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Treatment of Truncal Incompetence and Varicose Veins with a Single Administration of a New Polidocanol Endovenous Microfoam Preparation Improves Symptoms and Appearance☆

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WHAT THIS PAPER ADDS

Polidocanol endovenous microfoam (PEM) is a proprietary treatment for the symptoms and appearance of varicose veins in patients with saphenofemoral junction (SFJ) incompetence. PEM is intended to treat all incompetent veins of the great saphenous vein (GSV) system, including the proximal and distal GSV and associated trunk veins, tortuous veins, and/or visible varicosities.

Objective: This multicenter, parallel group study was designed to determine if a single administration of ≤15 mL of pharmaceutical-grade polidocanol endovenous microfoam (PEM, now approved in the United States as Varithena [polidocanol injectable foam], BTG International Ltd.) could alleviate symptoms and improve appearance of varicose veins in a typical population of patients with moderate to very severe symptoms of superficial venous incompetence and visible varicosities of the great saphenous vein (GSV) system.

Methods: The primary endpoint was patient-reported venous symptom improvement measured by change from baseline to Week 8 in 7-day average VVSymQ score. Co-secondary endpoints measured improvement in appearance of visible varicose veins from baseline to Week 8, as measured by the Independent Photography Review–Visible Varicose Veins (IPR-V^3) and Patient Self-assessment of Visible Varicose Veins (PA-V^3) scores. Patients were randomized to five groups: PEM 0.125% (control), 0.5%, 1%, 2%, or placebo. Adverse events (AEs) were recorded at each study visit. Tertiary endpoints measured duplex ultrasound response, changes in venous clinical severity score, and the modified Venous Insufficiency Epidemiological and Economic Study–Quality of Life/Symptoms.

Results: At Week 8, VVSymQ scores for the pooled PEM group (0.5% + 1% + 2%; $p < .0001$) and individual dose concentrations ($p < .001$) were significantly superior to placebo. Mean changes from baseline to Week 8 in IPR-V3 and PA-V^3 scores were significantly greater for pooled PEM than for placebo ($p < .0001$). Most AEs were mild and resolved without sequelae. No pulmonary emboli were reported.

Conclusions: This study demonstrated that a single administration of up to 15 mL of PEM is a safe, effective, and convenient treatment for the symptoms of superficial venous incompetence and the appearance of visible varicosities of the GSV system. Doses of 0.5%, 1%, and 2% PEM appear to have an acceptable risk-benefit ratio.

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INTRODUCTION

Varicose veins of the lower limbs affect between 25% and 35% of adults in the Western world. In more than 80% of cases the cause is saphenous vein incompetence.[1,2] Some people are asymptomatic, but many experience heaviness, achiness, swelling, throbbing and/or pain, and itching, which can negatively affect their health-related quality of life.[2,3]

A number of vein disease-specific quality of life instruments are available to assess the impact of varicose veins, but these do not measure patient-reported symptoms. The VVSymQ Instrument (BTG International, Inc., London, UK) was specifically designed to measure symptoms of superficial venous incompetence and detect clinically meaningful changes in patients' symptoms following intervention.[4] This instrument was developed following the United States Food and Drug Administration (FDA) guidelines for establishing a 'fit for purpose' patient-reported outcomes instrument to support the indication of a medical product.[5] The nature of questions and measurement scales used were based on several iterations of formal patient interviews. The instrument's performance attributes were validated in a separate clinical study.[6] The resultant VVSymQ Instrument assesses five symptoms of varicose veins: Heaviness, Achiness, Swelling, Throbbing, and Itching (HASTI), defined by patients as being their most important symptoms. The VVSymQ Instrument assesses these symptoms on a daily duration-based scale recorded by patients via an electronic daily diary.

Polidocanol endovenous microfoam (PEM) is a flexible treatment for varicose veins, the incompetent great saphenous vein (GSV), major saphenous accessory veins, and visible varicosities of the GSV system above and below the knee improving symptoms and appearance. This pharmaceutical grade, low-density sterile PEM is generated from a proprietary canister system. The gas mixture used to generate PEM is a precise mixture of oxygen and carbon dioxide (65:35), with low nitrogen content (<0.8%). It has a defined density, bubble size distribution, and half separation time (i.e. stability), with median bubble diameter of approximately 100 μm and no bubbles >500 μm, enabling efficient delivery of sclerosant to the venous endothelium. Each mL of PEM contains 1.3 mg of polidocanol.

PEM has been studied in more than 1300 patients. The first of two pivotal trials demonstrated that the 0.5% and 1.0% doses were effective and provided clinically meaningful benefit in treating the symptoms and appearance of varicose veins.[7] Here, the results of the second pivotal trial are presented.

METHODS

Patients

Male and female patients aged 18–75 years who had saphenofemoral junction (SFJ) incompetence, reflux (>0.5 seconds on duplex ultrasonography) of the GSV or other major accessory saphenous veins determined by duplex ultrasound, and both symptoms and visible varicosities were enrolled. The GSV diameter (mm) was measured 5 cm below the SFJ. Patients needed to be able to complete the VVSymQ electronic diary and have visible disease that was moderate, severe, or very severe, including leg ulcer C6. Exclusion criteria included: small saphenous and deep vein incompetence, history of or active deep vein thrombosis (DVT), pulmonary embolism (PE), or stroke; inability to comply with post-treatment compression or walk unaided. There were no exclusions for medications, including anticoagulants. Importantly, there were no restrictions on vein diameter or tortuosity of veins to be treated.

Table 1. Questions, responses, and method of scoring in the VVSymQ questionnaire.

"Since waking up today, how often have you had the following problem in your leg to be treated?" This question was asked for each of the following five symptoms: heaviness, achiness, swelling, throbbing, and itching. Response to question:	Scoring
"None of the time"	0
"A little of the time"	1
"Some of the time"	2
"A good bit of the time"	3
"Most of the time"	4
"All of the time"	5

Study design

This study evaluated the efficacy and safety of PEM (0.5%, 1%, and 2%) compared with 0.125% (control) and placebo. Here, reports are made on all patients through the primary efficacy endpoint at Week 8. Patients continued to be followed for 1 year. After completion of all assessments for the primary endpoint at Week 8, patients could receive open-label treatment with 1% PEM.

Primary endpoint

The primary endpoint was change from baseline to Week 8 in the 7-day average VVSymQ score. Data were collected using an electronic diary (invivodata, Inc. [now ERT], Pittsburgh, PA, USA). Patients completed evening reports on each of the 10 days preceding the treatment day (baseline), Week 4, and Week 8 visits, and data were automatically transferred to a secure server. Patients recorded duration and intensity of nine symptoms and activity levels during the previous 24 hours; in total they answered 20 questions, five of which contributed to the VVSymQ score. The VVSymQ score is the sum of the five HASTI symptoms scores on a 0–5 duration scale (0 = none of the time to 5 = all of the time) giving a daily symptom score of 0 to 25 (Table 1). A daily average was calculated for the 7 most recent days prior to each study visit (or a minimum of 4 days if there was a missing report) to calculate an average VVSymQ score.

Secondary endpoints

Appearance: Co-secondary efficacy endpoints measured improvement in the appearance of visible varicose veins from baseline to Week 8, as measured by the Independent Photography Review—Visible Varicose Veins (IPR-V^3) and Patient Self-assessment of Visible Varicose Veins (PA-V^3) scores.[8] The IPR-V^3 score was the median rating of an expert panel of three clinicians who assessed the severity of appearance of each patient's visible varicose veins by reviewing standardized digital photographs. The IPR-V^3 used a 5-point scale ranging from 0 to 4 (none, mild, moderate, severe, or very severe). Standardized digital photography was developed in conjunction with Canfield Scientific Inc. (Fairfield, NJ, USA), including controlled illumination to aid in capturing surface contours. Each reviewer independently scored each leg photograph using a high-resolution monitor and specialized software that allowed the reviewer to zoom and pan thus approximating a live review. The images were presented, in random order to each reviewer, one at a time. The reviewer was blinded to patient, time point, and treatment assignment.

The PA-V^3 score was the patient's self-assessment of their varicose veins. Similar to the IPR-V^3, the PA-V^3 used a 5-point noticeability scale and each patient was instructed to choose one of five statements that best described the actual appearance of visible varicose veins of the study leg at baseline, Week 4, and Week 8: not at all noticeable (0), slightly noticeable (1), moderately noticeable (2), very noticeable (3), or extremely noticeable (4).

Clinically meaningful change: Patients completed separate global impression of change questionnaires to determine if changes in symptoms and appearance at Weeks 4 and 8 were clinically meaningful. The patient global impression of change questionnaires used a 7-point scale (similar to a Likert scale) to report overall patient benefit (or decline) following treatment. Clinically meaningful change was defined as the percent of patients whose symptoms or appearance had "moderately improved" or "much improved," which were the two highest scores on the 7-point scale.

Tertiary endpoints

(1) Duplex ultrasound defined as: the elimination of SFJ reflux and/or complete occlusion of the target vein(s), that is incompetent GSV and/or major saphenous accessory vein; (2) change in the revised venous clinical severity score (VCSS)[9]; and (3) change in the modified VEINES-QOL/Sym (Venous Insufficiency Epidemiological and Economic Study—Quality of Life/Symptoms) score for the previous week's recall.[10,11] All tertiary endpoints were assessed at Week 8.

Ethics

This study complied with the International Conference on Harmonisation Good Clinical Practice and the Declaration of Helsinki (1996).[12] The protocol and all associated materials were approved by Schulman Associates IRB or local IRBs. Registered on http://clinicaltrials.gov/show/NCT01072877.[13]

Randomization

Patients were equally randomized to PEM 0.125% (control), 0.5%, 1%, 2%, or placebo. Randomization was stratified by baseline symptom score and site using an automated interactive voice recognition system (IVRS, United States, Biosource Corporation, San Francisco, CA, USA).

Treatment

All patients underwent blinded treatment session, a maximum volume of 15 mL of study drug (in 5 mL aliquots) was allowed regardless of treatment assignment. All PEM dose concentrations were in identical canisters identified only by an individual numeric code assigned by the IVRS. Placebo (agitated diluent solution, 5 mL aliquots) was prepared immediately prior to injection. The vein(s) to be treated was cannulated at the mid-thigh under ultrasound guidance. Up to 5 mL of study drug was injected proximally under ultrasound guidance from the site of the cannulation to a point 5 cm distal to the SFJ. Additional study drug was injected distally to fill both the GSV from the mid-thigh catheter and visible varicose tributaries. The treated leg was wrapped in a short-stretch bandage with compression pads that provided eccentric pressure over the treated venous segments. An overstocking and thigh-length 30—40 mmHg compression stocking with waist band (Venosan North America, Asheboro, NC, USA) were placed over the dressing. The compression bandages and stocking were worn continuously for 48 hours. The compression stocking alone was worn continuously for an additional 12 days. Patients were mobilized when treatment was complete and were encouraged to walk for at least 5 minutes during each waking hour for the week following treatment.

Safety

Documentation of adverse events (AEs), regardless of severity or causality, began after the patient had signed the informed consent and continued until the patient had completed Visit 5/Week 8 (or Visit 8 for patients who received optional, open-label 1% PEM following Visit 5). At each study visit after the initial treatment, AEs, concomitant medications, and procedures were recorded.

Duplex ultrasound surveillance

One week after study treatment (initial or optional treatment), patients had a follow-up visit to evaluate for safety using detailed per-protocol duplex ultrasound assessments of the deep veins. This involved repeated compression and color flow at regular intervals from the medial malleolus upward. If a thrombus AE was identified, patients underwent additional duplex scans 1 and 2 weeks later, and then monthly until any thrombi stabilized or resolved. Patients were evaluated for symptoms of venous thromboembolic events. Management of thrombi was according to clinical

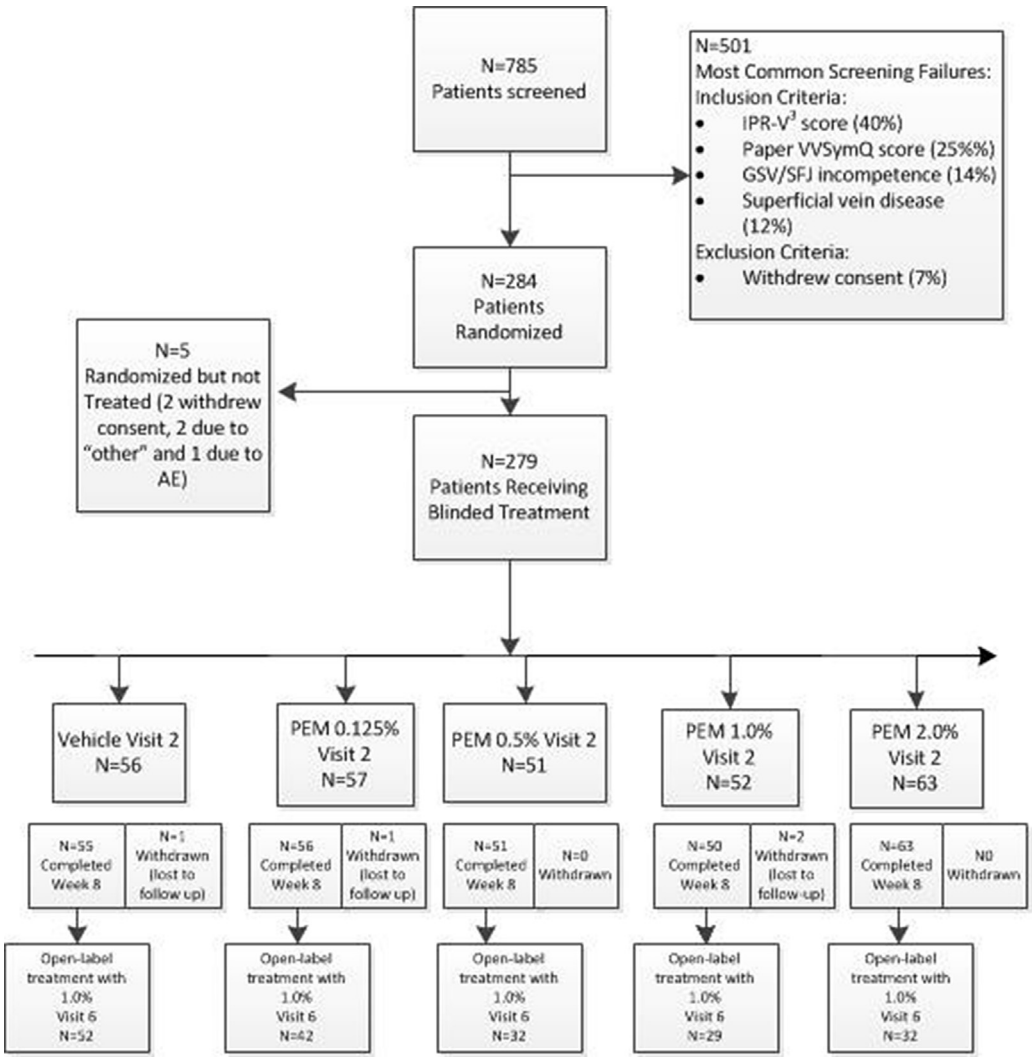

Figure 1. A total of 785 patients were screened. Five-hundred and one patients (64%) failed screening. Two-hundred and eighty-four (284) patients were randomized. During the blinded phase of the study (through Visit 5/Week 8), patients received PEM 0.125%, 0.5%, 1.0%, 2.0% or Vehicle placebo at Visit 2. Following the Week 8 visit (Visit 5), patients could receive open-label treatment with PEM 1.0% at Visit 6.

presentation and usual clinical practice. Recommendations consistent with the American College of Chest Physicians guidelines were provided for anticoagulation.[14] All venous thrombotic events were reviewed by the sponsor and an independent safety review board, which met at least every 6 months during the trial.

Blinding

It was not possible to create placebo foam that is indistinguishable from PEM; thus physician and ultrasonographer were unblinded to placebo. The PEM 0.125% arm was added, 0.125% being the lowest concentration of polidocanol that can generate foam, which was presumed to be sub-therapeutic, to allow blinded evaluation of duplex response results. Placebo solution contained the excipients of PEM, and was visible on ultrasound when agitated using the Tessari method after administration.[15] Importantly, assessors for all primary and secondary endpoints were completely blinded. Drapes or screening were used to obscure the patient's view of the treatment procedure. An evaluation of patient blinding to treatment assignment was obtained after the initial blinded study treatment session, and at Weeks 4 and 8.

Statistical analysis

The primary endpoint was absolute change from baseline in VVSymQ score at Week 8. Sample size was selected to provide 95% power to detect an absolute mean difference between pooled PEM (0.5%, 1%, and 2%) and placebo. Forty-five patients per treatment group with at least one VVSymQ score by Week 8 were required, assuming a SD of ± 4.75, using a two-sample t test and two-sided $\alpha = 0.05$. Under these same assumptions, demonstration of statistical superiority between individual concentration and placebo would have 84% power. The study was not powered to demonstrate differences between PEM concentrations. Data management and statistical analysis were conducted by United BioSource Corporation (Blue Bell, PA, US).

Table 2. Patient demographics.

	Placebo $n = 56$	PEM 0.125% $n = 57$	PEM 0.5% $n = 51$	PEM 1% $n = 52$	PEM 2% $n = 63$	All patients $N = 279$
Age, years Mean (SD)	46.0 (11.31)	51.6 (9.60)	48.2 (11.78)	48.8 (8.78)	49.7 (10.49)	48.9 (10.54)
Sex, female, *n* (%)	44 (78.6)	42 (73.7)	37 (72.5)	38 (73.1)	47 (74.6)	208 (74.6)
Race, white	52 (92.9)	51 (89.5)	46 (90.2)	50 (96.2)	61 (96.8)	260 (93.2)
BMI (kg/m^2) Mean (SD)	27.7 (5.95)	28.8 (5.77)	27.4 (5.75)	28.6 (5.41)	28.3 (5.40)	28.2 (5.64)
GSV diameter (mm) Mean	7.70 ($n = 50$)	7.26 ($n = 52$)	7.59 ($n = 45$)	7.91 ($n = 48$)	7.68 ($n = 61$)	7.63 ($n = 256$)
C class, *n* (%)						
C2	22 (39.3)	32 (56.1)	25 (49.0)	26 (50)	32 (50.8)	137 (49.1)
C3	24 (42.9)	14 (24.6)	13 (25.5)	15 (28.8)	13 (20.6)	79 (28.3)
C4	10 (17.9)	11 (19.3)	10 (19.6)	9 (17.3)	17 (27.0)	57 (20.4)
C5 and C6	0	0	3 (5.9)	2 (3.8)	1 (1.6)	6 (2.2)

Table 3. Improvement in symptoms of varicose veins as measured by VVSymQ at Week 8.

		VVSymQ				
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1%	PEM 2%	PEM (0.5%, 1%, 2%)
Baseline score, mean	8.60 (n=55)	9.01 ($n = 56$)	9.30 ($n = 51$)	8.82 ($n = 50$)	9.49 ($n = 63$)	9.23 ($n = 164$)
Adjusted mean change from baseline: Week 8	−2.13 (n=55)	−4.63 ($n = 56$)	−5.68 ($n = 51$)	−4.87 ($n = 50$)	−5.78 ($n = 63$)	−5.44 ($n = 164$)
Clinically meaningful improvement in symptoms: Week 8	6% (n=53)	44% ($n = 50$)	81% ($n = 47$)	63% ($n = 46$)	81% ($n = 59$)	7% ($n = 152$)
Comparison vs. placebo: Week 8, *p* value, adjusted mean change		<.0001	<.0001	<.0001	<.0001	<.0001

For VVSymQ, lower scores and/or negative change scores indicate better outcomes.

RESULTS

Patients

Seven-hundred and eighty-five patients were screened at 19 US study sites; 284 were randomized and 279 were treated with either placebo ($n = 56$) or PEM 0.125% ($n = 57$), 0.5% ($n = 51$), 1% ($n = 52$), or 2% ($n = 63$). Two-hundred and seventy-five patients completed the study to Week 8. Fig. 1 depicts patient disposition for this study.

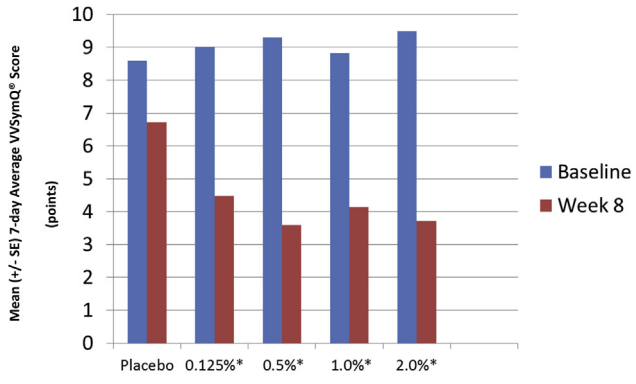

Figure 2. At Week 8, for patients in the PEM 0.5%, 1.0%, and 2.0% treatment groups, the mean VVSymQ score had decreased by approximately 60% of the baseline mean value compared with a decline of approximately 20% in the Vehicle group. No significant difference was seen across the three dose concentrations.

Demographics

Baseline characteristics were similar across treatment groups (Table 2). Most patients were Caucasian women, with a mean age of 49 years and mean BMI of 28 kg/m^2. Approximately 98% of patients had venous disease (C2-C4). Mean GSV diameter at baseline was 7.63 mm (range 1.5—25.9 mm).

Treatments

Of the 284 patients randomized, five withdrew before treatment. For patients receiving PEM at Visit 2, median total volume administered was 13.0 mL in the 0.125% group and 12.0 mL in the 0.5%, 1%, and 2% groups. At Visit 6, patients could receive optional treatment with open-label 1% PEM; 93% of placebo patients, 74% of 0.125% patients, 63% of 0.5% patients, 56% of 1% patients, and 51% of 2% patients received open-label treatment. For 96% of placebo patients, the reason for open-label treatment was treatment failure compared with 60% of 0.125% patients, 55% of 0.5% patients, 34% of 1.0% patients, and 39% of 2.0% patients.

Primary outcome measure: relief of symptoms

At Week 8, VVSymQ scores for pooled PEM (0.5% + 1% + 2%) patients were significantly superior to placebo ($p < .0001$). VVSymQ scores decreased significantly ($p < .0001$) from baseline to Week 8 for all PEM individual doses (Table 3 and Fig. 2).

Table 4. Improvement in appearance of varicose veins as measured by IPR-V[3] and PA-V[3] at Week 8.

	Placebo	PEM 0.125%	PEM 0.5%	PEM 1%	PEM 2%	Pooled PEM (0.5%, 1%, 2%)
IPR-V[3]						
Baseline score,[a] mean (n[b])	1.82 ($n = 55$)	1.95 ($n = 56$)	2.12 ($n = 51$)	1.98 ($n = 49$)	2.10 ($n = 61$)	2.07 ($n = 161$)
Adjusted mean[c] change from baseline: Week 8	−0.01	−0.46	−0.77	−0.76	−0.91	−0.81
Comparison vs. placebo: Week 8, p value[d]		0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PA-V[3]						
Baseline score,[a] mean (n[b])	3.49 ($n = 55$)	3.57 ($n = 56$)	3.45 ($n = 51$)	3.46 ($n = 50$)	3.68 ($n = 63$)	3.54 ($n = 164$)
Adjusted mean[c] change from baseline: Week 8	−0.15	−0.93	−1.40	−1.60	−1.75	−1.58
Comparison vs. placebo: Week 8, p value[d]		.0001	<.0001	<.0001	<.0001	<.0001

[a] Visit 2 (baseline).
[b] Number of patients with both a baseline value and a value at the corresponding visit.
[c] Least square means from analysis of covariance (ANCOVA) model with treatment group and site as class variables and corresponding baseline score from the questionnaire as a continuous covariate.
[d] Two-sided significance level for paired comparisons.

Secondary outcome measures: change in appearance

Mean changes from baseline to Week 8 in IPR-V3 and PA-V3 scores were significantly greater in the pooled PEM group compared with the placebo group ($p < .0001$; Table 4). All therapeutic PEM dose concentrations were significantly superior to placebo ($p \leq .0001$) in reduction of IPR-V3 and PA-V3 scores at Week 8.

Tertiary outcome measures: measured response

Tertiary endpoints measured response to treatment at Week 8 by duplex ultrasound, VCSS, and VEINES-QOL/Sym. Duplex ultrasound response rates for patients treated with PEM 0.5%, 1%, 2% foam (pooled and individually) ranged from 59% to 83%, and were significantly superior to those in patients treated with PEM 0.125% foam (42%, $p < .0001$; Table 5). Additionally, a statistically significant trend between response and PEM concentration was evident ($p < .001$) (Fig. 3). A formal dose response analysis was conducted and non-zero correlation (linear trend) was $p < .0001$. For pooled PEM and individual PEM dose concentrations, improvements in revised VCSS and VEINES-QOL/Sym scores at Week 8 were statistically superior to changes observed in the placebo group ($p \leq .0001$ in all

Table 5. Response to treatment as measured by duplex ultrasound, rVCSS, and VEINES-QOL/Sym at Week 8.

Duplex response	Placebo n[a] = 56	PEM 0.125% $n = 57$	PEM 0.5% $n = 51$	PEM 1% $n = 51$	PEM 2% $n = 63$	Pooled PEM (0.5%, 1%, 2%) $n = 165$
Responders, n (%)	3 (5.4)	24 (42.1)	30 (58.8)	41 (80.4)	52 (82.5)	123 (74.5)
Comparison of 0.125% vs. pooled PEM: Week 8, p value[b]			.0539	<.0001	<.0001	<.0001
Revised VCSS	**Placebo $n = 55$**	**PEM 0.125% $n = 55$**	**PEM 0.5% $n = 51$**	**PEM 1% $n = 49$**	**PEM 2% $n = 63$**	**Pooled PEM (0.5%, 1%, 2%) $n = 163$**
Baseline score,[c] mean	7.11	7.40	7.18	7.39	7.13	7.22
Adjusted mean[d] change from baseline: Week 8	−0.75	−2.97	−3.79	−3.70	−4.39	−3.96
Comparison vs. placebo: Week 8, p value[b]		<.0001	<.0001	<.0001	<.0001	<.0001
VEINES-QOL	**Placebo $n = 55$**	**PEM 0.125% $n = 54$**	**PEM 0.5% $n = 51$**	**PEM 1% $n = 50$**	**PEM 2% $n = 62$**	**Pooled PEM (0.5%, 1%, 2%) $n = 163$**
Baseline score,[c] mean	53.12	53.65	53.15	54.86	51.51	53.05
Adjusted mean[d] change from baseline: Week 8	7.67	16.28	20.44	19.25	23.79	21.16
Comparison vs. placebo: Week 8, p value[b]		0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[a] Number of patients with a baseline value and a value at the corresponding visit.
[b] Two-sided significance level for paired comparisons.
[c] Visit 2 (baseline).
[d] Least square means from ANCOVA model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate.

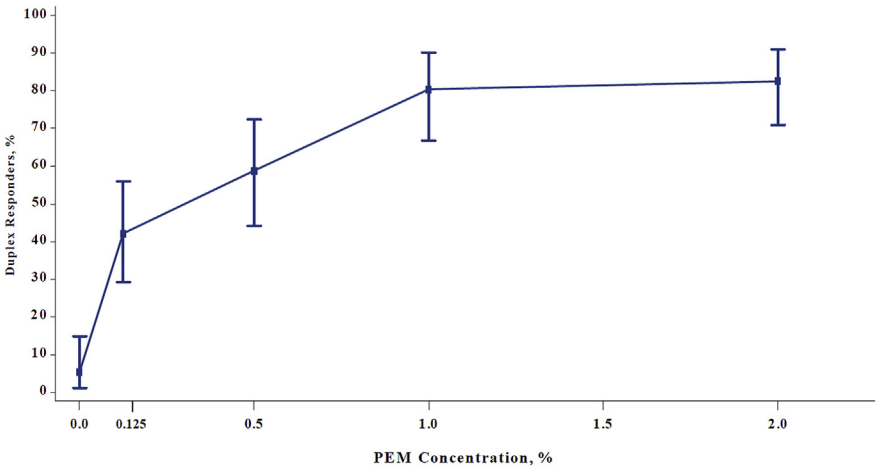

Figure 3. A statistically significant trend between response and polidocanol microfoam concentration was evident; 42.1% of the PEM 0.125% treatment group, 58.8% of the PEM 0.5% treatment group, 80.4% of the PEM 1.0% treatment group, and 82.5% of the PEM 2.0% treatment group were responders to treatment ($p < .0001$).

cases). Mean changes in revised VCSS and VEINES-QOL/Sym scores at Week 8 for patients in the pooled PEM group were also statistically superior to changes observed in the PEM 0.125% group ($p = .0038$ and $p = .0073$, respectively).

Safety

There were no serious AEs and no PEs. Most AEs were mild, resolved without sequelae, and were assessed by the investigator as related to study treatment. In the blinded phase of the study, patients treated with PEM 1% and 2% foam had a lower rate of AEs than patients treated with PEM 0.125% and 0.5% foam; however, patients receiving higher PEM dose concentrations (1% and 2%) had higher rates of severe AEs. The percent of patients with treatment-emergent AEs was similar across PEM dose concentrations. The most common AEs occurring in ≥3% of patients in any

Table 6. Treatment-emergent adverse events in ≥3% of patients, safety population.

Adverse reaction	Treatment group, *n* (%) Blinded treatment					Open label	Total receiving PEM
	Placebo ($n = 56$)	PEM 0.125% ($n = 57$)	PEM 0.5% ($n = 51$)	PEM 1.0% ($n = 52$)	PEM 2.0% ($n = 63$)	PEM 1.0% ($n = 187$)	$n = 275$
Pain in extremity	5 (8.9)	11 (19.3)	10 (19.6)	10 (19.2)	6 (9.5)	23 (12.3)	58 (21.1)
Thrombophlebitis, superficial	1 (1.8)	17 (12.3)	5 (9.8)	4 (7.7)	8 (12.7)	5 (2.7)	29 (10.5)
Injection site hematoma	1 (1.8)	3 (5.3)	8 (15.7)	4 (7.7)	3 (4.8)	4 (2.1)	22 (8.0)
Limb discomfort	2 (3.6)	2 (3.5)	3 (5.9)	3 (5.8)	6 (9.5)	6 (3.2)	19 (6.9)
Venous thrombosis, limb	0	1 (1.8)	3 (5.9)	6 (11.5)	4 (6.3)	1 (0.5)	15 (5.5)
Injection site pain	2 (3.6)	3 (5.3)	4 (7.8)	3 (5.8)	3 (4.8)	2 (1.6)	15 (5.5)
Infusion site thrombosis	0	0	3 (5.9)	3 (5.8)	6 (9.5)	13 (7.0)	25 (9.1)
Pruritus	3 (5.4)	2 (3.5)	2 (3.9)	2 (3.8)	6 (9.5)	2 (1.1)	14 (5.1)
Headache	3 (5.4)	2 (3.5)	2 (3.9)	3 (5.8)	3 (4.8)	2 (1.1)	12 (4.4)
Peripheral edema	2 (3.6)	3 (5.3)	3 (5.9)	2 (3.8)	1 (1.6)	4 (2.1)	13 (4.7)
Upper respiratory tract infection	0	3 (5.3)	2 (3.9)	0	3 (4.8)	0	8 (2.9)
Extravasation	1 (1.8)	1 (1.8)	1 (2.0)	4 (7.7)	1 (1.6)	0	7 (2.5)
Muscle spasms	1 (1.8)	1 (1.8)	2 (3.9)	2 (3.8)	1 (1.6)	4 (2.1)	9 (3.3)
Rash	2 (3.6)	2 (3.5)	0	2 (3.8)	0	1 (0.5)	5 (1.8)
Skin discoloration	1 (1.8)	2 (3.5)	1 (2.0)	0	1 (1.6)	0	4 (1.5)
Deep vein thrombosis	0	0	1 (2.0)	1 (1.9)	2 (3.2)	5 (2.7)	9 (3.3)
Nausea	0	2 (3.5)	0	1 (1.9)	0	1 (0.5)	4 (1.5)
Tenderness	1 (1.8)	0	0	2 (3.8)	1 (1.6)	4 (2.1)	7 (2.5)
Erythema	0	0	0	2 (3.8)	1 (1.6)	1 (0.5)	4 (1.5)
Visual impairment	0	0	2 (3.9)	0	0	0	2 (0.7)
Injection site discomfort	0	0	2 (3.9)	0	0	0	2 (0.7)
Contusion	0	0	0	2 (3.8)	0	0	2 (0.7)
Dizziness	0	0	2 (3.9)	0	0	1 (0.5)	3 (1.1)

PEM treatment group are shown in Table 6. Treatment-emergent AEs that occurred with the highest incidence in the patients treated with PEM were superficial thrombophlebitis, pain in the extremity, and injection site hematoma. No patient discontinued the study because of an AE. In the 174 PEM-treated patients with AEs, most were mild or moderate (42% and 18%, respectively), but were severe in 12 patients (4%). Approximately half of these AEs were considered related to treatment and 91% resolved without sequelae.

Venous thrombus AEs in a non-target vein occurred in 27 patients treated with PEM. Fifteen were classified as a common femoral vein thrombus extension (analogous to endovenous heat induced thrombosis [eHITs][16] described in association with endovenous thermal ablation); five as proximal DVT (popliteal vein or above); four as distal DVT; and three as isolated gastrocnemius and soleal vein thrombosis. No patients experienced a thrombus in more than one location. One patient receiving PEM 2.0% reported with common femoral vein thrombus extension and had symptoms that could be considered consistent with a PE (i.e., pleuritic chest pain and dyspnea) which resolved the same day; a clinical diagnosis of PE was not made, and was neither confirmed nor excluded as the patient refused CT. All thrombi were generally small and detected during the protocol-required duplex ultrasound procedures; no patient presented spontaneously with signs or symptoms of a venous thrombus, despite specific inquiry. Most (88%) thrombi were asymptomatic, and all resolved within 100 days (median time to stabilization or resolution: 21 days) regardless of whether the patient was observed, or received a short course ($\leq$2 weeks) of low molecular weight heparin or 3 months of anticoagulation.

DISCUSSION

This was the second of two pivotal phase-3 clinical studies designed to evaluate the efficacy of a proprietary pharmaceutical-grade PEM compared with placebo as part of an FDA investigational new drug application. The efficacy results reported are at 8 weeks; longer-term results will assess durability of benefit at 1 year and out to 5 years. This randomized, controlled study demonstrated the significant and clinically meaningful patient benefit of treatment with PEM in the improvement of symptoms and appearance of varicose veins in patients with an incompetent GSV and/or accessory saphenous veins and visible varicosities. Significant improvements in disease-specific quality of life and the clinical severity of varicose veins also were demonstrated. This confirms the results of the VANISH-2 study,[7] which showed that PEM 0.5% and 1% foam provided clinically meaningful benefit for patients with a range of GSV diameters (1.5—25.9 mm). There were no restrictions on inclusion criteria related to vein diameter, vein tortuosity, or prior treatments in either study. There was a low rate of deep venous thrombi, no PEs, and no cerebrovascular or neurological events.

Instruments used to assess the efficacy endpoints in this study were specifically designed to evaluate the clinical benefit of treatment in patients with superficial venous incompetence. Each of these instruments was developed in accordance with an FDA guidance document.[17] The content validity of the VVSymQ and PA-V[3] was established through concept elicitation and cognitive debriefing in patients with superficial venous incompetence. In contrast, many of the instruments used in previous studies of venous disease, such as the Specific Quality of Life Outcomes Response—Venous (SQOR-V) instrument[18] and the VEINES-QOL/Sym instrument,[11] were developed without direct patient input. The IPR-V[3] was developed by expert clinicians who treat patients with saphenous vein incompetence.

The current standard of care for the treatment of varicose veins usually requires multiple procedures. Most commonly, the proximal GSV is treated with endovenous thermal ablation, and additional procedures of either phlebectomy or sclerotherapy are necessary to provide a complete treatment. In contrast, PEM can treat all veins trunk vein or varicose tributaries.

Simple “closure” of the GSV, on duplex ultrasound, is the usual efficacy measure for endovenous thermal ablation. However, GSV closure alone does not measure the full hemodynamic effects of treatment, because accessory saphenous veins might also be incompetent or can become incompetent following GSV closure. As a result, SFJ reflux and symptoms might not be eliminated. In this study, a more comprehensive and challenging ultrasound endpoint was used, requiring either occlusion of all incompetent veins and or elimination of SFJ reflux. The instruments used for the primary and secondary endpoints in the present study assess what is most important to patients.

Treatment with PEM is a minimally invasive, generally safe, non-surgical procedure. Slightly more than half of all study patients experienced at least one AE. In the 174 PEM-treated patients with AEs, most were mild or moderate (42% and 18%, respectively), and were severe in only 12 (4%) patients. Approximately half of these AEs were considered related to treatment and most (91%) resolved without sequelae. No PEs were reported. Safety results are consistent with the general safety profile reported in previous studies.

PEM offers several advantages for patients. This ultrasound-guided technique requires no tumescent anesthesia. Patients are ambulatory immediately after the procedure. In contrast, a recovery period of as long as 7 days has been reported with thermal ablation.[19—24] Efficacy can be achieved in a single treatment. However, the recommendation is to limit the amount of PEM to 15 mL per session. Therefore, patients with more extensive disease might need more than one treatment.

CONCLUSION

PEM is a safe, effective, and convenient therapy for the treatment of symptoms and appearance of varicose veins of the GSV system in patients with superficial venous incompetence. This study confirmed the results of

VANISH-2, which compared PEM doses of 0.5% and 1% to placebo. PEM 0.5%, 1%, and 2% have an acceptable risk-benefit ratio. Treatment with PEM 1% and 2% resulted in similar side effects, were equally effective in improving symptoms and appearance, and had a similar duplex response rate.

CONFLICT OF INTEREST

Dr T. King was an investigator for the study and a consultant to BTG Educational Steering Committee, for which he received financial compensation. Dr. M. O'Byrne and Dr. M. Vasquez were Investigators for the study and are consultants to BTG. Dr D Wright is a full-time employee of BTG Ltd (UK).

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APPENDIX A. SUPPLEMENTARY DATA

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