that subject collects the following using the sDCT:
    - Photograph of wound area, or wound if reccurred
    - NPRS
- EQ-5D-5L quality of life assessment (only collected at 12 Months)

8.1.8 Month 12 Visit (±1wk) Post-Treatment *(Clinic)*

The following are performed and entered into the iDCT at this visit:

- Assessment for VLU recurrence
- Collection of photograph of wound area, or wound if recurred
- VCSS
- NPRS
- EQ-5D-5L quality of life assessment
- Assessment of medical compression therapy compliance

8.2 Evaluations and Procedures

Evaluations and procedures performed to establish eligibility and baseline may be performed within the 14 days prior to treatment, inclusive of day of treatment, provided subject has adequate time to consider and have all questions answered before treatment is initiated.

8.2.1 Informed Consent Process

Patients with the potential to meet eligibility criteria may be offered the opportunity to be evaluated for participation in this registry. All such patients must sign an ICF approved by the relevant Institutional Review Board (IRB) or Research Ethics Board (REB) before any trial-related evaluations can be performed.

Investigator or qualified delegate reviews the treatment plans with the patient and the patient has an opportunity to ask questions about trial procedures, the follow-up schedule, risks and benefits of the treatment and alternative treatment options prior to signature. The patient receives a copy of the signed ICF to keep for their records.

Subjects will be informed of any revisions of the ICF and relevant revisions are signed and kept in the subject's file.

The consenting process, acquisition of the ICF and any revisions should be documented in the subject's medical record and the ICF should be signed and dated by the individual who conducted the informed consent discussion.

8.2.2 Eligibility Review

A physical evaluation of the wound as well as data regarding venous insufficiency, medical history and prior treatment are reviewed against the eligibility criteria to determine eligibility of the subject for the registry. Subjects who complete a consent form and are found to be ineligible for the registry are recorded on the Screening Log with the exclusionary criteria indicated. Subjects who are found to meet all inclusion criteria and no exclusion criteria are entered into the iDCT.

8.2.3 Assignment of Subject Idendification Code (SIC)

Subjects who meet all inclusion and no exclusion criteria for the registry are assigned an SIC by Investigator or delegate. The SIC is used to deidentify subject data and should be used on source worksheets and for data entry purposes. The Investigator or delegate maintains an SIC list, a confidential list of subjects' names and associated SICs which allows Investigator to determine identity of all subjects.

The SIC is formatted as a six digit number: a three digit assigned site code followed by consecutive three digit numbers, beginning with 001 (e.g., 321-001). The site code is provided to investigational site during site inititation.

8.2.4 Demographics

For each subject, date of birth and gender are collected.

8.2.5 Physical Examination

All patients undergo a physical examination at screening, in accordance with Investigator's current practice, to include height and weight.

The venous evaluation includes:

- Examination of the external appearance of the leg to be treated
- Confirmation of CEAP classification (Appendix A)
- Venous duplex ultrasound to review for duplex reflux duration, GSV, AASV, major perforator, and SSV incompetence

The wound examination includes:

- Location of index wound
- Number of current ulcers
- Signs of infection or bioburden

8.2.6 Wound History and Prior Treatments

Information is collected regarding wound age at first encounter (defined as time since current episode began), total previous episodes of current ulcer and other ulcers, duration of compression therapy for current wound, and medical compression therapy compliance.

The following information is recorded for previous treatments (e.g., heat ablation, grafting) for the current ulcer. Treatment should only be listed for the current location of venous insufficiency and the resulting current ulcer:

- Procedure type
- Date (start date in the case of a long term treatment, like compression therapy)
- Outcome (i.e. Healed/Non Healed)

8.2.7 Wound Photographs

Wound photographs for the registry are collected via the iDCT and sDCT. Photographs are analyzed for wound characteristics by Tissue Analytics®. Wound photographs are collected by Investigator or delegate at Baseline/Screening, Day 0 before treatment and Week 12 Follow-up visit using iDCT. Wound photographs are collected by subject via sDCT at Week 1 Follow-up visit, weekly during dressing changes at the WCC and at the 3, 6 and 12 month follow-up assessment time points. All photographs for a given subject are linked back to Investigator data using the SIC and are accessible by Investigator or delegate within the iDCT.

Investigator or delegate provides Tissue Analytics® sDCT training module to subject during Week 1 Follow-up visit and ensures subject can use sDCT. The photograph(s) collected at this visit should be collected by subject using the sDCT.

If the wound is circumferential, wound can be captured using two or more photographs. The subject should be able to view and photograph the entire wound using multiple photographs. The photographs should be taken from directly above and perpendicular to the wound (straight on). As this may be difficult for wounds that reach the back of the leg, it should be confirmed at screening that the subject is able.

8.2.8 Varithena® Treatment Record

The following data is recorded in the iDCT for the initial treatment with Varithena® and any touch up treatment:

- Treatment date
- Volume injected above the knee
- Volume injected below the knee
- Total number of injection sites (for specified treatment date)

8.2.9 Numeric Pain Rating Scale

An 11-point NPRS is used to assess subject's level of pain. Subject is asked "What was your pain level at the ulcer location over the last 24 hours?" and selects a score between 0 and 10, with 0 meaning no pain and 10 meaning the worst pain. Investigator or delegate assesses and records this directly into the iDCT. The subject answers this question in the sDCT at Week 1 Follow-up visit, at each weekly WCC visit during dressing changes and at 3 months post wound closure, and 6 and 12 month follow-up assessment time points (phone contacts).

8.2.10 Venous Clinical Severity Score (Revised)

The VCSS 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. The revised VCSS clarifies ambiguities in category descriptions and contains an additional category for compression. Investigator or delegate should complete assessment on source worksheet (SW) and enter data into iDCT.

8.2.11 EQ-5D-5L Quality of Life Assessment

The EQ-5D-5L is a validated, widely used quality of life assessment. It is a patient reported outcome 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. Subjects should complete questionnaire on SW and data is entered into iDCT.

9. ADVERSE EVENTS

9.1 Definitions

Adverse Event (AE) any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment[22]

An undesirable event can be, but is not limited to, symptoms experienced by a subject or objective findings, such as significant clinical laboratory abnormalities.

Serious Adverse Event (SAE) any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (Note: The term "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,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event 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 above[22]

Adverse Drug Reaction (ADR) a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.[22]

Unexpected Adverse Event an AE for which the nature or severity is not consistent with information in the relevant source document(s).[22]

9.2 Reporting Adverse Events

AEs can occur from the time of initiation of treatment until the subject completes the registry or withdraws. If Investigator or delegate becomes aware of an AE and wishes to report it to the Sponsor/Manufacturer, Investigator or delegate should report the event by sending an Adverse Event Form (Apendix H) via email to vigilance@btgplc.com. Questions about AEs or other safety-related concerns can also be sent via the same email address.

In some cases, Sponsor/Manufacturer may need additional information from investigational site in order to provide a report to the Food and Drug Administration (FDA) to comply with mandatory regulatory reporting. Sponsor will request additional medical information about subject as needed.

If additional safety information becomes available during the course of the registry, Sponsor will amend protocol and ICF as necessary.

[22] ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 1994.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis

The statistical analysis plan (SAP) will be a separate document and will be updated as required, in association with any protocol amendments prior to database lock. The SAP will include detailed descriptions of statistical methodology.

Summary statistics for continuous variables will include number of patients, means, medians, standard deviations, standard errors, minima and maxima. For categorical variables, frequencies and percentages will be given; 95% CI will be calculated using the Clopper-Pearson (exact) method for binary proportions. For time to event variables, the number of patients, number of events, the median and 95% CI of the median, and quartiles will be provided by the Kaplan Meier (KM) method.

Missing data will not be imputed.

Baseline is defined as the last available measurement taken before the first treatment.

10.2 Determination of Sample Size

No formal statistical hypotheses are being tested and no formal sample size calculation has been performed. The aim of the registry is to collect additional data on treatment of a specific indication for which Varithena® is approved but has not been examined in detail. Previous feasibility metrics indicate approximately 200 subjects can be enrolled within one year.

10.2.1 Analysis Populations

The Efficacy Population will include all patients who are treated with Varithena® and who have at least one post treatment primary endpoint assessment.

10.3 Primary Efficacy Analyses

The three primary endpoints are:

- Rate of epithelial migration (mm/week) by perimeter
- Wound closure at 12 weeks post-treatment
- Time to wound closure

Summary statistics with 95% CI will be provided for all primary endpoints. The Clopper-Pearson method will be used for binary proportions (wound closure at 12 weeks post-treatment). Additionally, distribution of time to wound closure will be estimated using the Kaplan Meier (KM) method and the 25th percentile, median, and 75th percentile will be presented along with 95% CIs.

The primary endpoint, rate of epithelial migration, will be evaluated for skewness using the Kolmogorov Smirnov test. In the event of significant skewness, the interquartile range will be reported in addition to the 95% CI.

10.4 Secondary Efficacy Analyses

The secondary endpoints are:

- Wounds remaining closed at 3 months post-wound closure
- VLU recurrence (at same site) at 6 months and 12 months post-treatment
- Change in pain on NPRS compared to baseline at 12 weeks, 6 months, 12 months post-treatment
- Change on EQ-5D-5L quality of life assessment compared to baseline at 12 weeks and 12 months post-treatment
- Change in VCSS from Baseline to 12 week and 12 month follow-up
- Number of ulcer free weeks

The proportion of wounds remaining closed at 3 months post-wound closure will be presented with frequencies and percentages with 95% CIs based on Clopper-Pearson. Similarly, recurrence at 6 months and 12 months post-treatment will be presented with frequencies and percentages with 95% CIs.

Change from baseline for pain on the NPRS, the index health state based on EQ-5D-5L and VCSS will be presented by summary statistics with 95% CIs.

Summary statistics for the number of ulcer free weeks will be presented along with the distribution of the number of ulcer free weeks (time to recurrence) estimated using the KM method and the 25th percentile, median and 75th percentile will be presented along with 95% CIs.

10.5 Additional Efficacy Analyses

A cox regression model will be presented for the time to wound closure investigating effects of subject age, wound age, presence of infection, ambulatory method and total wounds/ulcers of any type. The NPRS scale will be grouped into categories by severity (no pain, mild pain, moderate pain and severe pain) and presented in a shift table. Similarly, each EQ-5D-5L dimension will be summarized by a shift table. The overall visual analogue scale (VAS) and change from baseline will be descriptively summarized.

The Wound Healing Index (WHI)[23] is the predicated probability of a specified wound becoming healed and is created from multiplying the logistic regression parameter estimates by the values of the significant variables for a wound category type. The WHI will be calculated by entering eight pre-specified parameters into a portal via the US Would Registry to get a score per patient. The eight pre-specified parameters are:

1) Patient age in years at first treatment
2) VLU age (duration) in days at first encounter
3) VLU area in cm^2 at first encounter
4) Signs of infection or bioburden
5) Wound on lateral leg?
6) Patient's primary ambulatory method
7) Total wounds or ulcers of any type
8) Encounter ends with patient being sent to emergency department or hospital

[23] Horn S, Fife C, Smout R, Barrett R, Thomson B. Development of a wound healing index for patients with chronic wounds. Wound Rep Reg 2013;21:823-32.

The WHI will be used to stratify ulcers into simple, complex and severe categories.

Additionally, Varithena® outcomes from this study will be compared to historical data from the US Wound Registry.

10.6 Sub-group Analyses

Sub-group analyses will be performed for the rate of epithelial migration, wound closure at 12 months post-treatment and time to treatment. The following sub-group analyses will be performed:

- Ulcer severity (simple, complex, severe)
- Wound area (< median, ≥ median)
- Largest circle area (< median, ≥ median)
- Largest circle perimeter (< median, ≥ median)

An additional sub-group analyses will be performed on all analyses by wound type (single plane and circumferential).

10.7 Safety Analyses

No safety analyses are planned.

10.8 Interim Analyses

An interim futility analysis will be performed on the primary endpoints when approximately 50 – 75 subjects have enrolled.

11. DATA MANAGEMENT

Data from the registry is collected via the Tissue Analytics® tablet application and website, collectively referred to as the data capture tool (DCT). There are two versions of the DCT: physician-facing, referred to as Investigator data capture tool (iDCT), and subject-facing, referred to as subject data capture tool (sDCT). All data is transferred to Sponsor Clinical Development and Data Management (DM) groups in a secured format on a weekly basis, or as requested if needed more frequently. All processes are documented in the Data Management Plan (DMP). Delegated personnel are trained to use the iDCT and enter data on the observations, tests and assessments specified in this protocol and according to the data entry instructions. Each user has an individual login and password and is assigned a specific permission level, based on their study function. A Clinical Research Associate (CRA) reviews the data to check for missing, inconsistent or illogical data.

Data entered in the DCTs are immediately saved to a central database and changes tracked to provide an audit trail. Data validation checks are performed by Sponsor DM utilizing electronic edit checks comprised of validated computer programs and manual data review. Any data discrepancies are referred back to Investigator.

When data have been entered, reviewed and edited, as necessary, Investigator is notified and asked to sign the data electronically via the Investigator Signature section in the iDCT. After the database has been declared clean, it will be locked to prevent further editing. Editing in the database will only be allowed with the proper documentation. Each investigational site will receive a copy of the data for each subject they enrolled for archiving.

After database lock, data will be extracted to SAS® (SAS Institute, Inc., Cary, NC, USA) for analysis as defined in the SAP.

12. LEGAL/ETHICS AND ADMINISTRATIVE PROCEDURES

12.1 Good Clinical Practice/Regulatory Compliance

The procedures set out in the this protocol, pertaining to the conduct, evaluation, and documentation of this registry, are designed to ensure that Sponsor and Investigators abide by the Declaration of Helsinki and International Conference on Harmonisation (ICH) Guideline E6 (R1): Good Clinical Practice (GCP).

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

12.2 Site and Investigator Qualification

All participating investigational sites are assessed by Sponsor to verify that they are able to conduct the registry. Each participating institution must have an established IRB/REB and clinical protocol review process that is compliant with the code of federal regulation (CFR): 21 CFR 56, ensuring the clinical protocol can be adequately evaluated and approved at the institutional level. A centralized IRB is available to sites who do not have an established IRB/REB, or those who receive a deferral from their local IRB/REB.

The Institution must have appropriately qualified investigators, and clinical and administrative support staff in place to adequately conduct the registry according to ICH GCP in general and must have the adequate expertise and staff to conduct this registry in compliance with the relevant guidelines and regulations and to treat chronic venous insufficiency with resulting leg ulcers with Varithena®.

This registry is scheduled to be performed by qualified, experienced investigators at up to 40 research facilities in the United States and Canada. Given that the registry is intended to collect data related to SoC treatment with Varithena®, special care will be taken to select investigators with extensive experience in the treatment of venous insufficiency with Varithena®.

Site and Investigator qualification is primarily accomplished through a Site Qualification Form and a qualification phone interview. In some cases, an on-site qualification visit may be performed.

12.2.1 Investigator Curriculum Vitae (CV)

Investigator and all investigational site staff provide Sponsor with his/her current (dated within two years) curriculum vitae and any revisions/updates.

12.2.2 Statement of Investigator

Investigator must sign and date the Statement of Investigator/Protocol Signature Page (page 4) of this protocol for the original and each subsequent amendment of the protocol and return a signed copy to Sponsor.

12.3 Institutional Review Board (IRB)

12.3.1 Institutional Approval of the Protocol

It is the responsibility of Investigator or delegate to submit this protocol (submitted by Sponsor for sites using centralized IRB), the ICF (approved by Sponsor), relevant supporting information and all types of subject recruitment information to the IRB/REB for review and approval prior to investigational site initiation. A copy of the written approval of the protocol and ICF must be received by Sponsor prior to recruitment of subjects.

Investigator or delegate is responsible for keeping the IRB/REB apprised of the progress of the registry, any changes to the protocol, deviations from the protocol and reportable adverse events.

12.3.2 IRB/REB Membership Roster

Investigator or delegate must submit a complete and current roster of the IRB/REB to Sponsor. Some institutions, due to reasons of confidentiality, may not release their roster. In such instances, the institution's General Assurance Number, assigned by the Department of Health and Human Services, is an acceptable substitute.

12.4 Informed Consent – Ethical Compliance

Investigator or delegate provides Sponsor with a copy of the IRB or REB-approved consent forms and a copy of the IRB/REB written approval, prior to investigational site initiation. Additionally, if the IRB/REB requires modifications to the sample ICF provided by Sponsor, the documentation supporting this requirement must be provided to Sponsor.

It is the responsibility of Investigator or delegate to obtain written informed consent from subjects prior to the conduct of any trial procedures. All consent documentation must in accordance with applicable regulations and ICH GCP Guidelines. Each subject or the subject's legally authorized representative is requested to sign the ICF after the subject has received and read written information and received an explanation of the registry, including but not limited to: the objectives, treatment plan, potential benefits and risk, inconveniences, alternative treatment options and the subject's rights and responsibilities. A copy of the ICF must be given to the subject or the subject's legally authorized representative. If applicable, it is provided in a certified translation of the subject's local language.

Acquisition of the informed consent should be documented in the subject medical record and the ICF should be signed and personally dated by the subject and the individual who conducted the informed consent discussion. Signed consent forms must remain in each subject's registry file and must be available for review by CRA or auditor at any time.

12.5 Subject Privacy and Confidentiality

Sponsor and Investigator affirm and uphold the principle for the subject's right to protection against invasion of privacy. Throughout this registry, all data collected and analyzed by Sponsor is treated confidentially and identified by a SIC.

To verify compliance, Sponsor may require access to the subject's primary medical record to review those portions that directly concern this registry (including but not limited to radiology images and hospital and outpatient records).

As part of required content of the ICF, the patient must be informed that his/her records may be reviewed by Sponsor, Sponsor representative and/or a representative of the appropriate regulatory agency. The ICF or related document must also state that patient privacy will be maintained pursuant to the HIPAA and 21 CFR 21. Should access to such medical records require a waiver or authorization separate from the statement of informed consent, Investigator obtains such permission in writing from the subject before the subject is entered in the registry.

Data collected during this registry may be used to support the development or marketing of Varithena®. Collected data may be reviewed by Sponsor and/or its representatives, independent auditors who validate the data on behalf of Sponsor, national or local regulatory authorities and the IRB/REB which granted approval for this registry to proceed.

12.6 Monitoring

Monitoring the subject data is preformed using three methods: centralized, remote and on-site. All monitoring activities are performed by qualified personnel from Sponsor. Investigator and his/her staff are expected to cooperate with the CRA and be available during the visit to answer questions and resolve action items.

Monitoring activities are documented through various means, which include monitoring visit reports and documentation of centralized monitoring activities. For on-site visits, the CRA records the date, a summary of the status and progress of the registry, and proposed actions.

12.7 Modification of the Protocol

All amendments to this protocol must be documented in writing, reviewed and approved by Investigator, Sponsor, and IRB/REB prior to implementation. If the protocol amendment substantially alters the design or potential risk to the subject, new written informed consent must be obtained from each subject for continued participation in the registry.

12.8 Suspension or Termination of Registry

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

Sponsor has the right to terminate this registry at any time. Examples of situations where this might occur include:

- It becomes apparent that 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 registry indicate a potential health hazard caused by the treatment.

12.8.1 Protocol Deviations/Violations

Protocol deviations/violations not related to the informed consent process or eligibility are not required to be reported to Sponsor for this registry. Every attempt should be made to perform procedures and collect data according to this protocol. Protocol deviations/violations related to informed consent or eligibility should be reported to the IRB/REB, per reporting requirements. Copies of these reports and IRB/REB notification of receipt of these reports shall be submitted to Sponsor.

12.9 Recording, Access to and Retention of Source Data

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

- Documents that verify eligibility criteria
- Records covering subject participation in the registry including basic identification information, results of physical examinations and diagnostic tests, treatment administration, and visit/consult notes

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

The CRA, auditors, IRB/REB, or regulatory inspectors may check data entered against the source documents. The consent form must include a statement by which the subjects allow the above-named access to source data that substantiate data entered in the iDCT. These personnel, bound by privacy laws and professional secrecy, will not disclose any personal information or personal medical information.

As described in the ICH GCP Guidelines, 'essential documents', including final data set, source documents and consent forms should be retained by Investigator until at least two years have elapsed since the formal discontinuation of the registry. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with Sponsor. Investigator must obtain written permission from Sponsor prior to destruction of any registry document.

12.10Final Data

Investigator is responsible for maintaining adequate and accurate source documents from which accurate information is transcribed into iDCT, which is designed to capture all pertinent data for the registry. Data entry should be completed by Investigator or delegate, as delegated on the Delegation of Authority Log.

Once the data have been reviewed by the CRA, queries may be raised if the data are missing, unclear or contradictory. Queries are documented on data clarification forms (DCFs) and provided to the investigational site for timely resolution. Once all data is entered and all queries resolved, Investigator signs the completed data electronically via the Investigator Signature section of the iDCT and the database is locked. The final data set is provided to the site by Sponsor for archiving.

12.11Publications

No individual Investigator may publish results from his/her investigational site until after publication of the primary manuscript describing the full population.

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

The registry is listed in a publicly accessible registry of trials, clinicaltrials.gov.

12.12Audit/Inspections

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

13. SUPPLEMENTS/APPENDICES

13.1 Appendix A: CEAP Classification

American Venous Forum
Promoting venous and lymphatic health

Revised CEAP Classification of Venous Disorders

Bo Eklöf, MD et al for the American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification[7]

The CEAP classification for chronic venous disorders (CVD) was originally developed in 1994 by an international ad hoc committee of the American Venous Forum, endorsed by the Society for Vascular Surgery, and incorporated into "Reporting Standards in Venous Disease" in 1995. This classification system was designed to more clearly and accurately describe the form and severity of the venous disease being discussed.

Rather than allowing it to stand as a static classification system, an ad hoc committee of the American Venous Forum recommended a number of changes in 2004. These included refinement of several definitions; refinement of the C classes of CEAP; addition of the descriptor "n" (no venous abnormality identified); elaboration of the date of classification and level of investigation; and introduction of a basic CEAP version. The authors noted that CEAP is a descriptive classification, whereas venous severity scoring and quality of life scores are instruments for longitudinal research to assess outcomes.

The letter "C" is based on the clinical findings, usually easily seen on physical examination.

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

After this number, the letter "a" is assigned if the patient is asymptomatic, and the letter "s" is assigned if the patient experiences symptoms. An additional number may follow the "s" to denote the severity of the symptom. More than one number may be assigned if the patient has several findings on clinical examination.

The "E" stands for etiology, and the options are "c" for congenital disease, "p" for primary disease (not due to another cause), and "s" for secondary venous disease (postthrombotic), and “n” is for no venous cause identified.

The "A" refers to anatomic findings, and is usually based on Duplex ultrasound examination. The options are as follows:

Superficial veins (As)

1. Telangiectasias or reticular veins
2. Greater saphenous vein - above the knee
3. Greater saphenous vein - below the knee
4. Lesser (short) saphenous vein
5. Nonsaphenous

Deep veins (Ad)

6. Inferior vena cava
7. Common iliac
8. Internal iliac
9. External iliac
10. Pelvic: gonadal, broad ligament, etc.
11. Common femoral
12. Deep femoral
13. Superficial femoral
14. Popliteal
15. Crural: anterior tibial, posterior tibial, peroneal
16. Muscular: gastrocnemius, soleus, etc.

Perforator Veins (Ap)

17. Thigh
18. Calf

No venous location identified (An)

"P" refers to the pathophysiologic component, and the notations "r" for reflux, "o" for obstruction, or "r,o" for both reflux and obstruction may be used.

To improve the assignment of designations under E, A, and P, a new descriptor, n, has been added and is now recommended for use where no venous abnormality is identified. The n can be added to E (E_n, no venous cause identified), A (A_n, no venous location identified), and P (P_n, no venous pathology identified).

Using the CEAP classification routinely in your patient records and in the medical literature will allow us to compare the efficacy of our treatments and to follow the progress of patients in an intelligent and meaningful way. Implementation of this classification is an easily achieved goal, and all phlebologists are encouraged to use this tool in their daily practice.

Reference: Eklöf B, Rutherford RB, Bergan JJ, et al for the American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification. Revision of the CEAP classification for chronic venous disorders: Consensus statement. *J Vasc Surg*. 2004;40:1248-1252.

13.2 Appendix B: Venous Duplex Assessment

1. **Guidelines for Duplex Venous Assessment**

1.1 **Position of patient**: Where possible, patients are assessed while standing, with the majority of weight on the opposite limb. The limb being scanned is slightly flexed at the knee and the foot is turned outwards. The patient should be observed throughout the procedure for possible syncope. When assessing the proximal deep veins for compressibility, the patient should be semi-supine (upper body raised to 30^{o} to promote vein filling in the leg); however, when assessing the distal deep veins the patient should be in the sitting position.

1.2 **Ultrasound settings, choice of probes, assessment criteria**: The selected ultrasound device should have color flow and pulsed Doppler available. The operator has the right to select their choice of probe frequency, but a linear array is essential for accurate measurements. A venous default setting is selected on the machine, or color flow velocity maps are selected to identify low velocity blood flow.

Calf compression and release and Valsalva are used to assess venous flow in both the deep and superficial veins. The normal color setting is blue for proximal flow and red for reflux. All veins should fill from wall to wall; if the vein does not fill wall-to-wall thrombus may be present, but different steering angles and lower color flow velocity profiles should be used to optimize color filling. On release of the calf pressure, reflux is indicated by red color filling in excess of 0.5 seconds.

1.3 **Assessment of deep veins**: A transducer is placed in the groin and the common femoral vein is identified medial to the common femoral artery. Turning the transducer by 90 degrees to view the common femoral vein in a cross-section (grayscale image) the patient is asked to perform a Valsalva maneuver. This should result in an increase in common femoral diameter. If no increase is seen, a proximal obstruction should be considered. Proximal obstruction can be confirmed by placing the Doppler sample volume in the lumen (longitudinal section); common femoral venous flow will be continuous and aphasic, a Valsalva maneuver will not result in a movement of blood towards the probe (i.e., in the same direction as arterial flow). If there is absence of phasicity of flow with respiration, detailed proximal vein scanning is to be undertaken (i.e., iliac veins).

The Doppler sample volume is steered to a 60-degree Doppler angle, with the common femoral vein flow and the sample volume size increased across the full diameter of the lumen. Augmentation of flow by calf compression will result in venous return and a negative deflection on the spectral display. On release of the calf pressure, reflux will be seen as a positive deflection of greater than 0.5 seconds. A positive deflection of less than 0.5 seconds is probably due to valve closure and should be ignored. Moving distally a deep junction is identified. The deeper vein is the profunda femoris vein and should be assessed for competency using color flow and Doppler assessment. The more superficial vein is the femoral vein and should be traced along its length to assess competency and patency.

Viewing the common femoral vein in cross-section, pressure is applied by the probe on the medial aspect of the leg and at the same time pressure is applied by the hand on the lateral aspect of the leg. This procedure is repeated at regular intervals (2-3 cm) along the length of the common femoral and femoral veins. Failure to fully compress the veins indicates the presence of thrombus. The echogenicity of the thrombus indicates its age, with fresh thrombus appearing as a similar echogenicity to

the blood and old thrombus appearing as a similar echogenicity to the surrounding muscle tissue.

The transducer is placed over the popliteal fossa and the popliteal vein is identified. As before, it is checked for competency and compressibility. It is important to note that proximal to an incompetent small saphenous vein, a segment of the popliteal vein may appear incompetent. This can be excluded by rechecking for popliteal vein incompetence when the small saphenous vein (SSV) is occluded by external compression. Distally a deep vein just within the fascia may be seen to extend down the posterior aspect of the leg this is the gastrocnemius vein. The soleal veins are embedded in the soleus muscle and are less easily identified than the gastrocnemius veins. Several soleal veins can be present. They are laterally orientated and are lower in the calf than the gastrocnemius veins.

The anterior tibial vein may be seen as the first deep communication with the popliteal vein. Distal to this junction the tibio-peroneal trunk veins divide to form the posterior tibial and peroneal veins. It is easier to trace the deep calf veins from the ankle proximally. Placing the transducer posterior to the medial malleolus the posterior tibial artery and two veins can be visualized. Augmentation of flow by compressing the sole of the foot with a hand should result in good color filling. The posterior tibial veins should be traced proximally ensuring both are viewed along their length with no evidence of deep vein thrombosis. If the probe is angled slightly posterior the peroneal artery and veins should be visualized deep to the posterior tibial vessels. Placing your thumb and first finger on the anterior-medial and anterior-lateral aspects of the ankle and applying pressure can augment the peroneal vein flow. Placing the transducer on the anterior aspect of the ankle the anterior tibial artery and veins can be visualized and traced to the proximal calf.

All deep calf veins should be checked for patency, competency and compressibility and details recorded.

1.4 **Assessment of superficial veins**: Returning to the groin and moving distally along the common femoral vein, the great saphenous vein will appear as a superficial medial tributary. Care should be taken to view both color flow and perform Doppler assessment to determine whether the saphenofemoral junction is competent or incompetent. The sample volume should be placed immediately distal to the SFJ within the first 3 cm of the great saphenous vein (GSV). As for the deep veins augmentation of flow by calf compression will result in venous return and a negative deflection on the spectral display. On release of the calf pressure, reflux will be seen as a positive deflection of greater than 0.5 seconds. A positive deflection of less than 0.5 seconds is probably due to valve closure and should be ignored. The great saphenous should be traced along its length as isolated segments of incompetence and perforators may be identified. Any incompetent tributaries/perforators should be noted. The probe should be regularly turned to cross-section as perforators may be missed in longitudinal views. The great saphenous vein diameter (mm)) should be measured 5 cm below the saphenofemoral junction.

The SSV can be viewed either with the patient sitting or standing facing away from the operator. When sitting on the edge of the bed, the patient places their foot on the technologist's lap and the leg is slightly flexed at the knee and relaxed. When standing the leg must be slightly flexed and this position makes identification of the superior branch and posterior thigh connections and incompetence easier to identify.

The SSV is identified in the popliteal fossa, where it is usually deep to the deep fascia. It is then traced distally into the calf and the point at which it becomes superficial, perforating the deep fascia, is noted. The SSV is checked for competency and patency and then traced proximal to its junction with the popliteal vein. The popliteal vein must be viewed proximal and distal to the saphenopopliteal junction (SPJ) to determine whether the junction is incompetent. Incompetence can be proximal into the superior branch of the small saphenous. In some cases a SPJ may not be identified and the SSV may communicate with the vein of Giacomini, which lies just beneath the fascia and extends into the proximal posterior thigh. The diameter of the SSV should be measured 5cm distal to the junction.

13.3 Appendix C: Varithena® (polidocanol injectable foam) 1% Full Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VARITHENA™ safely and effectively. See full prescribing information for VARITHENA™.

Varithena™ (polidocanol injectable foam), for intravenous use
Initial U.S. Approval: 2013

INDICATIONS AND USAGE

Varithena™ (polidocanol injectable foam) is a sclerosing agent indicated for the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein system above and below the knee. Varithena™ improves the symptoms of superficial venous incompetence and the appearance of visible varicosities. (1)

DOSAGE AND ADMINISTRATION

For intravenous use under ultrasound guidance only. Use up to 5 ml per injection and 15 ml per treatment session (2)
Separate treatments sessions by a minimum of 5 days (2)

DOSAGE FORMS AND STRENGTHS

Injectable foam delivering a 1% polidocanol solution. (3)
Each mL of Varithena™ injectable foam contains 1.3 mg of polidocanol. (3)

CONTRAINDICATIONS

- Known allergy to polidocanol (4)
- Acute thromboembolic disease (4)

WARNINGS AND PRECAUTIONS

- Be prepared to treat anaphylaxis. (5.1)
- Tissue ischemia and necrosis: Do not inject intra-arterially. (5.2)
- Venous Thrombosis (5.3)

ADVERSE REACTIONS

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.(6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biocompatibles Inc. at 1-855-971-VEIN or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

There are no known drug interactions with Varithena™. (7)

USE IN SPECIFIC POPULATIONS

Do not use Varithena in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

Varithena™ is intended for 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. Use up to 5 ml per injection and no more than 15 mL per session.

Physicians administering Varithena™ must be experienced with venous procedures, possess a detailed working knowledge of the use of the duplex ultrasound in venous disease and be trained in the administration of Varithena™.

Activate Varithena™ using the Varithena™ Oxygen Canister and Polidocanol Canister *(see Instructions for Use).* Once a Varithena™ Transfer Unit is in place, foam can be generated and transferred to a syringe. Discard the syringe contents if there are any visible bubbles. Administer the injectable foam within 75 seconds of extraction from the canister to maintain injectable foam properties. Use a new sterile syringe after each injection. Use a new Varithena™ Transfer Unit for each treatment session.

Local anesthetic may be administered prior to cannula insertion but neither tumescent anesthesia nor patient sedation is required. Cannulate the vein to be treated using ultrasound guidance to confirm venous access.

Inject freshly generated Varithena™ slowly (approximately 1 mL/second in the GSV and 0.5 mL/second in accessory veins or varicosities) while monitoring using ultrasound. Confirm venospasm of the treated vein using ultrasound.

When treating the proximal GSV, stop the injection when Varithena™ is 3-5 cm distal to the Saphenofemoral Junction (SFJ).

Apply compression bandaging and stockings and have the patient walk for at least 10 minutes, while being monitored. Maintain compression for 2 weeks after treatment.

Repeat treatment may be necessary if the size and extent of the veins to be treated require more than 15 mL of Varithena™. Separate treatment sessions by a minimum of 5 days.

Retained coagulum may be removed by aspiration (microthrombectomy) to improve comfort and reduce skin staining.

3 DOSAGE FORMS AND STRENGTHS

Polidocanol Solution, 180 mg/18 mL (10 mg/mL) must be activated before use.

Once activated, Varithena is a white, injectable foam delivering a 1% polidocanol solution.

Each mL of Varithena™ injectable foam contains 1.3 mg of polidocanol.

4 CONTRAINDICATIONS

The use of Varithena™ is contraindicated in patients with:

- known allergy to polidocanol *[see Warnings and Precautions (5.1)]*
- acute thromboembolic disease

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Severe allergic reactions have been reported following administration of liquid polidocanol, including anaphylactic reactions, some of them fatal. Observe patients for at least 10 minutes following injection and be prepared to treat anaphylaxis appropriately.

5.2 Tissue Ischemia and Necrosis

Intra-arterial injection or extravasation of polidocanol can cause severe necrosis, ischemia or gangrene Patients with underlying arterial disease, such as marked peripheral arteriosclerosis or thromboangiitis obliterans (Buerger's Disease) may be at increased risk for tissue ischemia. If intra-arterial injection of polidocanol occurs, consult a vascular surgeon immediately.

5.3 Venous Thrombosis

Varithena™ can cause venous thrombosis *[see Adverse Reactions (6)]*. Follow administration instructions closely and monitor for signs of venous thrombosis after treatment. Patients with reduced mobility, history of deep vein thrombosis or pulmonary embolism, or recent (within 3 months) major surgery, prolonged hospitalization or pregnancy are at increased risk for developing thrombosis.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under controlled but widely varying conditions, adverse reaction rates observed in clinical trials of Varithena™ cannot be directly compared to rates in the clinical trials of other drugs or procedures and may not reflect the rates observed in practice.

A total of 1333 patients in 12 clinical trials were evaluated for safety when treated with Varithena™ at dose concentrations of 0.125%, 0.5%, 1.0% or 2.0%, including 437 patients treated with Varithena™ in placebo-controlled clinical trials.

Adverse reactions occurring in 3% more patients receiving Varithena™ 1% than receiving placebo are shown in Table 1.

Table 1: Treatment-emergent adverse reactions (3% more on Varithena™ 1% than on placebo) through Week 8 (n=588)

Adverse Reaction	Placebo (N=151)	Varithena™ 1.0% (N=149)	Pooled[a] Varithena™ (N=437)
Pain in extremity	14 (9.3)	25 (16.8)	65 (14.9)
Infusion site thrombosis[b]	0	24 (16.1)	46 (10.5)
Contusion/injection site hematoma	9 (6.0)	23 (15.4)	38 (8.7)
Limb discomfort	5 (3.3)	18 (12.1)	32 (7.3)
Tenderness/injection site pain	5 (3.3)	16 (10.7)	30 (6.9)
Venous thrombosis limb[c]	0	12 (8.1)	24 (5.5)
Thrombophlebitis superficial	2 (1.3)	8 (5.4)	40 (9.2)
Deep vein thrombosis	0	7 (4.7)	10 (2.3)

[a] Includes Varithena™ 0.125%, 0.5%, 1.0%, and 2.0% from the placebo-controlled trials.
[b] Retained coagulum.
[c] Common femoral vein thrombus extension (non-occlusive thrombi starting in the superficial vein and extending into the common femoral vein).

In Varithena™-treated patients, 80% of pain events in the treated extremity resolved within 1 week.

In the 1333 patients treated with Varithena™, the following venous thrombus adverse events occurred: common femoral vein thrombus extension (2.9%), proximal deep vein thrombosis (DVT) (1.7%), distal DVT (1.1%), isolated gastrocnemius and soleal vein thrombosis (1.4%).

Proximal symptomatic venous thrombi occurred in 0.9% of patients treated with Varithena™ 49% (n=35) of these patients required treatment with anticoagulants.

Since Varithena™ induces thrombosis in the treated superficial veins, D-dimer is commonly elevated post-treatment and is not useful diagnostically to assess patients for venous thrombus following treatment with Varithena™.

Neurologic adverse events (cerebrovascular accident, migraines) have been reported in patients following administration of physician compounded foam sclerosants. None of the 1333 patients in the Varithena™ trials experienced clinically important neurological or visual adverse events suggestive of cerebral gas embolism. The incidence of neurologic and visual adverse events within 1 day of treatment in the placebo-controlled studies was 2.7% in the pooled Varithena™ group and 4.0% in the placebo groups.

Skin discoloration adverse events were reported in 1.1% of the pooled Varithena™ group and 0.7% of the placebo group in the placebo-controlled studies.

7 DRUG INTERACTIONS

No specific drug interaction studies have been performed. There are no known drug interactions with Varithena™.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of Varithena™ in pregnant women. Do not use Varithena™ during pregnancy.

Animal Studies

Developmental reproductive toxicity testing was performed in rats and rabbits using intravenous administration of polidocanol solution. In rabbits, dose levels up to and including 10 mg/kg/day (approximately 12 times the proposed maximum human dose of 15 mL of 1% Varithena™ based on body surface area) did not produce any indication of adverse effects on embryo-fetal mortality, fetal weight or the incidences of fetal abnormalities and variants. In rats administered 27 mg/kg/day of polidocanol solution (approximately 13.5 times the human dose based on body surface area), there were no adverse effects on pregnancy performance or fetal development. In a peri- and post-natal study in rats, dose levels of polidocanol up to 9 mg/kg/day (approximately 4.5 times the human dose based on body surface area) were without effects on the development of the conceptus and offspring, and at a dose level of 27 mg/kg/day of polidocanol solution (approximately 13.5 times the human dose based on body surface area), effects were confined to an equivocal reduction in body weights of first-generation males, and an associated equivocal delay in the age of preputial separation.

8.2 Labor and Delivery

The effects of Varithena™ on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

It is not known whether polidocanol, the active pharmaceutical ingredient in Varithena™, is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, avoid administering Varithena™ to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1333 subjects in clinical studies treated with Varithena™, 9.1% (n=121) were ≥65 years of age. No clinically important differences in safety or efficacy were observed between older and younger patients in all studies.

10 OVERDOSAGE

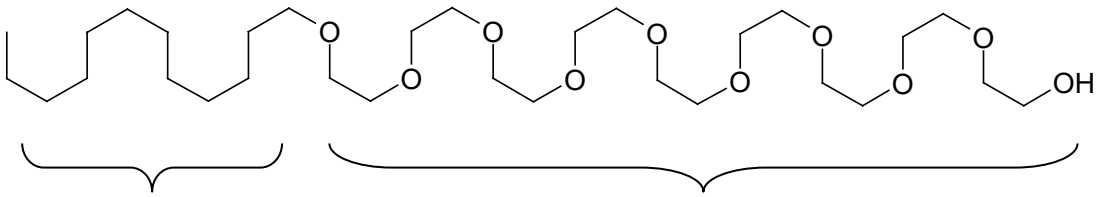
There are no known cases of overdosage with Varithena™. In clinical studies, total volumes of up to 60 mL of Varithena™ per treatment session have been administered.

11 DESCRIPTION

Varithena™ injectable foam contains the sclerosant, polidocanol. It is intended for intravenous use only.

Chemically, polidocanol is polyoxyl lauryl ether. The structural formula is represented below:

Polidocanol structural formula – 9-mole adduct



$C_{12}H_{25}$ $C_{18}H_{37}O_{10}$

$= C_{30}H_{62}O_{10}$

Polidocanol has the molecular formula $CH_3(CH_2)_{11}(OCH_2CH)_nOH$ and molecular weight 582.9 when the average ethylene glycol moieties is nine (n = 9). Polidocanol is a white to almost white, waxy, hygroscopic solid that is soluble in water and alcohol and melts at temperatures above 20°C.

Varithena™ is a sterile, injectable foam of an aqueous polidocanol solution (1%) containing the following inactive ingredients: ethanol (4.2% w/w), disodium hydrogen phosphate dihydrate (0.24% w/w), and potassium dihydrogen phosphate (0.085% w/w) with pH adjustment using 0.1 M sodium hydroxide solution and 0.1 M hydrochloric acid solution to achieve a pH of 6.0-7.5.

Activate the Varithena canister to enable foam generation from polidocanol solution, 180 mg/18 mL (10 mg/mL). Once activated, Varithena is a white, injectable foam delivering a 1% polidocanol solution. Each mL of Varithena™ injectable foam contains 1.3 mg of polidocanol. An activated canister of Varithena™ generates 90 mL of injectable foam which, following purging instructions contained in the IFU, is sufficient to yield 45 mL of usable injectable foam for intravenous injection. The polidocanol solution is stored under a carbon dioxide atmosphere in an aluminum canister prior to use.

The injectable foam is generated after activation of the polidocanol canister with oxygen from a second aluminum 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 injectable foam has a liquid to gas ratio of approximately 1:7 by volume. The median bubble diameter is less than 100 µm and no bubbles are greater than 500 µm.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Varithena™ is drug/device combination product that generates injectable foam. The injectable foam is composed of a liquid and gas phase, both of which are necessary to have its therapeutic effect. Varithena™ is intended to act as follows: (1) the foam displaces blood from the vein to be treated, (2) thepolidocanol then scleroses the endothelium.

The active pharmaceutical ingredient of Varithena™ is polidocanol, a non-ionic surfactant sclerosing agent. The hydrophobic pole of the polidocanol molecule attaches to the lipid cell membrane of the venous endothelium, resulting in disruption of the osmotic barrier, destruction of the venous endothelium, and vasospasm. Following exposure to polidocanol, the interior surface of the vein becomes thrombogenic, which leads to thrombus formation and venous occlusion. The occluded vein is eventually replaced by fibrous connective tissue. Polidocanol is deactivated upon contact with blood, thus limiting the sclerosant action to the endothelium near the site of injection.

12.2 Pharmacodynamics

The active pharmaceutical ingredient in Varithena™ is polidocanol. Polidocanol has a concentration dependent damaging effect on the endothelium of blood vessels.

12.3 Pharmacokinetics

The pharmacokinetics of Varithena™ (as a weighted sum of 4 oligomers: E5, E9, E12 and E14) were evaluated at two concentrations (1% and 2%) randomly assigned within gender in 20 patients with GSV incompetence.

When administered as an intravenous injectable foam as two fixed 5 mL doses separated by 10 minutes, polidocanol was rapidly detected in plasma, reaching maximum concentration of drug in the body after dosing (C_{max}) within 15 minutes of the first injection and within 5 mins of receiving the second injection of Varithena™ 1% or Varithena™ 2%. The mean volume of distribution (Vd) of polidocanol ranged from 35L to 82L.

Mean systemic clearance (CL) of polidocanol ranged from 0.2 to 0.4 L/min. The clearance of E5 was significantly greater than is that of longer oligomers. Mean terminal elimination half-life ($t_{1/2}$) ranged from 102 to 153 minutes, with most plasma samples below the limit of quantitation (BLQ) at the end of the 8 hour collection period. The increase in plasma polidocanol concentrations was less than proportional with increasing Varithena™ concentration. Weight normalized data demonstrated no consistent differences in C_{max} or AUC between males and females.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of Varithena™. No mutagenic activity was observed in the *in vitro* bacterial reverse mutation assay at non-toxic concentrations. No mutagenic activity was observed in the *in vitro* mouse lymphoma assay in the absence of S9 mix and was weakly mutagenic in the presence of S9 close to the limit of acceptance for

the accompanying level of toxicity. No micronucleus induction was detected in the *in vivo* assay on mouse bone marrow cells up to the maximum tolerated dose of 80 mg/kg.

There was no adverse effect on fertility in both male and female rats at 27 mg/kg/day. This dose level is approximately 13.5 times the proposed maximum human dose based on body surface area.

13.2 Animal Toxicology and/or Pharmacology

The pharmacological effects of polidocanol solution on the renal function of the rat were evaluated and at the highest dose tested (10 mg/kg) hematuria occurred in 67% of animals. This dose is 5 times higher than the proposed maximum human dose based on body surface area. Blood was no longer detectable in urine 24 hours after dosing. In the 28 day repeated dose toxicity study in rat blood pigments were noted in the urine for animals in all treatment groups, including male controls, at the end of the 4 week treatment period with up to 27 mg polidocanol/kg/day. Following the 2 week recovery period there was still evidence that blood pigments were present in the urine but the incidence and severity was decreased when compared to the main study animals. There were no histopathological findings in the urinary bladder in any study animals.

In a cardiovascular pharmacology study in the anesthetized dog at 20 mg/kg (approximately 33 times the human dose based on body surface area) statistically significantly higher values for P-Q interval were measured before and during dosing and at all time points up to 30 minutes after dosing. An increase in QRS interval was also measured after dosing of 20 mg/kg and at 5 and 10 minutes after dosing. This effect was short lived and was no longer seen at 15 minutes after dosing. In addition, there was an increase in diastolic pressure with increasing dose of polidocanol. This increase became significantly greater ($p<0.05$) than baseline before injection of the final and highest dose (20 mg/kg).

In a further cardiovascular pharmacology study conducted with a once weekly, for four weeks, intravenous bolus injection of Varithena™ in the conscious dog, dose levels of up to 8.0 mL/kg (approximately 17 times the human dose based on body surface area) to beagle dogs caused only a transient, but consistent, effect on respiration, evidenced by a decrease in tidal volume and RMV at 15 minutes post-dose, resolving by one hour post-dose. Histopathology of the lung at the end of the 3 month follow-up period showed no abnormalities.

14 CLINICAL STUDIES

Varithena™ was evaluated in two 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 in patients with SFJ incompetence as evidenced by reflux of the GSV or major accessory veins. In both studies, a Varithena™ 0.125% treatment group was included as a control for blinding of the duplex ultrasound assessment. Patients with history of deep vein thrombosis or pulmonary embolism, inability to comply with post-treatment compression due to severe peripheral arterial disease or leg obesity, incompetence of the small saphenous vein or deep venous reflux as a major source of reflux, or reduced mobility, or major surgery, pregnancy, or prolonged hospitalization within 3 months were excluded. Patients were randomized in an equal distribution to each treatment group; the primary time point for analyses of the primary, secondary and tertiary efficacy endpoints was Week 8.

In these clinical trials, the maximum volume of injectable foam or placebo to be administered per treatment session was 15 mL.

In VANISH-1, patients received one blinded treatment and in VANISH-2, patients received one blinded treatment with an option for a second blinded treatment 1 week later. In VANISH-2, patients in the Varithena™ 1.0% treatment group received an average of 1.4 blinded treatments. All patients received post-procedure compression therapy for 14 days following treatment.

Of the 519 patients randomized into VANISH-1 and VANISH-2, a total of 511 were treated with either Varithena™ 0.5% (n=111), 1.0% (n=110), or 2.0% (n=63), Varithena™ 0.125% as control (n=114), or placebo (n=113). Ninety-nine percent of the patients in VANISH-1 and VANISH-2 completed the blinded treatment period.

In the Varithena™ 1% group in VANISH-2, 23 of 58 patients received an additional blinded treatment. Two of these patients had retreatment of veins treated in the initial treatment session. The remaining 21 patients received treatment for additional veins not treated in the initial treatment session.

The mean age was approximately 50 years and approximately three-fourths of the patients were women. The mean BMI was similar in VANISH-1 and VANISH-2, at 28 kg/m^2 (range 16 to 44 kg/m^2) and 30 kg/m^2 (range 17 to 48 kg/m^2), respectively. The mean baseline GSV diameter was also similar in VANISH-1 and VANISH-2, at 7.6 mm (range 1.5 to 25.9 mm) and 8.7 mm (range 3.1 to 19.4 mm), respectively. Overall, 22% of patients in VANISH-1 and 25% of patients in VANISH-2 reported one or more prior varicose vein procedures in the leg to be treated.

For both clinical trials, the primary efficacy endpoint was improvement in patient symptoms, as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ™ score. The VVSymQ™ score 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. Results are shown in Table 2.

For both VANISH-1 and VANISH-2, treatment with 1.0% was superior to placebo in improving symptoms as measured by VVSymQ™, when either a duration or an intensity scale was used to measure patients' symptoms.

Table 2: Improvement in Symptoms of Varicose Veins as Measured by VVSymQ™ at Week 8, VANISH-1 and VANISH-2

	VVSymQ™					
	VANISH-1			**VANISH-2**		
	Placebo	**Varithena™ 1.0%**	**Pooled Varithena™***	**Placebo**	**Varithena™ 1.0%**	**Pooled Varithena™***
N	55	50	164	54	57	117
Baseline Score, mean	8.60	8.82	9.23	9.26	7.82	8.67
Adjusted Mean Change from baseline at Week 8	-2.13	-4.87	-5.44	-2.00	-5.06	-5.53

	VVSymQ™					
	VANISH-1			VANISH-2		
	Placebo	Varithena™ 1.0%	Pooled Varithena™*	Placebo	Varithena™ 1.0%	Pooled Varithena™*
Clinically meaningful improvement in Symptoms at Week 8**	5.4% (n=56)	64.7% (n=51)	76.4% (n=165)	19.6% (n=56)	75.9% (n=58)	79.7% (n=118)
Comparison vs. Placebo at Week 8, *P*-value, Adjusted Mean Change		<0.0001	<0.0001		<0.0001	<0.0001

*VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.
**Percent of patients who reported their symptoms had "moderately improved" or "much improved" compared with baseline.

The co-secondary endpoints in VANISH-1 and VANISH-2 were the improvement in appearance of visible varicosities from baseline to Week 8 as measured by: 1) patients scoring the appearance of their varicose veins in the medial view of their study leg (PA-V^3 score) from "Not at all noticeable" (a score of 0) to "Extremely noticeable" (a score of 4); and 2) an independent photography review panel rating the severity of the patient's varicose vein appearance in standardized digital photographs of the medial view of each patient's study leg (IPR-V^3 score) from "None" (a score of 0) to "Very severe" (a score of 4). Results are shown in Table 3.

Table 3: Improvement in Appearance of Visible Varicosities as Measured by IPR-$V^3$and PA-V^3at Week 8, VANISH-1 and VANISH-2

	VANISH-1			VANISH-2		
	Placebo	Varithena™ 1.0%	Pooled Varithena™*	Placebo	Varithena™ 1.0%	Pooled Varithena™*
IPR-V^3						
n	55	49	161	56	57	117
Baseline Score, mean	1.82	1.98	2.07	2.18	2.02	2.11
Adjusted mean change from baseline at Week 8	-0.01	-0.76	-0.81	-0.07	-0.83	-0.86
Clinically meaningful improvement in Appearance at Week 8†	8.9% (n=56)	70.6% (n=51)	79.4% (n=165)	0 (n=56)	70.7% (n=58)	72.9% (n=118)
Comparison vs. Placebo, *P*-value at Week 8, Adjusted Mean Change		<0.0001	<0.0001		<0.0001	<0.0001

	VANISH-1			VANISH-2		
	Placebo	**Varithena™ 1.0%**	**Pooled Varithena™***	**Placebo**	**Varithena™ 1.0%**	**Pooled Varithena™***
PA-V[3]						
N	55	50	164	56	57	117
Baseline Score, mean	3.49	3.46	3.54	3.30	3.49	3.54
Adjusted mean change from baseline at Week 8	-0.15	-1.60	-1.58	-0.32	-1.79	-1.82
Clinically meaningful improvement in Appearance at Week 8†	3.6% (n=56)	54.9% (n=51)	64.2% (n=165)	7.1% (n=56)	69.0% (n=58)	74.6% (n=118)
Comparison vs. Placebo, *P*-value at Week 8, Adjusted Mean Change		<0.0001	<0.0001		<0.0001	<0.0001

*VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.
†Percent who reported the appearance of varicose veins had "moderately improved" or "much improved" compared with baseline.

Tertiary endpoints in VANISH-1 and VANISH-2 included response to treatment as determined by change from baseline in Venous Clinical Severity Score (VCSS), by duplex ultrasound, and by change from baseline in Venous Insufficiency Epidemiologic and Economic Study – Quality of Life/Symptoms (VEINES-QOL) score.

VCSS 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 VCSS 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 are statistically significant ($P<0.0001$).

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 versus the Varithena™ 0.125% (control) group. Results are shown in Table 4.

Table 4: Response to Treatment as Measured by Duplex Ultrasound at Week 8, VANISH-1 and VANISH-2

Parameter	Treatment Group, %				Comparison of Pooled Varithena™* vs. Varithena™ 0.125% (control)
	Placebo	Varithena™ 0.125% (control)	Varithena™ 1.0%	Pooled Varithena™*	*P*-value
Responders, VANISH-1**	5.4% (n=56)	42.1% (n=57)	80.4% (n=51)	74.5% (n=165)	<0.0001
Responders, VANISH-2	1.8% (n=56)	59.6% (n=57)	86.2% (n=58)	84.7% (n=118)	0.0002

* VANISH-1 Varithena™ (pooled): 0.5% + 1.0% + 2.0%; VANISH-2 Varithena™ (pooled): 0.5% + 1.0%.
**In VANISH-1, a significant dose-response trend was evident between the percent of responders and the dose concentration of Varithena™ (P<0.0001).

VEINES-QOL 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 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).

For efficacy endpoints, Varithena™ treatment effects were consistent across subgroups of age, sex, BMI (up to 48 kg/m^2), CEAP clinical class, GSV diameter (up to 25.9 mm) and VCSS.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Varithena™ is supplied in a convenience box (NDC 60635-133-01) that contains:

- A Tyvek pouch containing two sterile, connected 303 mL aluminum alloy canisters: one containing Polidocanol Solution, 180 mg/18 mL (10 mg/mL), under a carbon dioxide atmosphere, the second containing pressurized oxygen at approximately 5.4 bar absolute. The connector joins the two canisters and allows activation of the product. Once activated, Varithena injectable foam delivers a 1% polidocanol solution. Each mL of Varithena injectable foam contains 1.3 mg of polidocanol. One canister of Varithena generates 90 mL of foam which, following purging instructions in the IFU, is sufficient to yield 45 mL of usable foam for injection.
- Three Varithena™ Transfer Units to dispense injectable foam;
- Three administration boxes each containing:
    - Three 10 mL silicone-free Luer syringes;
    - A 20-inch manometer tube;

- Two compression pads.

16.2 Storage and Handling

Do not shake Varithena™ canisters.

Avoid contact with eyes.

Store the Varithena™ convenience box at 68° to 77°F (15° to 25°C); excursions are permitted to between 59° to 86°F (15° and 30°C). Do not refrigerate or freeze.

Unused, non-activated Varithena™ canisters may be stored in the flat or upright position.

Contains gas under pressure: May explode if heated. Store in a well-ventilated place. Store the canisters away from sources of heat including strong light conditions.

Pressurized Oxygen: May cause or intensify fire; oxidizer. Store away from combustible materials.

Once activated, the canister of Varithena™ must be used within seven (7) days.

Store activated canisters of Varithena™ upright, with the Varithena™ Transfer Unit attached, under the same temperature conditions as the Varithena™ convenience box. Use a new Varithena™ Transfer Unit for each treatment session.

Discard aerosol canisters after use in accordance with state and local requirements.

For more information, please refer to the IFU.

17 PATIENT COUNSELING INFORMATION

Advise the patient to keep post-treatment bandages dry and in place for 48 hours and to wear compression stockings on the treated legs continuously for 2 weeks. Compression stockings should be thigh or knee high depending upon the area treated in order to provide adequate coverage. Advise the patient to walk for at least 10 minutes immediately after the procedure and daily for the next month. Following treatment, advise the patient to avoid heavy exercise for 1 week and extended periods of inactivity for 1 month.

If you would like more information, please talk with your doctor. For more information about Varithena™ you can also call us at *{1-855-971-VEIN}* or go to www.varithena.com.

Manufactured for Provensis Ltd by:

Biocompatibles UK Ltd

Chapman House, Weydon Lane, Farnham, UK, GU9 8QL.

BTG

Distributed by:

Biocompatibles, Inc.

115 Hurley Road, Building 3, Oxford, CT 06478

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13.4 Appendix D: Varithena® (polidocanol injectable foam) 1% Instructions for Use

Varithena™
(polidocanol injectable foam) 1%

Varithena Delivery System
Instructions for Use

Please read all prescribing information before using the product.

The Instructions for Use are for the entire Varithena system. There are 2 packaging configurations:

Option A: Bi-Canister box and Administration Pack*

Option B: Convenience box (Bi-Canister Box + 3 Ancillary Packs + 3 Varithena transfer units)*

*The components in each packaging configuration are to be used only in conjunction with each other for activation of Varithena.

Administration Packs can be used for either configuration for further treatment sessions.

Always write the activation date and time on the canister and verify the product has not expired prior to use.

Once the Varithena canister has been activated, the shelf life for the product is thirty days.

Rx Only

A canister of Varithena generates 90mL of foam which, following purging instructions contained in this IFU, is sufficient to yield 45mL of usable foam for injection. The gas mix of the foam is 65:35 O_2:CO_2.

WARNINGS:

As the foam fills the syringe and before injecting, inspect the syringe full of foam for any visible bubbles. If there are any present, the foam should be emptied into the Varithena transfer unit waste chamber and the syringe refilled.

Do not shake Varithena canisters.

Always use a fresh pair of sterile gloves when handling the Bi-Canister and Varithena transfer unit.

A new Varithena transfer unit must be used for each treatment session.

Notes: Use a new sterile syringe after each injection. Never fill a syringe until just before the foam is required. The activated Varithena canister should always be stored with a Varithena transfer unit in place in the upright position at controlled room temperature in an appropriately controlled clean area to limit contamination.

Use foam within 75 seconds of generation or discard and generate new foam.

Unpacking Varithena:
Option A: Bi-Canister Box and Administration Pack

Gather all the items needed for the generation of foam: the Varithena Bi-Canister box (Figure 1a), Administration Pack (including: Varithena transfer unit, manometer tube, compression pad and silicone-free syringes) (Figure 1b), and the following items that are not supplied: scissors, pen, sterile alcoholic wipes, timer and gloves (Figure 1c).

Open the Varithena Bi-Canister box and remove the Varithena Bi-Canister pouch. Open the Administration Pack and remove the components. Inspect the pouch and components for damage (do not use product if there are any visible signs of damage to pouch or components).

Figure 1a Varithena Bi-Canister

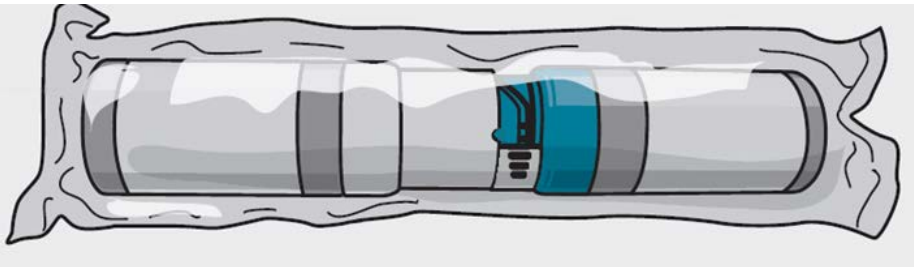
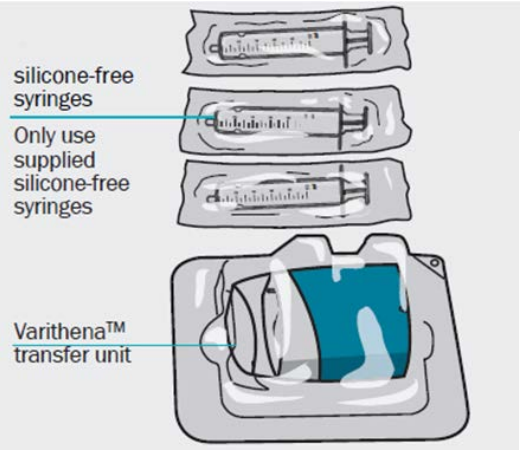


Figure 1b Administration Pack



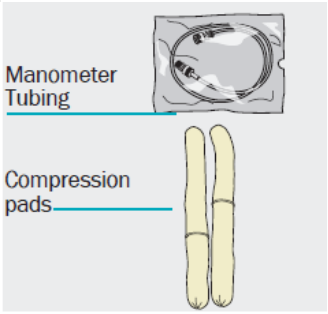
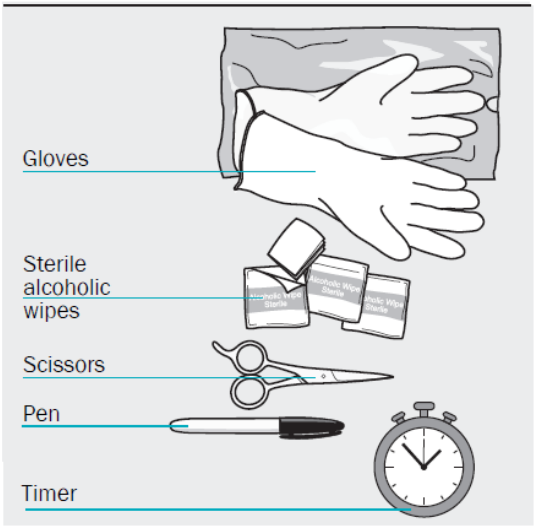


Figure 1c Additional Procedure Items (not supplied)



Unpacking Varithena:

Option B: Convenience Box (Bi-Canister Box + 3 Ancillary Packs + 3 Varithena transfer units)

Gather all the items needed for the generation of foam: the Varithena Bi-Canister Box (Figure 2a), Ancillary Pack (including silicone-free syringes, manometer tubing, and compression pads and Varithena transfer unit (Figure 2b), and the following items that are not supplied: scissors, pen, sterile alcoholic wipes, timer and gloves (Figure 2c).

Open the Varithena Convenience box and remove all the components. Open the Varithena Bi-Canister box and remove the Varithena Bi-Canister pouch. Open an Ancillary Pack and remove the components. Inspect the pouch and components for damage (do not use product if there are any visible signs of damage to pouch or components).

Figure 2a – Varithena Bi-Canister

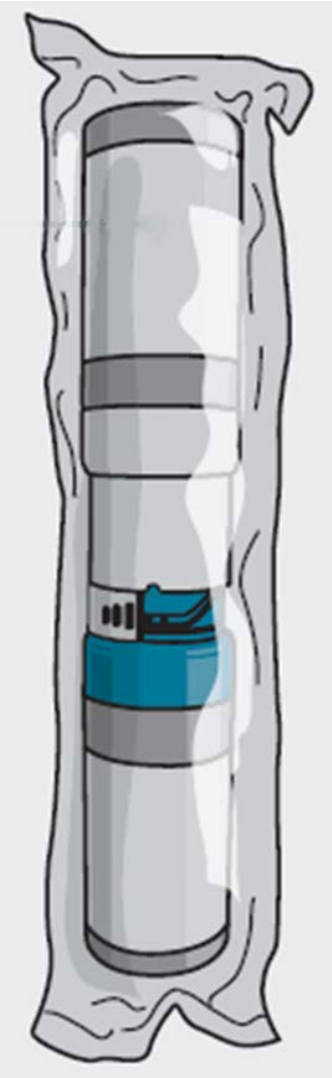


Figure 2b – Three Ancillary Packs

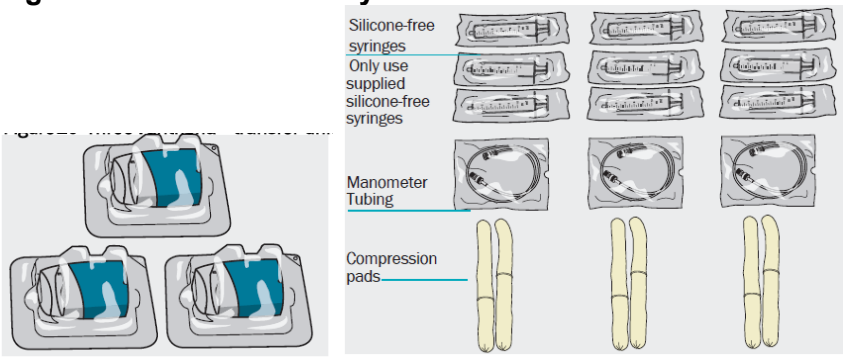
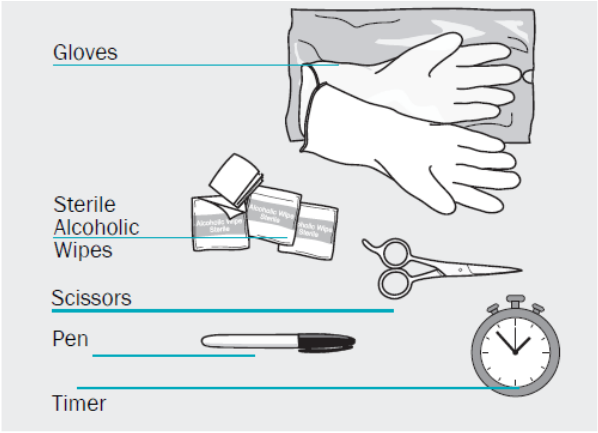


Figure 2c – Additional Procedure Items (not Supplied)



Preparing the Patient

Preparations for treating the patient with Varithena should include the following steps:

- Position the patient comfortably on the treatment table in a supine position with their hip externally rotated to facilitate access to the GSV.
- Use ultrasound to find the best site for venous access.
- Using an aseptic technique, infiltrate the skin over the venous access point with local anesthetic.
- Obtain venous access under ultrasound guidance.
- IV catheters that are 16 to 22 gauge and 40 - to 50 - mm long or micropuncture sets are recommended for venous access.
- Prefill the manometer tube with sterile heparinized normal saline solution and connect to the IV catheter.
- Confirm venous access by aspirating with a syringe, blood should be dark and under low pressure.
- Flush the IV catheter and manometer tube with heparinized normal saline and secure it to the skin with adhesive tape, leave the saline syringe connected.
- With the IV catheter in place and secure, place the patient supine and elevate the leg to approximately 45 degrees.

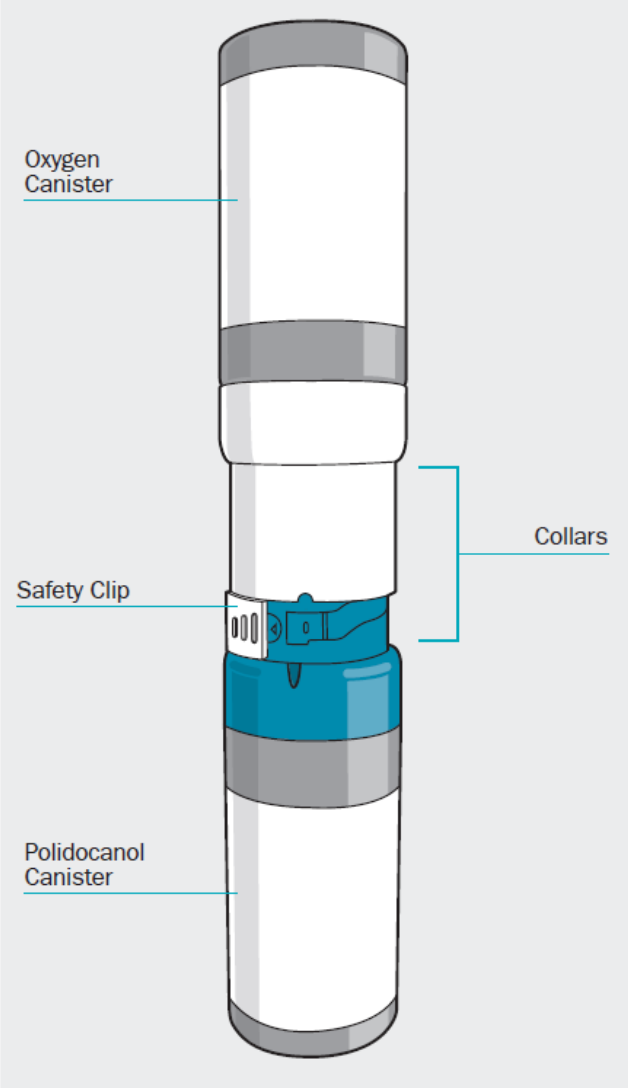
Complete all preparation of the patient and preparations for Varithena injectable foam injection before generation of the foam.

Varithena Preparation

1

Wearing appropriate sterile gloves, open Bi-Canister pouch using a pair of scissors. Place canisters upright on a cleaned (sterile wipes) stable surface with the white oxygen canister on top (Figure 3). Discard empty pouch.

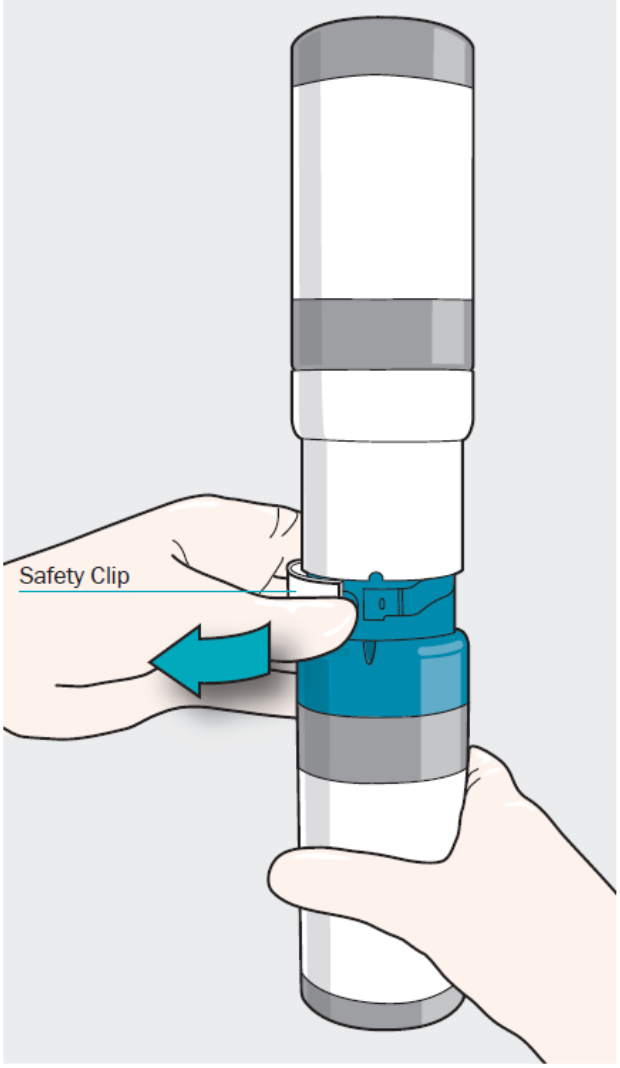
Figure 3



2

Remove the safety clip by lifting one corner of the clip out (Figure 4). Discard the safety clip.

Figure 4



Gas Activation of the Varithena Canister

3

To begin the gas transfer, twist the canisters together clockwise (Figure 5) until they come to a stop and the small indicators/marks on the collars are aligned (Figure 6). You may hear a bubbling sound.

While the canisters are activating, keep them upright on the clean flat surface for 1 minute. Use a timing device to keep track of the 1 minute time.

Figure 5

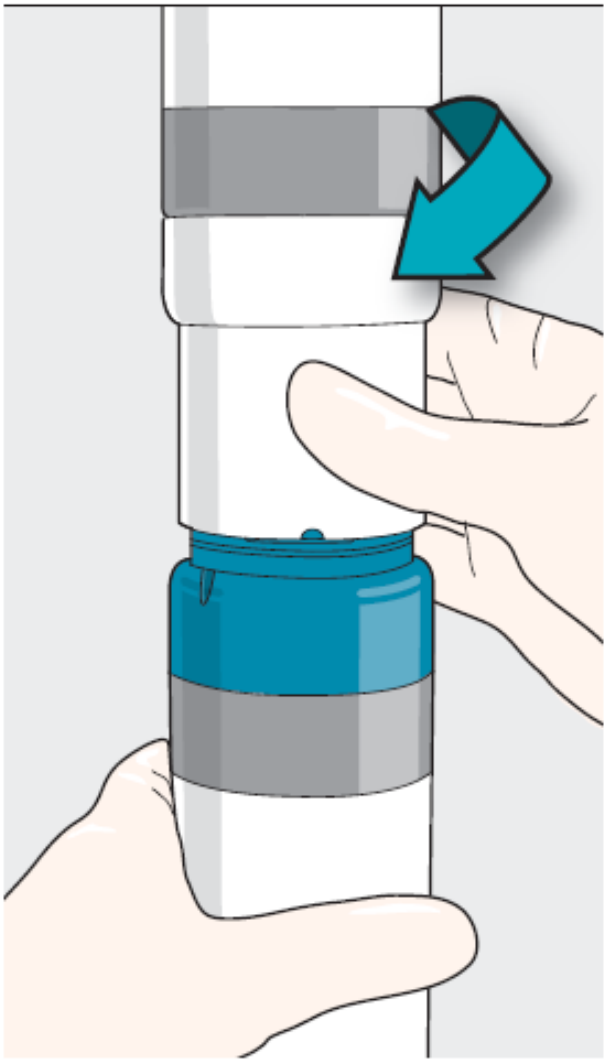
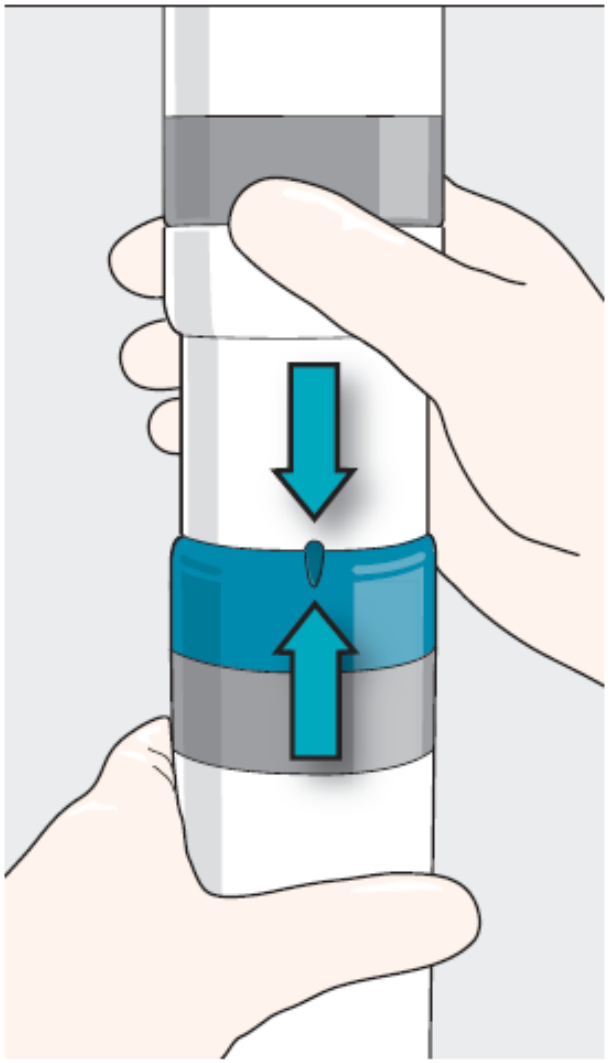


Figure 6

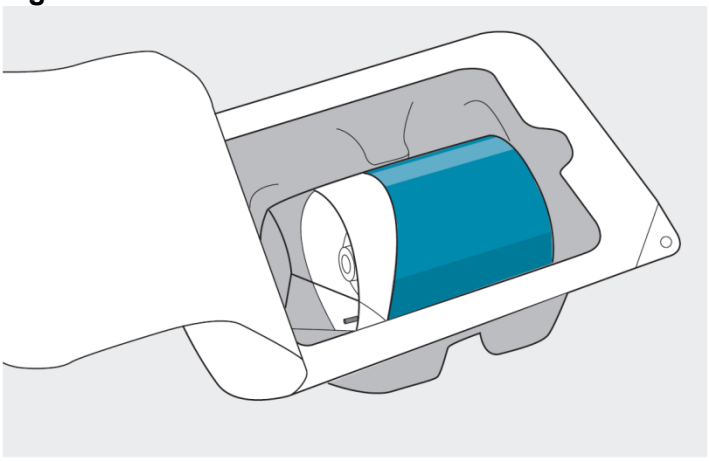


Gas Activation of the Varithena Canister

4

Note: In order to maintain sterility of the Varithena transfer unit, the following steps must be followed. While waiting 1 minute for the gas transfer, open a new Varithena transfer unit, blister pack, but leave the Varithena transfer unit in the package (Figure 7).
The manometer tubing (20 inch) should have been previously filled with sterile heparinized normal saline solution.

Figure 7



Gas Activation of the Varithena Canister

5

After 1 minute,

- Twist the two canisters by turning them in the opposite direction (counterclockwise) as before (Figure 8).
- Pull straight up to separate the oxygen canister from the Varithena canister, as shown (Figure 9). Do not separate canisters until you have a Varithena transfer unit ready to place onto the Varithena canister (See step 6).
- Put the oxygen canister (with white collar) aside.
- The Varithena canister (with blue collar) should remain on a clean flat surface, in the upright position.

Figure 8

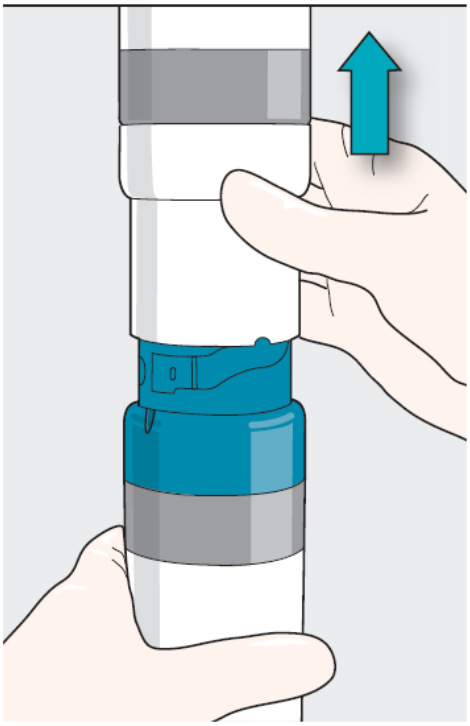
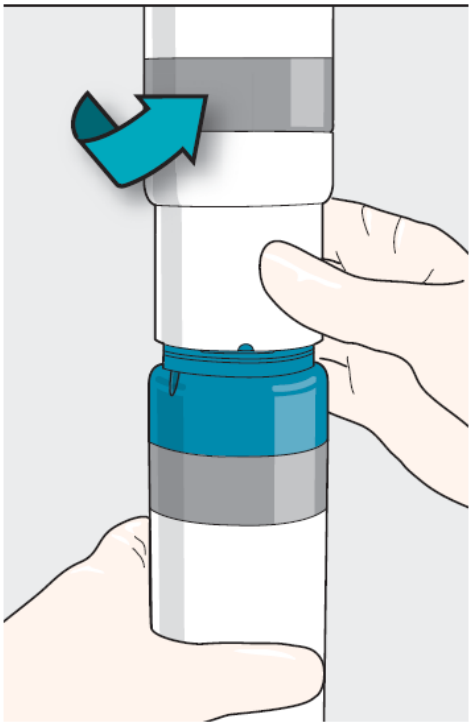
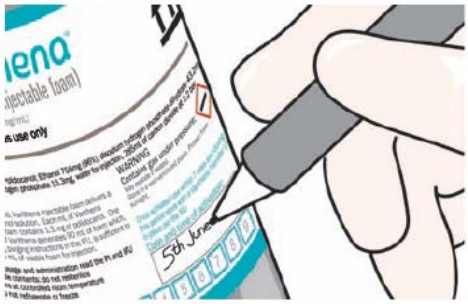


Figure 9



Write today's date and time in the "Date and Time of Activation" box on the Varithena canister (Figure 10)

Figure 10



Connecting a new Varithena transfer unit and syringe

6

Remove the Varithena transfer unit from the blister pack, wearing a fresh pair of sterile gloves. Make sure not to touch the sterile underside of the Varithena transfer unit, (discard Varithena transfer unit if contaminated).

Immediately place the Varithena transfer unit on top of the blue Varithena canister. Gently rotate the Varithena transfer unit clockwise as indicated (Figure 11) until it drops into the collar threads then twist the Varithena transfer unit (clockwise) until it reaches a stop (Figure 12).

Figure 11

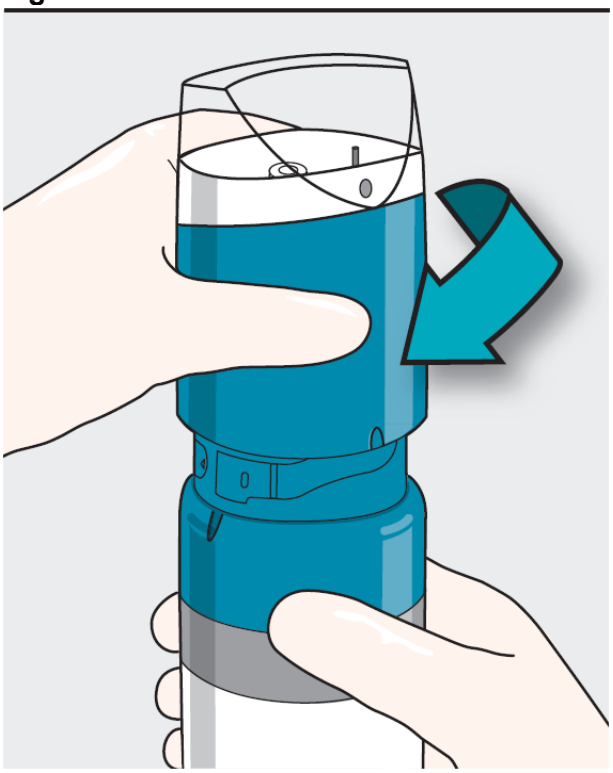
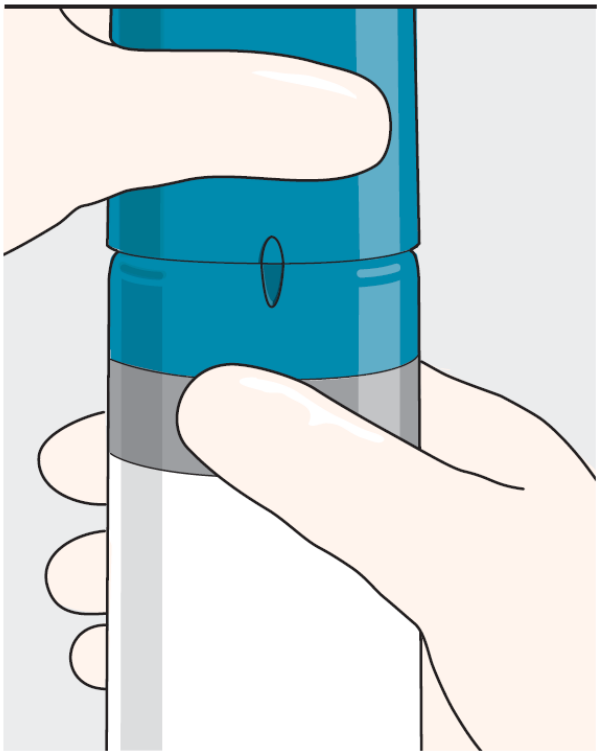


Figure 12



The system is now activated and ready for use.

Connecting a new Varithena transfer unit and syringe

7

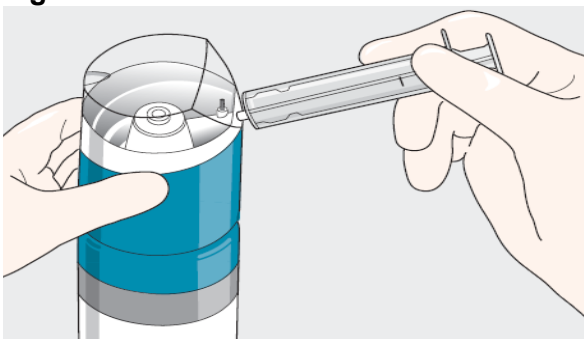
Change the Varithena transfer unit immediately before each new treatment session.

Once all preparations for injection are complete, i.e., cannula *in situ*, patient's leg elevated and a good ultrasound view of the saphenofemoral junction (SFJ) obtained, foam may be generated for immediate use.

Open a sterile 10mL silicone-free syringe package and keep it in the package until needed.

Remove the syringe from the package, and connect it to the Varithena transfer unit as shown (Figure 13).

Figure 13



Priming a New Syringe

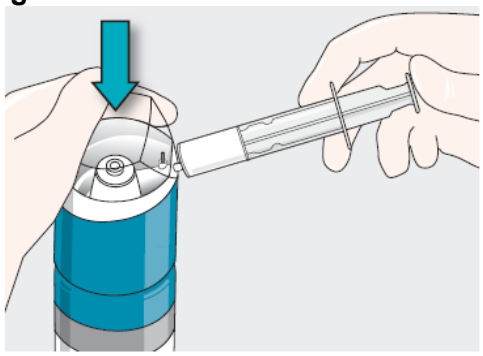
8

Gently press down the Varithena transfer unit to begin producing foam (Figure 14).

Using continuous pressure, allow the silicone-free syringe to fill between 3mL and 5mL.

Release the pressure on the Varithena transfer unit and leave the syringe connected.

Figure 14



Priming a New Syringe

9

Push the silicone-free syringe plunger in fully to discard its contents (Figure 15). Do not disconnect the syringe.

Note: The foam will automatically be diverted into the waste chamber within the Varithena transfer unit (Figure 16). This process eliminates the small quantity of air in the syringe and Varithena transfer unit.

Figure 15

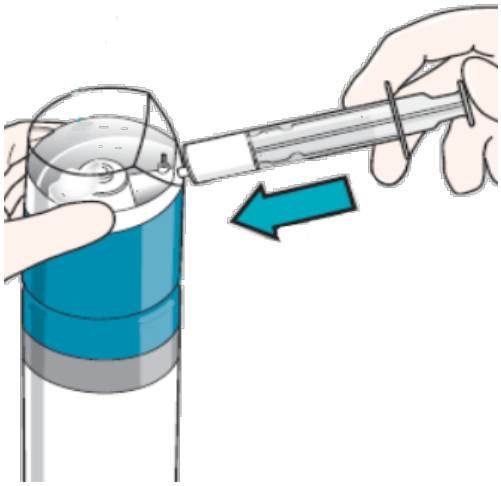
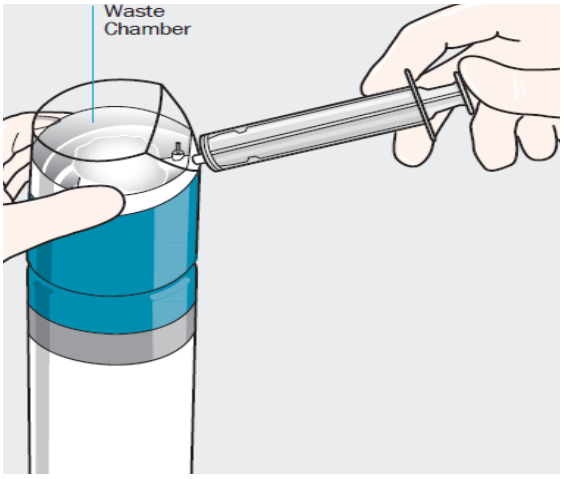


Figure 16



Generation of Foam

10

Foam Generation: The technique to produce usable foam requires a single purge cycle before filling the syringe, a process that takes less than 1 second.

Important Note: Foam must be generated by pushing down on the Varithena transfer unit continuously without pulling back on the plunger of the syringe (aspirating).

While holding the silicone-free syringe plunger in place, gently press down on the Varithena transfer unit to begin the purge cycle (Figure 17).

Visually inspect the flowing foam inside the Varithena transfer unit to make sure the visible air bubbles have been expelled (less than 1 second) before releasing the syringe plunger and allowing it to fill to the desired volume (Figure 18).

Draw up to 5mL of foam into the syringe.

Figure 17

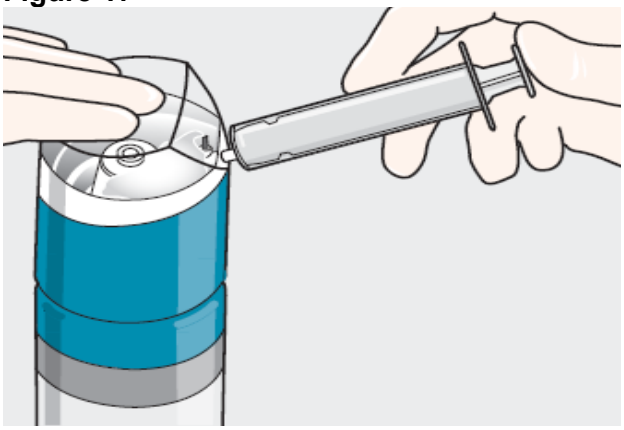
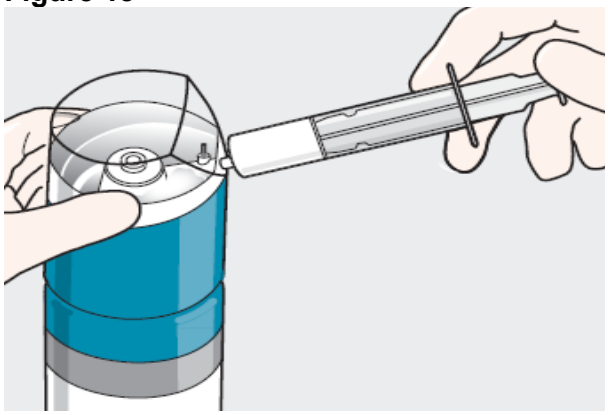


Figure 18



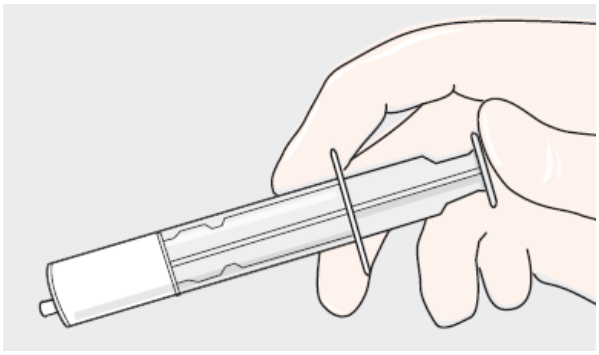
Inspecting and Injecting Foam

11

After the silicone-free syringe has filled to the desired volume, wait 10 seconds to allow the pressure to equalize before removing the syringe from the Varithena transfer unit (Figure 19).

WARNING: As the foam fills the syringe and before injecting, **inspect the syringe full of foam for any visible bubbles** (easily seen with the unaided eye at arm's length). If there are any present, empty the foam into the Varithena transfer unit waste chamber and refill the syringe.

Figure 19



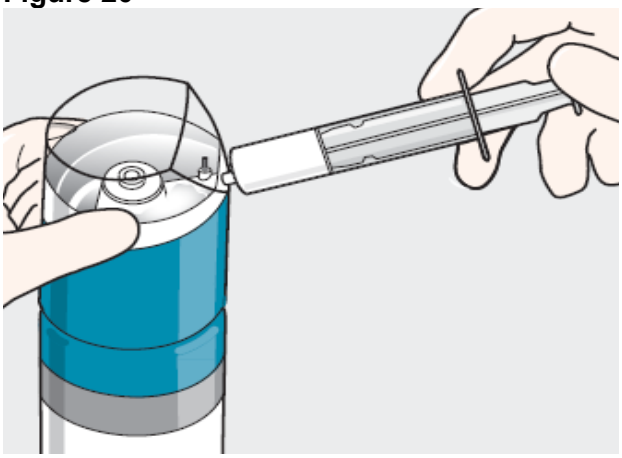
12

Remove the syringe from the Varithena transfer unit and inspect it for visible bubbles (Figure 20).

If no visible bubbles are present then the foam is ready for use.

Use the foam within 75 seconds of generation or discard and generate new foam.

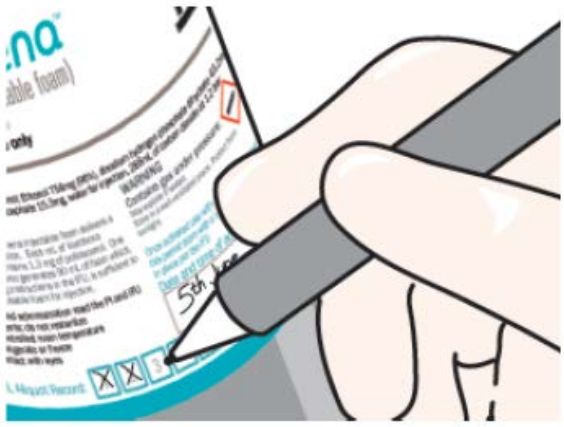
Figure 20



WARNING: The total amount of foam injected in any one treatment session must not exceed 15mL, comprised of individual injections of up to 5mL each.

After each treatment session, mark-off on the canister label the number of aliquots of up to 5mL of usable foam drawn from the canister per step 11 (Figure 21).

Figure 21



13

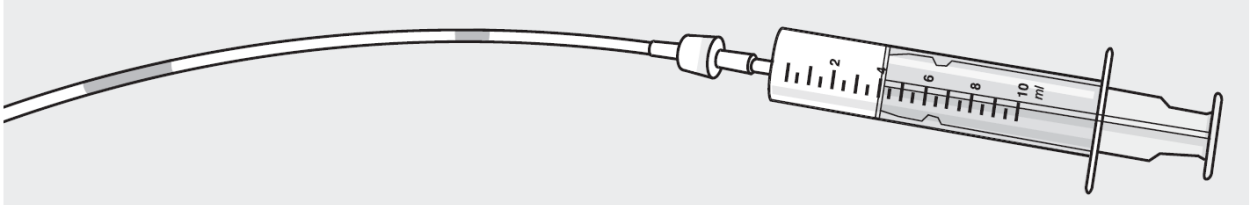
Connect a syringe of freshly generated foam to the manometer tubing, which is already connected to the cannula, in preparation for the initial injection. The manometer tubing (20) inch should have been previously filled with sterile heparinized normal saline solution.

Inspecting and Injecting Foam

14

Inject the foam at approximately 0.5mL to 1.0mL per second through the manometer tubing. Five (5) mLs of foam should be injected in approximately 10 seconds. Always inspect the foam as it passes through the manometer tubing for visible bubbles (Figure 22). If any visible bubbles are seen (easily seen with the unaided eye at arm's length) they should be aspirated back into the silicone-free syringe and the syringe contents discarded back into the Varithena transfer unit waste chamber, and a fresh syringe of foam generated.
Notes: Use a new sterile syringe after each injection.

Figure 22



WARNING: The total amount of foam injected in any one treatment session must not exceed 15mL, comprised of individual injections of up to 5mL each

Do not remove Varithena transfer unit if the Varithena canister is to be stored (see Storage)

Change sterile gloves appropriately, to limit any contamination of the Varithena transfer unit and Bi-Canister.

Compression Pads

15

Once treatment is complete, the Compression Pads should be used:

The objective of the pads is to focus the compression forces on the treated vein to keep them as free from blood as possible, thus minimizing retained thrombus.

The compression pads supplied should be placed along the course of the treated trunk vein in the thigh, and over raised treated varicose veins above and below the knee. The pads may be shaped to follow the course of the veins. The pads should be placed outside the first layer of limited stretch bandage and held in place by a second layer of bandage.

The appropriate length compression stocking is then applied.

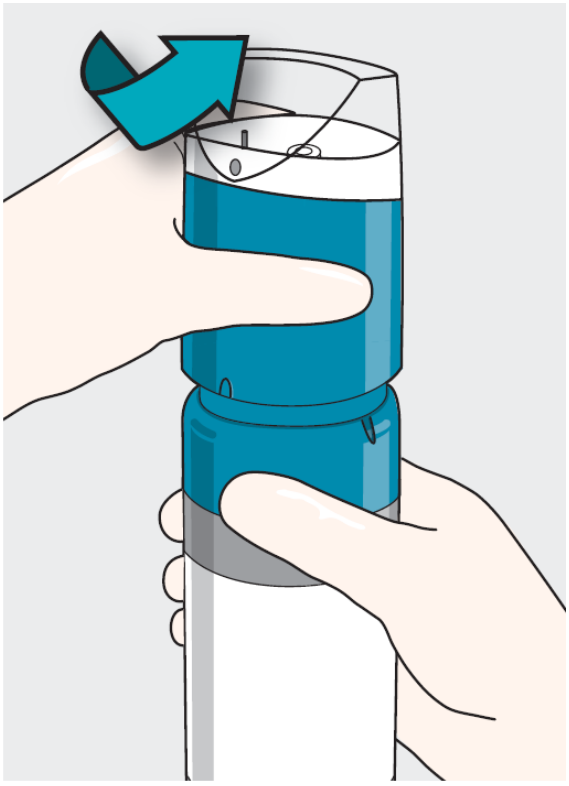
Replacing the Varithena transfer unit

Important Note: Do not replace the Varithena transfer unit if the canister is to be stored for future use. The activated Varithena canister should always be stored in an appropriately cleaned area with a Varithena transfer unit in place in the upright position at controlled room temperature. Replace the Varithena transfer unit just prior to the next treatment session.

16

Wearing appropriate new sterile gloves, hold the Varithena canister, twist the Varithena transfer unit counterclockwise and then pull up to separate from the canister (Figure 23).

Figure 23



17

Discard the old Varithena transfer unit and open a new Varithena transfer unit.

Make sure not to touch the sterile underside of the Varithena transfer unit.

Replacing the Varithena transfer unit

18

Swab the uncovered shuttle with a fresh sterile alcohol wipe (Figure 24) and immediately place the Varithena transfer unit on top of the Varithena canister.

Gently rotate the Varithena transfer unit clockwise until it drops into the collar threads (Figure 25), then twist the Varithena transfer unit (clockwise) until it reaches a stop (Figure 26).

Figure 24

Figure 25

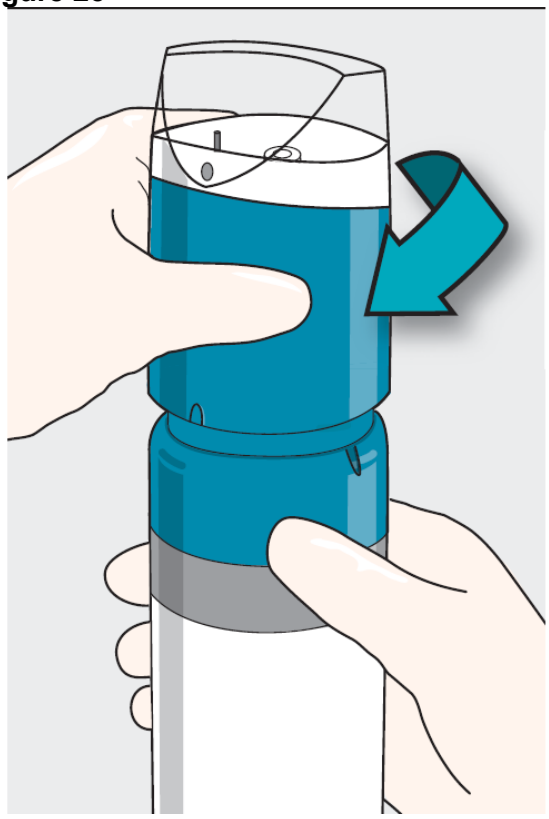
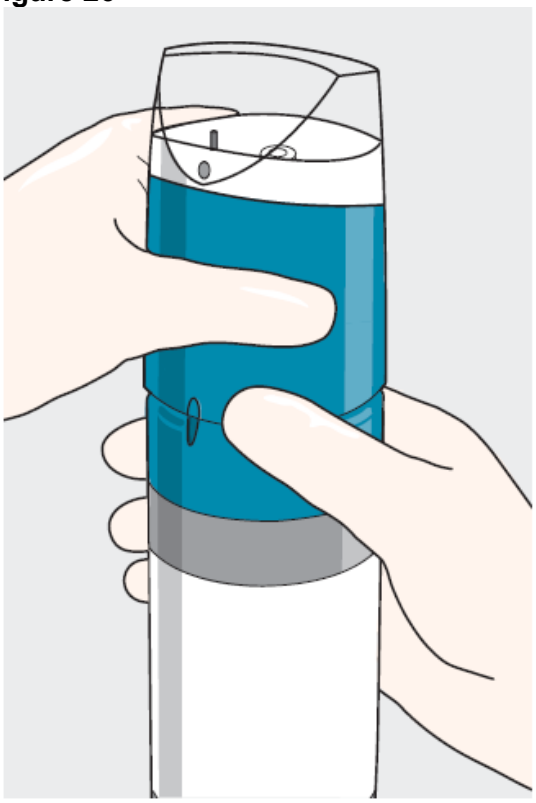


Figure 26



The Varithena device now ready for use for a new treatment session, following the instructions in Steps 7 to 15.

Storage and Disposal

Note: The activated Varithena canister should always be stored with a Varithena transfer unit in place in the upright position at controlled room temperature in an appropriately controlled clean area to limit contamination.

Once the Varithena canister has been activated, the shelf life for the product is thirty (30) calendar days.

Always write the activation date and time on the canister and verify the product has not expired prior to use.

Dispose of Varithena and oxygen canisters following local and state regulations for aerosol disposal.

The Varithena transfer unit can be disposed of as non-toxic non-clinical waste.

Net Contents: 18ml

One canister of Varithena contains:
180mg Polidocanol, ethanol 756mg (96%), disodium hydrogen phosphate dihydrate 43.2mg, potassium dihydrogen phosphate 15.3mg, water for injection.

One canister of Varithena generates 90mL of foam which, following purging instructions contained in this IFU, is sufficient to yield 45mL of usable foam for injection.
The gas mix of the foam is 65:35 O2:CO2.
NDC 60635-118-01 Varithena Bi-Canister
Administration Pack
NDC 60635-133-01 Varithena Convenience Pack

Manufactured for Provensis Ltd by:

Biocompatibles UK Ltd
Chapman House, Weydon Lane, Farnham, Surrey, UK, GU9 8QL

Distributed by:
Biocompatibles Inc., Five Tower Bridge, Suite 810, 300 Barr Harbor Drive, West Conshohocken, PA, 19428-2998, USA.

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Provensis Ltd, and Biocompatibles UK Ltd, are BTG International group companies

Varithena™
(polidocanol injectable foam) 1%

BTG

13.5 Appendix E: Use of Varithena® to manage patients with GSV-derived venous hypertension and chronic venous leg ulcer

Use of Varithena® to manage patients with GSV-derived venous hypertension and chronic venous leg ulcer

Abstract:

Venous leg ulceration (VLU) is increasingly prevalent with advancing age and places a large health care burden on western societies approximating to 1% of total health spending. Patients with VLU frequently suffer for months and years without adequate investigation or treatment of the underlying cause. This is in part a result of the view that ulcers should be healed first before intervention. Modern minimally invasive treatment can be delivered with little disruption to the patient and will contribute to ulcer healing and very significant reduction in risk of ulcer recurrence. Arguably chemical ablation of the trunk and tributary veins is most flexible and the least invasive of all technologies and so best suited to the elderly ulcer patient with complex vein disease.

In this report the authors present their consensus opinion of the management of patients with great saphenous vein incompetence and varicose veins with VLU treated with polidocanol injectable foam 1% (Varithena®).

Introduction:

Venous leg ulcer (VLU) is the culmination of years of chronic venous insufficiency. In cases of severe venous obstruction this process can be reduced to a few years between the thrombotic incident and ulceration. In the majority, however, injury develops over decades with incremental damage to the skin until the point at which the skin can no longer be sustained and an ulcer develops. Chronic venous disease, whether due to superficial or deep system incompetence, is prevalent. In fact, some epidemiological reports suggest that up to 56% of men and 60% of women suffer from superficial venous disease and associated sequelae[1]. The prevalence of VLU is approximately 1-2% of the population, with reports of 5% of older adults suffering from ulceration[2]. In Europe and North America venous disease has a substantial healthcare burden in excess of $14Bn each year (not including out of pocket or indirect costs), and more than 1% of overall health care costs (Bergan JJ)[3,4]. Despite the economic impact and the severe reduction in Quality of Life (QoL) on the individual, in most countries a systematic approach to reduce the burden of VLU has not been adopted even though there is clear evidence that venous interventions designed to correct underlying venous insufficiency can significantly reduce the absolute number of ulcers and associated cost.[5,6] The ESCHAR studies which evaluated the benefit of surgical intervention to correct the underlying superficial venous reflux, established that correction of reflux reduced 12-month ulcer recurrence.[7] In the UK the National Institute for Health and Care Excellence reviewed the available data (2013) and concluded that patients with skin

changes or active ulcerations should be referred to a venous specialists and to undergo correction of the underlying pathology where appropriate.[8]

Although clinical guidelines and specialist societies have stressed the importance of treating the underlying venous insufficiency there is reticence to investigate at an early stage in patients with venous skin changes and ulcers. Most patients fail to receive appropriate investigation or if investigated they still fail to receive timely intervention. With the availability of modern, minimally-invasive ablative techniques the arguments for delaying intervention are misplaced. The use of foamed sclerosant to ablate distal tributaries feeding the ulcer bed offers simple, effective treatment at the bedside. Foam allows for a less invasive approach to treating venous hypertension above the knee, while ablating distal veins with reflux that lead to skin changes below the knee, which may lead to more rapid healing of VLUs. The use of foams to treat patients with VLUs has increased with data to support the efficacy in expediting healing and reducing recurrence. [9,10] FDA-approved endovenous microfoam, Varithena®, offers improved safety profile and reduced risk of central complications such as neurological adverse events compared with air based physician compounded foam.[11] In this report, the authors who have had empirical success in treating leg ulcer patients with superficial vein disease describe their technical approach to using Varithena® endovenous microfoam to directly address the cause of the venous leg ulcer.

Diagnosis: As with all vein disease, the primary mode of diagnosis is with duplex ultrasound and color flow mapping.

1. Proximal incompetence in the saphenous system is identified and the relative contribution to overall incompetence is determined.
2. It is important to develop a complete venous map down to the ulcer area, noting sources of retrograde flow and re-entry perforators.
    a. In instances of leg ulcer it is beneficial for the physician and Registered Vascular Technologist (RVT) to map the routes of incompetence together. Veins should be traced towards the ulcer with scanning performed through the ulcer bed to determine their termination.
    b. Incompetent and dilated perforators that do not connect to superficial veins and conduct blood towards the foot, are re-entry perforators and are not contributing to overall venous hypertension.(diagram)
3. The majority of venous leg ulcers are caused by great saphenous incompetence and venous hypertension transmitted to the gaiter area by the incompetent tributaries. These are all within the label treatment for Varithena® chemical ablation. A small number of ulcers are caused by small saphenous incompetence, usually occupying the lateral aspect of the leg.

4. It is important to inspect the deep veins that the perforators connect to for competence. The presence of deep vein incompetence is not an absolute contra-indication to superficial vein treatment. The relative importance of superficial to deep incompetence is based on the duplex findings. If the superficial incompetence is dominant then its elimination will still yield benefit and may result in correction of the deep vein incompetence when the physiological disturbance and pressure (or 'overload') is eliminated. Some superficial veins feeding the ulcer are very superficial and can be seen visually and palpated. For these veins, ultrasound examination should be conducted with ample gel and minimal pressure so as not to occlude the vein with the probe and yield a false negative result.

Exclusion of other potential causes: The patient population with leg ulceration are predominantly older and have consequentially more co-morbidities. It is important to consider the comorbidities when making the diagnosis. Arterial disease is the most common co-existing disease. Ankle brachial pressure indices (ABI) should be measured in all cases and validated with Doppler pulse wave profiles or photoplethysmography (PPG) pulsatility, if available, beware of calcified vessels giving erroneously elevated ABI values. Reduced ABI may suggest the need for future arterial bypass; this should be considered before ablating the GSV. ABI as low as 0.8 can be treated normally but below 0.8, post treatment compression needs to be reduced. With an ABI below 0.6, it is necessary to investigate and treat the arterial disease first if appropriate.
If arterial intervention is not indicated, treatment with Varithena can still be carried out, though being careful to reduce the post treatment compression to take into account the reduction in arterial function.

Causes of immobility are common and significantly add to the impact of venous insufficiency since the calf pump is not engaged to facilitate emptying of the vessels. Patients with significant mobility restrictions should be monitored after treatment as per current practice since they are at an increased risk for deep vein thrombosis (DVT).
Rarer causes of ulcer should be considered but not limited to vasculitis, rheumatoid arthritis and neoplasia.
Morbid obesity and diabetes should be addressed and should be referred to a specialist physician or group for assistance.

Treatment: Treatment of patients with VLU is similar to patients with saphenofemoral junction (SFJ) and trunk vein incompetence, with additional emphasis on following and ablating any incompetent tributary varicose veins towards the ulcer. Treatment should be

performed with the leg elevated 30-45 degrees before treatment to empty the superficial veins.
Pre-operative marking is important to trace the varicosities towards the site of the ulcer. Frequently there may be a single dilated vein which may communicate with a perforator under the ulcer bed. The course of the vein(s) is mapped and marked using duplex ultrasound with the patient standing immediately before starting the procedure. The distal portion may be more easily mapped with the patient on the table in reverse Trendelenburg (foot down) in which case it is important to apply copious quantities of gel and apply little pressure with the probe. When multiple vessels have been identified, venous access should be obtained for each of the incompetent tributaries below the knee and towards the lipodermatosclerotic (LDS) skin or ulcer. If multiple incompetent vessels are identified they should be mapped and multiple venous access points planned.

As with the normal Varithena® procedure, injection of distal varices is accomplished from the access point and with a finger applying gentle pressure proximal to the access site. The foam is then injected at a steady rate (0.5-1 ml/s) and will travel distally. It remains important to monitor the re-entry perforators and not to permit foam to flow freely into the deep system. At the moment the foam column reaches the immediate intersection of superficial vein and perforator, the skin over the perforator is compressed and pressure above the access point is released. If there is significant extension of the incompetent vein beyond this point additional access with a butterfly needle will permit more distal filling. Forced dorsiflexion of the ankle (e.g. tell the patient to act as if they were pressing a gas pedal) will limit flow into the perforators, and repeated pumping of the ankle will stimulate flow in the deep calf veins and should minimize risk of thrombosis in these veins.

When all incompetent veins approaching or under the ulcer have been filled, or the maximum volume of Varithena® has been administered (15 ml/treatment) the procedure is complete. Secondary and additional treatments may be necessary if the condition is bilateral or if the varicosities are extensive and extremely tortuous. . As described in the Instructions For Use it is important to ensure that the treating physician is able to visualise the column of Varithena that is being injected. Varithena is relatively echogenic given the gas fraction and so this should be straightforward and this feature also allows close control of the foam column to ensure that it only passes along the target vessels. Digital compression or dorsiflexion of the ankle can be employed to minimise the risk of unintended passage of Varithena into the deep venous system via the perforators.

Post treatment compression The wound needs routine care after it has been exposed for treatment and should be cleaned with simple non-allergenic fluids, covered by non-adherent dressings and finally, compression bandaging. The leg should not be lowered before application of compression has been completed. The pressure applied by the bandaging should be modified to account for the pressure of the elastic stocking. The patient should be instructed to wear the compression bandaging for 48h. As for most leg ulcers, a once a week dressing change is sufficient. Dressings combined with multi–layer bandage and 20-30 mmHg thigh stocking will be adequate.

Special considerations

Incompetent perforators: Varithena® is not indicated for perforator treatment. However, if the superficial vein above and below the perforator is ablated there should be no flow in the perforator. In the rare case where a functionally incompetent perforator persists and is contributing to venous hypertension, it may be ablated with other techniques.

Preparation: Thorough skin prep of the leg and ulcer should take place using iodine, starting in the thigh and working distally towards, and including, the ulcer assuming there is no known allergy to iodine. Prophylactic antibiotics are not indicated.

Venous access: Access of the feeding vein to the ulcer can be made using the device of choice. Butterfly needles (21 or 23 G) are preferred and they should have a long extension tube. Alternatively, and when there is a straighter segment of vein, a venous access kit using the sleeve will provide secure access. In some cases, simple IV catheters can be used. Small gauge needles (>25G) and catheters should be avoided as they are too flexible and result in high velocity jets of foam which encourage mixing of foam and blood.

Follow-up: Routine follow-up should be provided with an assessment at 1 week post-treatment when dressings should be changed. At this time, a duplex assessment for completeness of treatment should be conducted. Reflux time and vein patency should be documented. Additional Varithena® treatment may be provided at this time if needed. Because veins in the ulcerated limb are frequently larger and more extensive, additional treatments are more common than for routine varicose vein patients.

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13.6 Appendix F: Venous Clinical Severity Score (VCSS)

Instructions for using the Revised Venous Clinical Severity Score
On a separate form, the clinician will be asked to:
"Please check 1 box for each item (symptom and sign) that is listed below."
The VCSS should be completed for the leg to be treated/treated leg.

Pain or other Discomfort (i.e., aching, heaviness, fatigue, soreness, burning)
The clinician describes the 4 categories of leg pain or discomfort that are outlined below to the patient and asks the patient to choose the category that best describes the pain or discomfort the patient experiences.
None= 0:None
Mild= 1:Occasional pain or discomfort that does not restrict regular daily
Moderate = 2: Daily pain or discomfort that interferes with, but does not prevent, regular daily activities
Severe = 3:Daily pain or discomfort that limits most regular daily activities

Varicose Veins
The clinician examines the patient's leg and chooses the category that best describes the patient's superficial veins. The standing position is used for varicose vein assessment. Veins must be ≥3 mm in diameter to qualify as "varicose veins".
None = 0:None
Mild = 1:Few, scattered, varicosities that are confined to branch veins or clusters. Includes "corona phlebectatica" (ankle flare), defined as >5 blue telangiectases at the inner or sometimes the outer edge of the foot
Moderate = 2:Multiple varicosities that are confined to the calf or the thigh
Severe = 3:Multiple varicosities that involve both the calf and the thigh

Venous Edema
The clinician examines the patient's leg and chooses the category that best describes the patient's pattern of leg edema. The clinician's examination may be supplemented by asking the patient about the extent of leg edema that is experienced.
None= 0:None
Mild= 1: Edema that is limited to the foot and ankle
Moderate = 2: Edema that extends above the ankle but below the knee
Severe= 3: Edema that extends to the knee or above

Skin Pigmentation
The clinician examines the patient's leg and chooses the category that best describes the patient's skin pigmentation. Pigmentation refers to color changes of venous origin and not secondary to other chronic diseases (i.e., vasculitis purpura).
None= 0:None, or focal pigmentation that is confined to the skin over varicose veins
Mild= 1:Pigmentation that is limited to the perimalleolar area
Moderate= 2:Diffuse pigmentation that involves the lower third of the calf
Severe= 3:Diffuse pigmentation that involves more than the lower third of the calf

Inflammation
The clinician examines the patient's leg and chooses the category that best describes the patient's skin inflammation. Inflammation refers to erythema, cellulitis, venous eczema, or dermatitis, rather than just recent pigmentation.

None= 0: None
Mild= 1: Inflammation that is limited to the perimalleolar area
Moderate= 2:Inflammation that involves the lower third of the calf
Severe= 3: Inflammation that involves more than the lower third of the calf

Induration
The clinician examines the patient's leg and chooses the category that best describes the patient's skin induration. Induration refers to skin and subcutaneous changes such as chronic edema with fibrosis, hypodermitis, white atrophy, and lipodermatosclerosis.
None= 0:None
Mild= 1:Induration that is limited to the perimalleolar area
Moderate= 2: Induration that involves the lower third of the calf
Severe= 3:Induration that involves more than the lower third of the calf

Active Ulcer Number
The clinician examines the patient's leg and chooses the category that best describes the number of active ulcers.
None= 0:None
Mild= 1:1 Ulcer
Moderate= 2:2 Ulcers
Severe= 3:≥3 Ulcers

Active Ulcer Duration
If there is at least 1 active ulcer, the clinician describes the 4 categories of ulcer duration that are outlined below to the patient and asks the patient to choose, for the leg that was treated, the category that best describes the duration of the longest unhealed ulcer.
None= 0:No active ulcers
Mild= 1:Ulceration present for <3 mo
Moderate= 2:Ulceration present for 3-12 mo
Severe= 3:Ulceration present for >12 mo

Active Ulcer Size
If there is at least 1 active ulcer, the clinician examines the patient's leg and chooses the category that best describes the size of the largest active ulcer.
None= 0:No active ulcer
Mild= 1:Ulcer <2 cm in diameter
Moderate= 2:Ulcer 2-6 cm in diameter
Severe= 3:Ulcer >6 cm in diameter

Use of Compression Therapy
Choose the level of compliance with medical compression therapy on the leg to be treated / treated leg.
None= 0:Not used
Mild= 1:Intermittent use
Moderate= 2:Wears stockings most days
Severe= 3:Full compliance: stocking

Revised Venous Clinical Severity Score (VCSS)

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

13.7 Appendix G: EQ-5D-5L

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

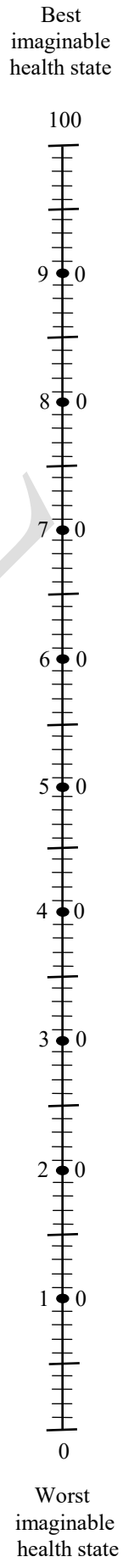
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



13.8 Apendix H: Adverse Event Form

Varithena® Venous Leg Ulcer Registry
Adverse Event Reporting Form V01

Please complete the following information:

Section 1. Patient Demographics

Age: _____years Gender: ☐ Male ☐ Female

Height: _____cm Weight: _____kg

Ethnic Origin:
- ☐ Caucasian
- ☐ Hispanic/Latin American
- ☐ Black/African American
- ☐ Western Asian
- ☐ East/Southeast Asian
- ☐ Other or unknown

Section 2. Varithena Administration

Treatment: _____mL Batch Number: _____

Date: ___/____/_____ Expiry Date: _____

Section 3. Adverse Events

Continued on a separate sheet? ☐ Y

Event No.	Adverse Event Term	Dates of Onset & Resolution (dd/mmm/yyyy)		Outcome of Event[1]	Causal Relationship[2]
1		*Onset*	/ /		
		Resolution	/ /		
2		*Onset*	/ /		
		Resolution	/ /		
3		*Onset*	/ /		
		Resolution	/ /		
4		*Onset*	/ /		
		Resolution	/ /		
5		*Onset*	/ /		
		Resolution	/ /		

(1) Outcome of Event (enter one code per event)**: 1 = Fatal 2 = Not Resolved 3 = Resolved 4 = Resolved with Sequelae 5 = Resolving**
(2) Causal Relationship to Varithena (enter one code)**: 0 = "Not related (no reasonable possibility)" 1 = "Related (reasonable possibility)"**

Section 4. Any relevant medical history/concurrent conditions and clinical progression of the adverse event including labs, diagnostics, etc.?

☐ **Y** ☐ **N** *(If yes, specify below)*

Please email the completed form to BTG Vigilance within 48hrs of awareness to

Vigilance@btgplc.com

Varithena® Venous Leg Ulcer Registry
Adverse Event Reporting Form V01

Section 5. Concomitant medications

Only include drugs given within the 30 days prior to AE onset excluding treatment for AE

Drug Name	Brand	Indication for use	Total Daily Dose Prior to this AE (include units)	Freq.	Route of admin.	Date of First Administration of Drug AND Date of Last Administration of Drug Prior to this SAE (dd/mmm/yyyy)	
						First	/ /
						Last	/ /
						First	/ /
						Last	/ /
						First	/ /
						Last	/ /
						First	/ /
						Last	/ /
						First	/ /
						Last	/ /

Section 6. Reporter information

HCP Name: _____

Position: _____

Hospital Name: _____

_____

Address: _____

_____

_____

State: _____

Contact details: _____

Form(s) completed by:

Print Name: _____	Signature: _____	Date of Completion: / /

Please email the completed form to BTG Vigilance within 48hrs of awareness to

Vigilance@btgplc.com