CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Division Director Review

Date	25 November 2013
From	Norman Stockbridge
Subject	Division Director memo
NDA/BLA # **Supplement#**	205098 000
Applicant	Provensis
Date of Submission	4 February 2013
PDUFA Goal Date	4 December 2013
Proprietary Name / **Established (USAN) names**	Varithena Polidocanol
Dosage forms / Strength	1% w/w foam
Proposed Indication(s)	1. Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV above and below the knee and improvement of the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.
Recommended:	Approval

I refer to reviews[1] of CMC (Wilson-Lee; 30 August 2013, 7 November 2013, 25 November 2013), CDRH Materials (McDermott; 23 October 2013), CDRH Bioengineering (Banik; 23 October 2013), CDRH Human Factors (Nguyen; 23 October 2013 (2), 18 November 2013), Microbiology (Langille; 12 September 2013), pharmacology/toxicology (Link; 5 September 2013), clinical pharmacology (Hinderling; 30 October 2013), clinical (U; 12 July 2013), and statistics (Bai; 2 July 2013). There is also a CDTL memo (U; 14 November 2013), with which I am in agreement.

CMC site inspections are complete. All outstanding CMC issues have been resolved..

There are no approvability issues with the device, materials or function. The product consists of a 1% w/w solution of polidocanol under carbon dioxide in one canister and oxygen in a second canister. The device combines the contents of the two canisters forming microfoam in a (b) (4) Microfoam is then administered through a syringe under ultrasound guidance.

Labeling contains Instructions for Use (IFU). The IFU was subject to a Human Factors study, the results of which were considered adequate. Subsequent to the Human Factors study, changes were made to the IFU pursuant to FDA requests. These are summarized in sponsor's submission 0047 dated 13 November 2013. The review team and I concur that the changes were trivial improvements that do not justify further study.

There are no outstanding issues with regard to pharmacology/toxicology or clinical pharmacology. The carbon dioxide/oxygen gas is readily soluble, so there appears to be a wide safety margin concerning circulating foam. Polidocanol is thought to be metabolized, but this has not been well characterized.

The two main studies supporting the approval of the final formulation are Study 015 (N=279; 0.5%, 1%, and 2% foam) and Study 016 (N=232; 0.5% and 1%), both double-blind, randomized, placebo-controlled, multicenter (all US) studies assessing symptoms (custom VVSymQ instrument) over 8 weeks. Appearance was also assessed by subjects and by blinded adjudication of photographs. Results of all of these assessments were highly statistically significant in both studies, at all doses studied (although 1% or higher was superior to 0.5%), and by baseline severity or diameter of the great saphenous vein at baseline.

The placebo-adjusted symptom improvement was about 30% (3 points from a 9-point baseline). The cumulative distribution curves (statistical review) look like a shift of the population mean response. By qualitative assessment, <20% of placebo subjects reported moderately or much improved, in contrast to >60% on Varithena 1%; I find the results not merely statistically significant, but clearly clinically significant as well.

The appearance metrics (subjects and investigators) also show 30-40% improvement.

Over 1300 subjects were exposed. Nearly 500 subjects were followed for a year. Sixty subjects with a patent foramen ovale were studied, only one of whom reported any neurological symptom, a transient complaint of "twinky lights" one hour after dosing that I find implausibly

[1] All dates are when finalized in DARRTS. CDRH reviews appear in DARRTS signed off by Mr. Monteleone, in some cases months after they were completed.

related to treatment. About 7% of subjects have venous thrombosis detectable by ultrasound, mostly asymptomatic.

The sponsor plans to make the product available to physicians who complete training. No one on the team thinks a REMS is needed, and neither do I.

The CDTL recommended approval, but that was, in fact, pending resolution of CMC issues. I concur, as the remaining issues have been resolved.

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/s/

NORMAN L STOCKBRIDGE
11/25/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-098
Priority or Standard	Standard
Submit Date	04-Feb-2013
Received Date	04-Feb-2013
PDUFA Goal Date	04-Dec-2013
Division / Office	DCRP/ODE I/OND
Reviewer Name	Khin Maung U, M.D.
Review Completion Date	12-Jul-2013
Established Name	Polidocanol Endovenous Microfoam (PEM)
(Proposed) Trade Name	VARITHENA™
Therapeutic Class	Sclerosant
Applicant	Provensis Ltd
Formulation(s)	A canister device to generate 1.0% (weight / volume) of polidocanol injectable microfoam
Dosing Regimen	The maximum recommended volume per treatment session is 15 ml. Individual injections of microfoam should not exceed 5 ml. Treatment sessions should be separated by ≥5 days.
Indication(s)	Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV system above and below the knee, and to improve symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system
Intended Population(s)	Patients with incompetent GSVs, accessory saphenous veins and visible varicosities of the GSV system above and below the knee

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

Background/Introduction

Polidocanol Endovenous Microfoam (PEM) is a proprietary, engineered microfoam produced using an aqueous polidocanol solution (in one canister) and a gas mixture of oxygen/carbon dioxide (65:35) with low nitrogen content (in another canister). A sterile microfoam transfer unit (MTU) is incorporated to the two canisters to deliver polidocanol at a solution concentration of 1.0% weight/volume as a microfoam of uniform, controlled density and bubble size (median bubble diameter < 100 micrometers (μm) and no bubbles > 500 μm). PEM is to be administered by a trained physician in the office.

The microbubbles in PEM have an appropriate (b) (4) and physically displace the blood in the vein, allowing polidocanol, which is neither diluted nor de-activated, to act upon the endothelium. PEM is also highly echogenic; with ultrasound it is possible to observe PEM filling the targeted segments of incompetent vein, allowing for controlled treatment of the intended incompetent vein segment. Intravenous injection of up to 15 mL of PEM directly into the target incompetent veins and related varicosities of the great saphenous system (GSV) using ultrasound guidance will ablate the varicose veins.

As a non-ionic surfactant, the hydrophobic pole of the polidocanol molecule attaches to the lipid membrane of venous endothelial cells and disrupts the osmotic barrier. The resulting cell destruction creates a highly thrombogenic exposed endothelial surface to which platelets attach followed by thrombus formation, obliterating the vein lumen which is later replaced by fibrous tissue.

Provensis Ltd., is submitting this NDA for the indication: “Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV system above and below the knee, and to improve symptoms of superficial venous incompetence and the appearance of visible varicosities (b) (4)

The efficacy data is derived from two pivotal studies: Study 015 (which evaluated PEM 0.5%, 1.0% and 2.0%) and Study 016 (which evaluated PEM 0.5% and 1.0%) as randomized, blinded, multi-center studies at 20 and 12 US sites, respectively.

The primary endpoint is “the improvement of symptoms as measured by the absolute change from baseline in the average 7-day electronic daily diary Varicose Vein Symptoms Questionnaire (VVSymQ) score at Week 8 in patients treated with PEM (pooled concentration groups) compared with Vehicle placebo,”

Both Study 015 and Study 016, and the integrated analyses show that the primary efficacy endpoint of symptom improvement is statistically significantly (P<0.0001) greater in the pooled PEM treatment group as well as in each of the individual PEM dose-concentration groups compared to the Vehicle placebo group.

Treatment with PEM also resulted in statistically significantly greater improvement in appearance as assessed by (i) the patient using the Patient Self-assessment of

Appearance of Visible Varicose Veins (PA-V^3) instrument (*P*<0.0001), and (ii) three blinded physicians using the Independent Photography Review – Visible Varicose Veins (IPR-V^3) instrument (*P*<0.0001) to rate photographs of the treated legs.

The results for the tertiary efficacy analyses – improvements in (i) duplex ultrasound response, (ii) clinician assessment of severity of venous disease using Venous Clinical Severity Score (VCSS), and (iii) patient-completed quality of life questionnaire (modified Venous Insufficiency Epidemiological and Economic Study-Quality of Life/Symptoms [VEINES-QOL/Sym]) – were highly statistically significant (*P*<0.0001) in favor of PEM vs. Vehicle placebo (or, for duplex ultrasound response, vs. PEM 0.125% control).

There was a statistically significant linear trend across PEM concentrations from 0.125% to 2.0% for dose-related improvement in appearance endpoints (IPR-V^3 and PA-V^3). The PEM 1.0% dose showed: (i) the least number of treatment failures and partial treatment failures, (ii) the highest Duplex ultrasound response compared to the other doses of PEM, and (iii) the lowest frequency of venous thrombosis adverse events. Thus, PEM 1% was selected for the proposed indication.

PEM is injected in small volumes at low total doses for a local sclerotic effect, usually only once, and, therefore, does not reach significant levels in the systemic circulation. The total dose of polidocanol in each volume of PEM administered to patients in the clinical trials exposed the patients to very small doses (<19.5 mg) of polidocanol (i.e., less than 1/5^{th} of the polidocanol contained in the maximal dose of liquid polidocanol).

The submission-specific AEs included the potential for stroke, neurological events, deep vein thrombosis, anaphylactic reactions and local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses and pigmentation).

Among 1,333 patients exposed to PEM, which included 60 patients with confirmed patent foramen ovale (PFO) and micro-bubbles detected in the middle cerebral artery by Transcranial Doppler, only one patient complained of “twinky lights” lasting about 20 seconds about one hour after treatment. Extensive screening for neurological effects with diffusion-weighted MRI at 24 hours and T2 MRI imaging at 28 days post treatment in a study of 82 patients (60 had demonstrable PFO) did not reveal abnormalities in the MRIs on post-treatment scans.

While there are individual case reports in the medical literature of neurological events following sclerotherapy, most of these patients recover from stroke with only 4 patients sustaining non-reversible neurological deficits. On the other hand, none of the large studies and randomized clinical trials (totaling > 37,000 treatments of varicose veins) in the medical literature reported any major neurological complications, underscoring the relative infrequency of major neurological complications associated with sclerotherapy.

In PEM Studies 015, 016, 017 and 008, duplex ultrasound surveillance of the leg veins was made at screening and on a minimum of 3 occasions following the initial study treatment and twice more after optional open-label treatments. The ultrasound images were reviewed by the Venous Thromboembolic Event Review Board (VTERB). 96 of 1,333 (7.2%) patients had venous thrombus detected by ultrasound following PEM

treatment; 2 patients had venous thrombus AEs 53 days to 9 months after treatment. Thus, 94 patients (7.1%) had treatment emergent venous thrombus AEs.

The most common type of venous thrombus was asymptomatic, non-occlusive, common femoral vein thrombus observed in 39 (2.9%) PEM-treated patients. The second type of venous thrombosis was the isolated gastrocnemius and soleal vein thrombosis (IGSVT) which were observed in 1.4% (19 patients) during detailed duplex ultrasound evaluations of the calf, and caused no symptoms.

Deep vein thromboses (DVT) were detected by ultrasound in 38 of 1,333 (2.8%) PEM-treated patients: distal DVT in 1.1% and proximal DVTs in 1.7%. One percent of 1,333 PEM-treated patients had proximal, symptomatic thrombi. The venous thrombi AEs resolved or stabilized rapidly irrespective of whether or not the patient was treated with anticoagulants in all but 3 patients. Most patients with DVT (79%) or IGSVT (84%) did not receive anticoagulants. No patient had a diagnosis of pulmonary embolism.

There were no anaphylactic or major hypersensitivity reactions. Severe possible hypersensitivity events were reported by 5 patients (two experienced localized swelling, and one each reported chest discomfort, cough and pruritus). Two more patients reported AEs of “allergy.”

The AEs most commonly observed in the clinical studies of PEM are local AEs which include infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, and superficial thrombophlebitis

In the clinical studies of PEM, the only signal for a treatment-related change in laboratory parameters was a slight but consistent decrease from baseline in hemoglobin (by 0.1 to 0.3 g/dL), and hematocrit (by 0.2% to 1.0%) in PEM-treated patients.

Thus, no unexpected safety signals were found.

1.1 Recommendation on Regulatory Action

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is **approvable** (§21 CFR 314.110) pending the sponsor’s response to comply with postmarketing requirements and the changes suggested in the proposed labeling.

1.2 Risk Benefit Assessment

The benefits of treatment with PEM seen in Studies 015 and 016 are improvement in:

- The symptoms of chronic venous insufficiency, as measured by a validated, patient-completed Varicose Vein Symptoms Questionnaire (VVSymQ);
- The appearance of visible varicosities, as evaluated by a blinded, independent panel of clinicians (IPR-V^3) and by patients using a validated questionnaire (PA-V^3);
- Hemodynamic function of superficial venous, (elimination of SFJ reflux and/or occlusion of the incompetent vein) as assessed by duplex ultrasonography;

- Clinical severity of venous disease, as evaluated by the physician using the Venous Clinical Severity Score (VCSS), and
- Patient quality of life, as measured by the patient using the Modified Venous Insufficiency Epidemiologic and Economic Study – Quality of Life/Symptoms (VEINES-QOL/Sym) instrument.

Statistically significant correlations are found between the improvement in symptoms and (i) the appearance of visible varicosities, and (ii) duplex ultrasound response.

Treatment with PEM 0.5%, 1.0% and 2.0% led to clinically meaningful improvements in both symptoms and appearance as evaluated by anchor-based responder analyses.

Treatment benefits of PEM were similar across sub-groups for all efficacy endpoints.

The risks of PEM treatment are predominantly local adverse events (AEs) that can be expected in a non-surgical procedure, such as infusion site thrombosis (retained coagulum), injection site hematoma, contusion, pain in extremity, limb discomfort, superficial thrombophlebitis and venous thrombus. Extravasation of PEM in 25 patients was not associated with necrosis or adverse sequelae, probably attributable to the small amount of polidocanol in each mL of PEM (1.3 mg).

Venous thrombosis is a clinically important AE related PEM treatment. It was observed in 7.2% of PEM-treated patients and 5.2% of PEM treatment sessions in the 1,333 PEM-treated patients evaluated with ultrasound studies:

- Common femoral vein thrombus extensions occurred in 2.9%;
- Proximal Deep vein thrombosis AEs occurred in 1.7%;
- Distal Deep vein thrombosis AEs occurred in 1.1%; and
- Isolated gastrocnemius and soleal vein thrombi occurred in 1.4%.

No pulmonary emboli were diagnosed.

Small, consistent and dose-dependent decreases in hemoglobin and hematocrit were observed in treated patients; these did not require intervention in any patient.

In 1,333 patients treated with PEM, there were no deaths or life-threatening SAEs, and no significant hypersensitivity events attributed to the study treatment or procedure. The risk of serious hypersensitivity reactions to PEM was low.

Despite the potential for neurological or visual events, transient ischemic attacks and strokes, which have been reported in patients treated with physician-compounded sclerosant foams, treatment with PEM was not associated with neurological or visual AEs in the placebo-controlled studies.

In summary, PEM at the dose-concentration (1.0%) and maximum volume (15 mL) per treatment session proposed for the treatment of patients with incompetence of the great saphenous vein, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee appears to provide a reasonable balance of benefit and risk for the treated patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The sponsor submitted a risk management plan to mitigate the risks of proximal DVT and common femoral vein thrombus extension, pulmonary embolism, hypersensitivity and anaphylactic reactions, neurological events and accidental intra-arterial injection.

In this NDA, there is no finding of an increased risk of neurological or visual events, pulmonary emboli, or anaphylactic reactions. DVTs and venous thrombus AEs were detected by ultrasound evaluations only, and were mostly asymptomatic and resolved or stabilized rapidly. Intravenous injection of PEM under ultrasound guidance prevented intra-arterial injection. Thus, there is NO reason to recommend a REMS for this NDA.

The purpose of a REMS is to help the patient and/or the physician reduce the risks of a potentially fatal or serious adverse event.

In the case of PEM treatment for varicose veins, a Medication Guide will not serve this purpose because this drug is not taken by the patient. PEM is injected to a maximal volume of 15 mL per treatment session, performed under visual ultrasound guidance by a qualified and trained physician. At the low total doses (19.5 mg maximum) used, polidocanol does not reach significant levels in the systemic circulation.

A physician communication plan does not help the patient or the physician because the application-specific safety issues of neurological events, deep venous thromboses or anaphylactic reactions are exceedingly rare with this drug product.

In >55 million sclerotherapy exposures to polidocanol injections (including various foam forms of polidocanol) spanning half a century of treatment in different clinical settings in many countries reported in the medical literature, there is no evidence that neurologic events, venous thromboembolic events and anaphylactic reactions are more frequent than one would expect with any other parenteral drug for cosmetic purposes (e.g., botulinum toxin (Botox) to treat glabellar lines) which do not require a REMS.

Based on the clinical data in the application and comprehensive safety data reported in the medical literature, my opinion is that a REMS is not necessary for approval.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor will submit to FDA a complete training manual and video that will be used to provide education and training to health care providers (physicians and clinical staff).

Only physicians who have completed this training will be able to order PEM from the designated distributor to administer or supervise administration of the PEM.

The sponsor will conduct an assessment of spontaneous reports of death, stroke, neurological or visual event, pulmonary embolism, deep vein thrombosis, and anaphylactic reaction in patients treated with PEM, and submit periodic safety update reports / periodic adverse drug event reports (PSURs/PADER).

2 Introduction and Regulatory Background

In 1993, Dr. Juan Cabrera invented the principle of polidocanol endovenous microfoam (PEM) sclerosant; the first patent was granted in Europe and in the US in 1997. Dr. Cabrera assigned rights to this product to BTG Plc. (London, United Kingdom [UK]) the same year. Provensis Ltd. (London, UK), established in 1999 as a subsidiary of BTG International, began clinical development of PEM, at that time called Varisolve, with the initiation in 2000 of a Phase 2 Study 0005 conducted in the UK. The initial clinical trial material was manufactured by (b) (4) The original canisters of PEM 1.0% were (b) (4) filled (b) (4)

During 2004, to minimize the risk of gas embolism, PEM was altered (b) (4) resulting in the current gas composition of oxygen and carbon dioxide in a ratio of 65:35. (b) (4) was introduced, which resulted in (b) (4). In 2009, the Microfoam Transfer Unit (MTU) was incorporated into the product to dispense PEM from the pressurized polidocanol in the canister into syringes. The MTU delivers polidocanol at a solution concentration of 1% weight per volume for the 1% solution. The MTU was used throughout the remainder of the PEM clinical development program.

2.1 Product Information

Proprietary Name: VARITHENA™ 1%

Non-Proprietary Names: USAN = Laureth 9

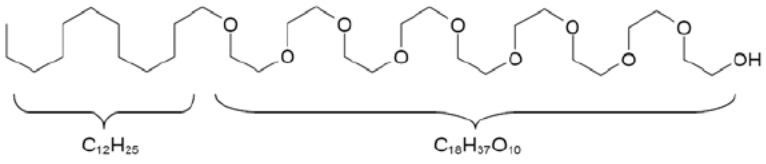
Generic Names: Varisolve, Polidocanol Endovenous Microfoam (PEM), Polidocanol Injectable Microfoam (US Pharmacopeia)

Compendial Name: Polyoxyl Lauryl Ether (USP); Macrogol Lauryl Ether (Ph.Eur)

Chemical Names: (i) α-dodecyl-α-hydroxypoly(oxyethylene),(ii) macrogol lauryl ether, (iii) oxypolyethoxydodecane, (iv) polyoxyl lauryl ether, (v) polyethylene glycol monolauryl ether

Active Ingredient: Polidocanol (1.0% w/v injectable endovenous microfoam)

Structural formula:



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

Molecular formula: $C_{12}H_{25}(OCH_2\text{-}CH_2\text{-})_nOH$ where *n* has an average value of 9. Nominally, $C_{30}H_{62}O_{10}$.

Mean Molecular Weight: Approximately 600.

Polidocanol, the active pharmaceutical ingredient in PEM, (b) (4) four oligomers (E5, E9, E12 and E14, which have different numbers of ethylene oxide units (5, 9, 12, and 14, respectively) were chosen for quantification.

The product is dispensed into a syringe via a sterile container system that produces injectable PEM of consistent, controlled density and bubble size (median bubble diameter <100 µm and no bubbles >500 µm) at the time of use. The product delivers polidocanol at solution concentration of 1.0% weight per volume. Once constituted, the PEM in the syringe must be administered to the patient within 75 seconds.

PEM is administered by injection directly into the lumen of the target incompetent veins and related varicosities of the great saphenous system (intravenously), using ultrasound guidance. The volume of PEM to be injected depends on the size and extent of the veins to be treated. After intravenous injection, it remains as a microfoam, displacing the blood in the treated vein (in contrast to liquid sclerosants which are diluted and/or deactivated by the blood present in large veins). As a result of the physical properties of the microfoam, which has a mean density of (b) (4) (approximate liquid:gas ratio of 1:7), the microfoam empties even large veins of blood and can therefore treat them with a small total dose of active sclerosant.

The maximum recommended volume per treatment session is 15 mL, comprising individual injections up to 5 mL each. Further treatments may be necessary if the extent of the varicose veins requires more than 15 mL of microfoam; these treatment sessions are to be separated by >5 days.

2.2 Tables of Currently Available Treatments for Proposed Indications

Sotradecol® (active ingredient Sodium Tetradecyl Sulfate) and Asclera® (liquid Polidocanol 0.5% and 1.0%) were approved by FDA (Table 1) for sclerotherapy of leg varices, including spider veins and reticular veins.

Table 1 Table of currently available treatment for the proposed indication

Application #	Drug	Approving Office	Approval date	Indication
ANDA 40-541	Sotradecol® (Sodium tetradecyl sulphate)	Office of Generic Drugs	12-Nov-2004	Treatment of varicose veins
NDA 21-201	Asclera® (Polidocanol liquid)	Office of Drug Evaluation I	30-Mar-2010	Treatment of uncomplicated spider and reticular veins

2.3 Availability of Proposed Active Ingredient in the United States

Sotradecol® and Asclera® are currently marketed in the United States for the treatment of varicose veins. They are liquid form products.

2.4 Important Safety Issues with Consideration to Related Drugs

There is a large amount of experiential data (published and unpublished) from widespread and off-label use of sclerosants in >55 million sclerotherapy exposures to polidocanol injections (liquid as well as foam) to treat varicose veins. This data spans over half a century of treatment in many different types of clinical settings in Europe, Australia, New Zealand and Latin America which suggest that adverse events and/or technical complications of the varicose vein sclerosis procedure have been very rare.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The major points in the history of this Drug Product with FDA are as follows:

The initial IND was filed on 11-Oct-2001 with the Division of Dermatology and Dental Products (DDDP) and was placed on clinical hold. A series of clinical hold complete responses by the sponsor followed. On 14-Nov-2003, a complete clinical hold was imposed on Protocol VAP.VV012 for safety concerns related to micro-bubbles detected in the heart (10 patients) and in the internal carotid artery (1 patient with patent foramen ovale who became symptomatic with visual and cognitive changes).

Following a consult by DDDP in March 2005, I reviewed the sponsor's initial amended protocol and recommended changes, notably requiring all patients to be hospitalized for 24 hours following the Varisolve® microfoam injection procedure, restricting the study to 50 events (of micro-bubbles in the MCA detected by Transcranial Doppler (TCD)), and outlining the schedule of MRIs (DWI and PWI) for the first five patients at baseline, 8-24 hours, day 7 and day 28. My review considerations were made in the context of widespread use of sclerosants (in microfoam form or liquid) for treatment of varicose veins within the US (off-label treatment at that time) and in Europe, Australia and New Zealand, Japan, Latin America, etc. The prevalence of patent foramen ovale (PFO) in the general population is about 20-30%. However, the published literature and presentations made at the "World Congresses" of Phlebology (involving several thousand patients) reported no occurrence of pulmonary embolism or scotoma (or neurological deficit). The relatively small volume of gas mixture (<20 ml) used for the Varisolve® microfoam injection procedure did not appear to post a high risk of gas embolism. Thus, I considered it appropriate to permit a closely monitored clinical study limited to the assessment of the effect of bubbles in the cerebral circulation.

The IND was transferred from DDDP to DCaRP in May, 2005.

The sponsor submitted a revised protocol (serial # 052) on 16-May-2005 which incorporated these recommendations. Subsequently, in a FDA letter dated 11-July-2005, the clinical hold was lifted.

On 27-Jan-2007, BTG International Ltd contacted me via e-mail to inform that a newly recognized potentially fatal adverse effect, nephrogenic systemic fibrosis, has been associated with gadolinium-based MR contrast agents used for PWI MRI, and that FDA issued a Public Health Advisory on this topic in December 2006. No patients had yet

been enrolled. I advised that PWI MRI, which uses gadolinium-based contrast agents, be excluded from this study. On 15-Mar-2007, the sponsor submitted a protocol amendment excluding the PWI MRI procedure.

On 15-Sep-2008, the sponsor submitted a new protocol VAP.VV013 designed to test some of the procedures (e.g., effectiveness of patient blinding for sham procedure, standardization of digital photographic images and Doppler/ultrasound techniques, and correlation between patients' subjective symptoms/cosmetic assessments and objective photographic and ultrasound evaluations) which the sponsor intended to use in future well-controlled trials. On 20-Aug-2009, the sponsor submitted a new protocol VAP.VV014 for an open-label pilot study to investigate the efficacy of the 0.125% and 0.2% concentrations of Polidocanol Endovenous Microfoam to be conducted at a single clinical site in the US.

The sponsor submitted two protocols for Special Protocol Assessments (SPAs): (i) on 28-Oct-2009, Protocol VAP.VV015, and (ii) on 11-Dec-2009, Protocol VAP.VV017. The Division issued no-agreement letters for both due to several flaws with study designs, the saline placebo proposed, the narrow range of doses and the primary endpoints. The sponsor requested withdrawal of their two SPAs on 26-Aug-2010 and 24-Sep-2010.

The sponsor submitted statistical analysis plans (SAPs) for Study VAP.VV016 on 18-Jan-2011, and for Study VAP.VV015 on 13-May-2011. In response to the Agency's comments, the sponsor also submitted to FDA a Usability Protocol and Instructions for Use for their drug-device product on 20-Feb-2012 and 22-Mar-2012.

Further discussions related to endpoints, safety reports and clinical pharmacology aspects of the NDA were discussed during a pre-NDA meeting between the Agency and the sponsor on 31-Jul-2012.

2.6 Other Relevant Background Information

In the US population, varicose veins due to failure of the terminal (proximal) valve of the great saphenous vein (GSV) at the saphenofemoral junction (SFJ) is very common, affecting up to 25% of adults[1], with the prevalence and severity increasing with age. The extent and severity of the appearance of visible varicosities varies greatly and does not necessarily correspond to the severity of a patient's symptoms which are the result of venous hypertension leading to dilation. The symptoms may include a sensation of tension, feeling tender to touch, swelling, tightness, heaviness, throbbing, aching and itching. Venous hypertension may also lead to progressive damage to the skin, edema, discoloration, hyperpigmentation, eczema and ulcerations, which are reported in about 20% of patients with varicose veins in the US. Symptoms motivate patients to seek treatment, with >400,000 patients treated in the US each year.[2]

One modality of management of varicose veins is sclerotherapy with liquid or foam sclerosants (including physician-compounded sclerosant foams prepared by a variety of methods and PEM). The physician-compounded foam sclerosants produced with room air may introduce nitrogen bubbles into the systemic circulation and may lead to gas

embolism, or, in the presence of a patent foramen ovale, may appear as micro-bubbles in the cerebral circulation which may cause stroke, seizure, visual disturbance or a transient ischemic attack, which were reported in about 2% of patients treated with foam sclerosants[3,4,5,7]. The initial drug product in this submission (b) (4) was associated with micro-bubbles in the heart and in the cerebral circulation (see section 2.5). In 2004, (b) (4) the gas mixture, using oxygen and carbon dioxide only; the product also added a transfer unit device which delivers a standardized polidocanol foam at a solution concentration of 1% weight per volume for the 1% solution, and was used in clinical trials in the development program.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor submitted documentation (audit certificates) that the following clinical trial sites that participated in the pivotal studies were audited by (b) (4) for data integrity:

(i) Study 015: Four sites including the sites in Laguna CA (Kenneth Deck, MD) and Aventura, FL (Ariel Soffer, MD) for which OSI is consulted for FDA GCP inspections. The data transfer error rate for these sites was 13.2 per 10,000 data points.

(ii) Study 016: Three sites including one in Dothan, AL (Kenneth Todd) for which OSI is consulted for an FDA GCP inspection. The data transfer error rate for these sites was 12.3 per 10,000 data points.

By convention[6], overall electronic data that have an average data transfer error rate of 10-50 per 10,000 data fields are considered acceptable. The data from the audited sites above were certified as acceptable by (b) (4) No records of BIMO-inspection type GCP audits were submitted in the NDA.

Audit certificates of electronic data for other sites that participated in other clinical trials and international trials of PEM were also included in the NDA; all had data that were certified acceptable by the auditor.

3.2 Compliance with Good Clinical Practices

The Division requested OSI for GCP inspection of the conduct of the pivotal studies VAP.VV015 and VAP.VV016 at five sites (Table 2) which enrolled large numbers of patients, showed strong positive results, and are found to also have relatively large number of protocol violations in addition to having patients who discontinued early and patients whose data were excluded from efficacy analysis.

Table 2 Sites selected for OSI – GCP Inspections

Site #	Investigator Name & address	N	Number of patients with:			Efficacy Results	COMMENT
			*Protocol violations	Early discontinuations	Exclusions from efficacy analysis		
VAP.VV015							
33	Brian Ferris, MD Lake Washington Vascular, PLLC 1135 116th Ave NE, Suite 305 Bellevue, WA 98004 and 12333 NE 130th Lane, Suite 425 Kirkland, **WA 98034**	43	10 (11)	0	2	Strongly positive	Largest enrollment, positive results, many protocol violations
37	Ariel D. Soffer, MD 21097 NE 27th Court, Suite 330 Aventure, **FL 33180**	33	5 (6)	1	2	Strongly positive	Large enrollment, strong positive results
39	Kenneth B. Deck, MD South Orange County Surgical Medical Center 24411 Health Center Dr, Suite 350 Laguna Hills, **CA 92653**	34	10 (13)	1	3	Strongly positive	Large enrollment, strong positive results, too many protocol violations
VAP.VV016							
74	Marcus Duane Stanbro, DO Vascular Health Alliance Vein Center, Greenville Hospital Greenville, **SC 29615**	19	18 (25)	1	1	Strongly positive	Strong positive results, too many protocol violations
75	Kenneth Todd, III, MD Southeast Vein and Laser Center, Dothan, **AL 36303**	32	8 (9)	1	1	Strongly positive	Large enrollment, strong positive results

* Numbers in parenthesis indicate the number of protocol violations (some patients had >1 protocol violations)

A clinical inspection summary from OSI dated 28-Jun-2013 informs that Sites #37 and #75 were NAI, and Sites #33, #39, and #74 were VAI. The inspectional (FDA Form 483) observations indicated no major issues with protocol compliance or reporting of AEs, and that they are unlikely to significantly impact the primary efficacy or safety analyses.

3.3 Financial Disclosures

The sponsor submitted certification that 57 clinical investigators who participated in the following studies had no disclosable financial interest: VV003, VV008, VV012, VV013, VV014, VV015, VV016 and VV017, and also submitted financial disclosures for:

(1) [redacted] (b) (6) who participated in pivotal Study VV015. He contributed ideas / services to Phase III study, assisted with training of physicians in the clinical program and obtained input from physicians in the development of patient reported outcome (PRO) assessments

(2) [redacted] (b) (6) who participated in pivotal Study VV016. She contributed to the direction of opinion leaders for marketing research, assisted with training of physicians in the clinical program and obtained input from physicians in the development of PRO assessments.

The sponsor submitted that all study sites and investigators remained fully blinded throughout the study, and that no blinded or unblinded information was provided to these (or any other participating) investigators during the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry reviewer requires the sponsor to submit functioning subunit samples containing the commercial formulation or a representative surrogate formulation of the drug product, and information related to the [redacted] (b) (4) procedure and the results of validation studies for all container closure components contacting the drug product.

4.2 Clinical Microbiology

The microbiology reviewer requires the sponsor to submit the results of the 12/24/36-hour modified antimicrobial effectiveness test on polidocanol.

4.3 Preclinical Pharmacology/Toxicology

There are no new pharm-tox issues.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of polidocanol is chemical (it acts as a non-ionic surfactant). The hydrophobic pole of the polidocanol molecule attaches to the lipid cell membrane and disrupts the osmotic barrier of cells causing cell destruction. After intravenous injection, polidocanol [redacted] (b) (4) induces endothelial damage with denudation of the vein lining. The absence of endothelial cells results in failure of nitric oxide production, with loss of smooth muscle relaxation leading to venospasm. The exposed surface is highly thrombogenic; platelets aggregate at the site of damage and attach to the venous wall. A mesh of platelets, cellular debris, and fibrin occludes the vessel. The vein is obliterated and is replaced later with connective fibrous tissue. Compression treatment after injection of polidocanol closes the vein lumen and facilitates fibrous tissue formation.

Polidocanol will attach to all cell membranes including red cells, and also to plasma proteins. When mixed with blood, polidocanol is rapidly deactivated by protein binding.

Mechanism of action of Microfoam: [redacted] (b) (4)

Although different types of polidocanol foam can offer more effective treatment compared with polidocanol liquid, not all may be safer. Homemade foams had variable gases used (including air or insoluble gases), variable doses of liquid sclerosant in a given volume of foam, and even more variable physical characteristics (i.e., variability in internal cohesion in the dose of liquid sclerosant that a given volume of foam contains in the diameter of the bubble). The diameter of the bubble, the gas-liquid proportion, the internal inter-bubble cohesion, the type of gas used, and the combination in which they are used are key parameters of the efficacy and safety of the procedure.

4.4.2 Pharmacodynamics

The pharmacodynamics were studied in 4 *in vivo* studies (studies 256146, 246696, 256277 and KMWW-0001) in non-rodent species (sheep and New Zealand white rabbit) to assess the sclerosant action of Polidocanol microfoam and solution. Study 256277 in the sheep showed no sign of vasospasm in the external jugular vein or saphenous vein when Polidocanol microfoam was injected, with minimal endothelial damage in histology. The sheep model was discarded, and the rabbit was used (in marginal ear vein studies). Polidocanol microfoam at concentrations of 0.25%, 0.5%, 1% and 2% were found to cause sclerosis in a dose-responsive manner with comparable effectiveness at concentrations of 1% and 2%.

No secondary pharmacodynamics studies were conducted.

4.4.3 Pharmacokinetics

No clinical pharmacology studies in healthy volunteers and no population PK studies were performed due to PEM's mode of action and route of administration.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The submission contains 12 clinical studies of PEM in patients with varicose veins, which were conducted using 2 different PEM formulations (Please see Section 5.3).

The pivotal clinical trials (Study 015 and Study 016) are summarized in Table 3. This efficacy review section pertains to these pivotal clinical trials. Clinical review of the remaining clinical trials is summarized in Section 9.4.2.

Table 3 Number of patients involved in pivotal clinical trials of PEM

Study Number, Number of Centers, Location	Design	Population Study Endpoints	Treatment(s) Administered, Number of Treatment Sessions Volume administered PEM Formulation	Age Range, Sex, Race	Number of Subjects in Safety Population and per Treatment Group	Planned Duration of Follow- up
Study 015 21 sites in the United States	MC, R, B	Male or female patients age of consent up to and including 75 years of age with SFJ incompetence and symptomatic, visible varicose veins Primary Endpoint: Absolute change from baseline to Week 8 in the 7-day average VVSymQ score in the pooled PEM group, vs. Vehicle placebo group. Co-secondary Endpoints: IPR-V[3] score and PA-V[3] score Tertiary Endpoints: Duplex Ultrasound Response, VCSS, VEINES-QOL	Patients were randomized 1:1:1:1:1 to PEM 0.125% (*control*), 0.5%, 1.0%, 2.0% or agitated Vehicle placebo. One blinded and one optional OL (PEM 1.0%) treatment session Up to 15 mL per treatment session Current PEM formulation (low N_2)	19-74 years M: 71, F: 208 White= 260; Black= 7; Asian= 1; Pacific Islander= 2; Native American/ Alaskan Native= 3; Other= 6	Total = 279 patients: PEM 0.125% (*control*)= 57; PEM 0.5% = 51; PEM 1.0%= 52; PEM 2.0%= 63; Vehicle placebo= 56; OL PEM 1.0% (after blinded treatment)= 187.	All = 1 year CSR: all patients through Week 8, plus an additional 4 weeks for patients treated with OL PEM 1.0%
Study 016 14 sites in the United States	MC, R, B	Male or female patients age of consent up to and including 75 years of age with SFJ incompetence and symptomatic, visible varicose veins Primary Endpoint: Absolute change from baseline to Week 8 in the 7-day average VVSymQ score in the pooled PEM group, vs. Vehicle placebo group. Co-secondary Endpoints: IPR-V[3] score and PA-V[3] score Tertiary Endpoints: Duplex Ultrasound Response, VCSS, VEINES-QOL	Patients were randomized 1:1:1:1 to treatment with PEM 0.125% (*control*), 0.5%, 1.0% or Vehicle placebo. Up to 2 blinded treatment sessions, 1 week apart Up to 15 mL /treatment session After Week 8, up to 2 optional OL (PEM 1.0%) treatment sessions, 1 week apart Current PEM formulation (low N_2)	21-73 years M: 63, F: 169 White= 215; Black= 6; Asian= 2; Native American / Alaskan Native= 1; Other= 8	Total = 232 patients: PEM 0.125% (control)= 57; PEM 0.5%= 60; PEM 1.0%= 58; Vehicle placebo= 57; OL PEM 1.0% (after blinded treatment)= 155.	All = 1 year Patients who consent to long-term follow-up: 5 years CSR: all patients through Week 8, plus additional 4 weeks for patients treated with OL PEM 1.0%

MC= multicenter; R= randomized, B= blinded; M=male; F= female; CSR= clinical study report; OL= open-label; N_2 = nitrogen
Source: Sponsor's Table 1, clinical overview.

5.2 Review Strategy

Strategy for efficacy review

In the pivotal Studies 015 and 016, the primary efficacy endpoint was the absolute change from baseline to Week 8 in the 7-day average VVSymQ score {as measured by the *patient* using a daily electronic diary (e-diary)} in the pooled PEM group, versus the Vehicle placebo group. The VVSymQ score, a PRO, is a subset of VEINES-QOL/Sym.

VVSymQ includes five symptom items (heaviness, achiness, swelling, throbbing and itching (HASTI)) which is reduced from an original proposal of 9 symptoms in VEINES-QOL/Sym that the Study Endpoints and Labeling Development (SEALD) team felt might be too burdensome for patients.

The SEALD team's view is that "… a primary efficacy endpoint would be acceptable if further cognitive interviews confirm that a severity assessment is interpretable to patients, and psychometric evaluation confirms adequacy of assessment."

Both pivotal studies were completed using VVSymQ while instrument validation was being conducted by the SEALD team, during which time it was not yet certain whether the 5 selected symptoms retain sufficient validity from the clinical and patient perspectives. There was a risk that the SEALD team may come up with a failed validation verdict despite the VVSymQ showing highly statistically significant results in Studies 015 and 016.

During this period, the important issues became (i) what to do with the primary endpoint if the SEALD team made the determination that it is not valid, (ii) what the regulatory statistical precedence was for looking at the secondary endpoints (because the primary endpoint was statistically significant at $P<0.0001$ level, and therefore no alpha had been spent) as the basis for approval or non-approval, and (iii) what other analyses should be used to further strengthen the ***clinical*** significance of the ***statistically*** significant primary and secondary endpoints.

The sponsor used responder rates to make analyses of "clinically meaningful changes" in the VVSymQ, IPR-V^3 and PAV^3 scores. However, the placebo responder rates for these "clinically meaningful changes" are different between Study 015 and Study 016, suggesting possible heterogeneity, and that these analyses may not be useful as supportive findings if the VVSymQ instrument failed validation.

Other review strategy considerations include the following:

(i) In a previously approved NDA of Polidocanol (NDA 21-201, Asclera®), the primary endpoint was improvement in the appearance of veins in digital photographs after 12 weeks evaluated as the change in mean values (5-grade scale) of the digital photographs assessed by blinded third party investigators. In a similar manner, one of the co-secondary endpoints in the current NDA is the IPR-V^3 score (Independent Photography Review Panel score of photographs of the treated leg). Since the pivotal studies 015 and 016 won their designated primary endpoints with $P<0.0001$, there had been no alpha corruption. Thus, I think that the IPR-V^3 endpoint can be reviewed as a "surrogate" primary endpoint since we have "regulatory precedence" with approving a similar product based on improvement in appearance of veins in photographs.

(ii) Secondly, we can try to "bridge" the VVSymQ score to the IPR-V^3 score by performing statistical tests of correlation/association between these two variables (e.g., using Kendall's tau and/or Spearman's rank correlation). A strong degree of correlation with high statistical significance would be reasonable ground on which to

make an approval/non-approval recommendation based on this correlation. In addition to the overall VVSymQ score, we can also test for correlations between the IPR-V^3 score and EACH of the five symptoms that make up the VVSymQ score (to determine which symptom is more closely related to the IPR-V^3 score and whether that is a clinically plausible and reasonable correlation).

(iii) Thirdly, we can determine the mechanistic validity of the primary and secondary efficacy endpoints by examining their relationship to the duplex ultrasound response (a tertiary endpoint) which demonstrates closure of the SFJ reflux > 5 sec.

On Feb 26, 2013, prior to the filing date, I requested the sponsor to provide the following information:

(1) To provide the reasons for the differences in the *placebo* responder rates in the analyses of "clinically meaningful changes" in the VVSymQ, IPR-V^3 and PAV^3 scores between Study 015 and Study 016 (which suggest some heterogeneity across the studies).

(2) To perform statistical test(s) of correlation/association between (a) the VVSymQ score and the IPR-V^3 score, (e.g., using Kendall's tau and/or Spearman rank correlation), and (b) the IPR-V^3 score and EACH of the five symptoms that make up the VVSymQ score.

(3) To perform statistical test(s) of correlation/association, (using Kendall's tau and/or Spearman rank correlation) between the following pairs of efficacy variables:
   a. the PAV^3 score and the IPR-V^3 score
   b. the IPR-V^3 score and the Duplex ultrasound response
   c. VVSymQ score and the Duplex ultrasound response

Thus, finding a consistent response in the primary (symptom improvement), secondary (appearance improvement) and tertiary (improvement in valve closure) endpoints can be considered a strong indicator of the efficacy of the drug product.

Strategy for safety review

Unlike other cardiovascular and renal drugs which have to be taken daily for a long time or life-long, the PEM is injected in small volumes usually once only without reaching any significant systemic levels. Thus, in addition to the conventional safety review, I will focus on review of the following submission specific safety concerns:

(i) The potential for stroke due to polidocanol microfoam (bubbles) reaching the cerebral circulation via a patent foramen ovale
(ii) Deep vein thrombosis (DVT)
(i) Potential allergic or anaphylactic reactions, and
(ii) Local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses, pigmentation)

I will perform a literature review of the neurologic AEs reported with use of foam sclerosants, including the safety data in the French Polidocanol Registry[7] of 12,173

sclerotherapy treatments in France which included **6,739** sessions with foam sclerosants in which 14 DVTs were reported (8 in relation to polidocanol foam) compared to 2 DVTs associated with liquid (non-polidocanol) sclerosants in 5,434 sessions with liquid sclerosant treatment.

5.3 Discussion of Individual Studies/Clinical Trials

The submission contains 12 clinical studies of PEM in patients with varicose veins, which were conducted using 2 different PEM formulations:

(i) The original formulation (Varisolve OF) (b) (4) and was administered in Studies COM001, 001, 003 and 0005, and to some patients in Study 011, and

(ii) A new formulation (polidocanol endovenous microfoam or PEM, which used a low-nitrogen gas mixture and was intended for licensure) was used in some patients in Study 011 (for comparison), and in all subsequent clinical studies of PEM, namely, Studies 008, 012 and 014, and in Phase 3 Studies 013, 015, 016 and 017 (and 2 patients treated in the prematurely-discontinued Study 007).

The pivotal studies 015 and 016 are reviewed in detail in Section 6.

Please see section 9.4.2 – 9.4.9 for brief reviews of the clinical study reports of the pivotal studies 015 and 016, as well as studies 008, 012, 013, 014 and 017.

I do not consider the studies COM001, 001, 003 and 0005, and 011 (b) (4) to be pertinent for clinical review.

6 Review of Efficacy

Efficacy Summary

For the proposed indication: "to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities in the Great Saphenous Vein (GSV) system," the efficacy data for the primary endpoint is derived from two pivotal studies, Study 015 and Study 016, which are randomized, blinded, multi-center Phase 3 studies. Study 015 evaluated PEM 0.5%, 1.0% and 2.0% and Study 016 evaluated PEM 0.5% and 1.0%, compared with PEM 0.1255 and with Vehicle placebo, at 20 and 12 US sites, respectively.

The objective of both studies was to measure changes in symptoms and appearance in patients with sapheno-femoral junction (SFJ) incompetence due to reflux of the GSV or major accessory veins. Patients received blinded treatment followed by the assessment of the primary, secondary and tertiary efficacy variables at Week 8, after which patients in both studies could receive 1 (in Study 015) or 2 (in Study 016) optional, additional, open-label (OL) treatment with PEM 1.0%. Following completion of study treatments and follow up for 8 weeks, patients entered a long-term safety and efficacy follow-up phase which is currently ongoing.

In both studies, the primary efficacy endpoint is the improvement of symptoms as measured by the absolute change from baseline in the average 7-day electronic daily diary (e-diary) Varicose Vein Symptoms Questionnaire (VVSymQ) score at Week 8 in patients treated with PEM (pooled concentration groups) compared with Vehicle placebo. The co-secondary endpoints are the improvement of appearance as measured by the absolute change at Week 8 from baseline in (i) the central Independent Photography Review – Visible Varicose Veins (IPR-V^3) score, and (ii) the Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V^3) score in the pooled PEM groups compared with Vehicle placebo. The tertiary endpoint variables include (i) duplex ultrasound response, (ii) clinician assessment of the severity of venous disease (Venous Clinical Severity Score [VCSS]), and (iii) a patient-completed quality of life questionnaire (Venous Insufficiency Epidemiological and Economic Study-Quality of Life [VEINES-QOL]). Three instruments (2 patient-reported outcome measures [VVSymQ and VEINES-QOL] and 1 clinician-reported outcome measure [VCSS]) –validated by the FDA Study Endpoints and Labeling Development (SEALD) Team – were used to assess the efficacy endpoints.

Both studies and the integrated analyses show that the primary efficacy endpoint (improvement in VVSymQ score from baseline to Week 8) was statistically significantly greater in the pooled PEM treatment group as well as in each of the individual PEM therapeutic dose-concentration groups (i.e., PEM 0.5%, PEM 1.0% in both studies, and, in Study 015 only, PEM 2.0%) compared to the Vehicle placebo group ($P<0.0001$).

Treatment with PEM also resulted in statistically significantly greater improvement in appearance as assessed by the patient using the PA-V^3 instrument ($P<0.0001$) and as

assessed by the blinded Independent Photography Review Panel (3 clinicians) using the IPR-V^3 instrument to rate photographs (*P*<0.0001) of the treated legs.

The results for the tertiary efficacy analyses – duplex ultrasound response, improvement in VCSS and improvement in the modified VEINES-QOL – were all highly statistically significant (*P*<0.0001) in favor of PEM vs. Vehicle placebo (or for duplex ultrasound response vs. PEM 0.125% control).

The effect of pooled PEM concentrations on the primary, secondary and tertiary efficacy endpoints are summarized in Table 4.

Table 4 Summary of results from the primary, secondary and tertiary endpoints in pivotal studies

Study Endpoint		Study 015[a]			Study 016[a]		
Change from Baseline to Week 8[b] in:		Treatment Effect	[95% CI]	*P*-value	Treatment Effect	[95% CI]	*P*-value
Primary	VVSymQ (LOCF)	-3.31	[-4.31,-2.30]	<0.0001	-3.53	[-4.63,-2.42]	<0.0001
Co-Secondary	IPR-V3 (LOCF)	-0.80	[-0.98,-0.62]	<0.0001	-0.79	[-0.98,-0.60]	<0.0001
	PA-V3 (LOCF)	-1.44	[-1.75,-1.12]	<0.0001	-1.50	[-1.81,-1.19]	<0.0001
Tertiary	Duplex Response (LOCF)[c]	32.4%	not calculated	<0.0001	25.1%	not calculated	0.0002
	VCSS	-3.21	[-3.88,-2.54]	<0.0001	-3.58	[-4.35,-2.80]	<0.0001
	VEINES-QOL	13.50	[9.97,17.02]	<0.0001	14.18	[10.47,17.89]	<0.0001

For Studies 015 and 016, using on the Patient Global Impression of Change (PGIC for VVSymQ and PA-V^3) and Clinical Global Impression of Change (CGIC for IPR-V^3) instruments as anchor-based methods, the primary endpoint (VVSymQ score) and co-secondary endpoints (PA-V^3 and IPR-V^3) were considered to show "clinically meaningful changes" in symptom burden and appearance based on the following:

- The percent of patients achieving at least moderate improvement favored PEM.
- Treatment with PEM 0.5%, 1.0% and 2.0% led to clinically meaningful (and statistically significant) improvements in both symptoms and appearance of varicose veins.
- Cumulative distribution curves plotting the percent of patients for VVSymQ, IPR-V^3 and PA-V^3 scores showed that the percent of patients with improvement was higher for the pooled PEM groups vs. Vehicle placebo group throughout the distribution.

There was a statistically significant linear trend across PEM concentrations from 0.125% to 2.0% for the improvement in appearance endpoints (IPR-V^3 and PA-V^3). The PEM 1.0% dose showed: (i) the least amount of treatment failures (SFJ Reflux >0.5 seconds) and partial treatment failures (GSV incompetence), (ii) the highest Duplex ultrasound response compared to the other doses of PEM, and (iii) the lowest frequency of venous thrombosis adverse events. Thus, PEM 1% was selected for the proposed indication.

6.1 Proposed Indication

Proposed indication: Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV system above and below

the knee, and to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities (b) (4)

The intended population comprises patients with incompetent GSVs, accessory saphenous veins and visible varicosities of the GSV system above and below the knee.

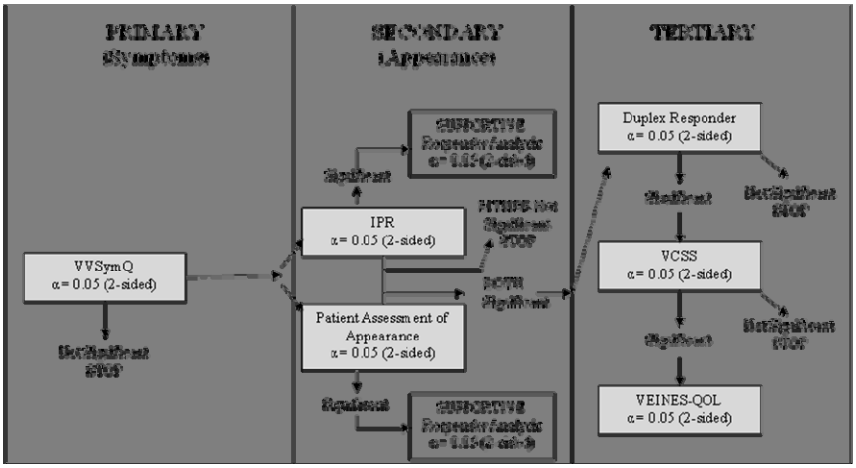
6.1.1 Methods

The primary efficacy endpoint in the pivotal Studies 015 and 016 was the absolute change from baseline to Week 8 (LOCF) in the 7-day average VVSymQ score { as measured by the patient using a daily electronic diary (e-diary)} in the pooled PEM group, versus the Vehicle placebo group.

A single primary comparison of a pooled PEM group (Study 015: 0.5% + 1.0% + 2.0%; Study 016: 0.5% + 1.0%) versus Vehicle placebo was employed for all efficacy comparisons (as defined in the SAP) except the tertiary endpoint analysis of Duplex ultrasound response, where the primary comparison for this efficacy analysis was with PEM 0.125% (control).

Across endpoints (i.e., primary, secondary and tertiary), each comparison of the pooled PEM treatment group versus Vehicle placebo was conducted at α=0.05 (two-sided) with study-wise Type I error controlled using a hierarchical approach (Figure 2).

Figure 2 Hierarchical approach to efficacy endpoint comparisons, Studies 015 and 016



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To evaluate whether the magnitude of change in the VVSymQ, IPR-V[3] and PA-V[3] scores was clinically meaningful, the sponsor made a responder analysis in which the patients completed a Patient Global Impression of Change (PGIC) in Symptoms and Appearance assessment and the clinicians completed a Clinician Global Impression of Change (CGIC) in Appearance assessment. In this responder analysis, the mean change in VVSymQ from baseline to Week 8 in patients with a response on the PGIC in Symptoms of:

(i) "moderately improved" was termed Responders-I; and

(ii) either "moderately improved" or "much improved" was termed Responders-II.

I reviewed these responder analyses and the supportive data shown in a cumulative distribution of response approach in which the entire distribution of responses for treatment and control groups were presented graphically as the change from baseline for VVSymQ on the x-axis and the percent of patients experiencing that change or better on the y-axis.

The secondary efficacy endpoints in Studies 015 and 016 were the absolute changes in the pooled PEM group vs. the Vehicle placebo group from baseline to Week 8 in:

(i) IPR-V^3 score {as assessed by the Independent Photography Review (IPR) Panel of three independent physician to score photographs of the treated leg}, and

(ii) PA-V^3 scores {as assessed by the patient to score the 'live' treated leg}.

Both secondary efficacy endpoints must be met to achieve the improvement of appearance endpoint.

I reviewed the IPR-V^3 scores made by the 3 independent reviewers pre- and post-treatment for every patient in Studies 015 and 016. I listed the patients who "improved" by two grades (e.g., from a baseline score of 4 to post-treatment score of 2) thus driving the efficacy results), and patients whose scores did not change or "worsened" (e.g., from a baseline score of 0 or 1 to post-treatment score of 1 or 2) in Table 5.

Table 5 List of patients whose photographic scores improved by 2 or worsened

Baseline score = 0 (None) Study VV015: 32-1007; 33-1004; 33-1057; 39-1091 Study VV016: 60-1015; 60-1041
Baseline score = 1 (Mild) Study VV015: 22-1078 Study VV016: 60-1011; 60-1022; 63-1003; 64-1052; 68-1051
Baseline score = 2 (Moderate) Study VV015: 21-1017; 21-1041; 27-2001; 29-1016; 32-1002; 33-1001; 33-1003; 33-1023; 33-1029; 33-1035; 33-1049; 33-1068; 34-1002; 34-1005; 35-1012; 39-1002; 39-1030; 39-1033; 39-1101 Study VV016: 60-1016; 63-1005; 63-1007; 63-1065; 64-1050; 64-1074; 67-1005; 67-1006; 67-1016; 68-1003; 69-1018; 75-1005; 75-1012; 76-1026
Baseline score = 3 (Severe) Study VV015: 21-1028; 28-1059; 29-1034; 29-1035; 34-1004; 39-1031 Study VV016: 61-1011; 63-1008; 63-1048; 64-1036; 64-1038; 67-1027; 68-1035; 69-1012; 72-1003; 72-1018; 75-1031; 75-1054; 76-1001; 76-1043
Baseline score = 4 (Very Severe) Study VV015: 36-1024; 37-1006 Study VV016: 75-1025;
Other - Study VV015: 23-1005 (cannot evaluate)

The data from these 69 patients appear to drive the results. I requested the sponsor to

provide pre-and post-treatment photographs and IPR-V^3 scores of 32 (16 from each of the Studies 015 and 016) of these 69 patients.

To evaluate the relationship between improvement in symptoms versus improvement in (i) appearance of varicose veins (digital photographs) and (ii) in function of varicose veins (as measured by SFJ reflux using Duplex ultrasound), I examined the correlations between the symptoms (VVSymQ score) and

(i) the digital photographic scores (IPR-V^3) and

(ii) the tertiary endpoint (Duplex ultrasound response).

I evaluated also the correlation between the improvement in individual symptoms (heaviness, achiness, swelling, throbbing and itching) in the VVSymQ score and the improvement in appearance in the IPR-V^3 score.

For Studies 015 and 016, as well as the integrated analysis, the Efficacy Population was defined as all patients in the Safety Population (i.e., all patients who received at least 1 study treatment) who provided data for at least 1 post-baseline primary or secondary efficacy endpoint assessment. The Integrated Safety Population consisted of 511 patients, and the Integrated Efficacy Population consisted of 509 patients; there were 2 patients who did not have at least 1 post-baseline primary or secondary efficacy endpoint assessment.

6.1.2 Demographics

The demographic and screening/baseline characteristics of the Integrated Efficacy Population by treatment group are displayed in Table 6.

No clinically meaningful differences in age, sex, race, height, weight, or BMI were noted across treatment groups. A slightly higher percentage of patients treated with Vehicle placebo (26%) were in the 18-40 year age group compared to patients in the PEM groups (13% to 23%), and a higher percentage of patients treated with PEM (69% to 79%) were in the 41-64 year age group compared to Vehicle placebo (67%). These differences in age groups were not clinically meaningful.

Varicose vein characteristics at baseline based on VVSymQ, IPR-V^3 and PA-V^3 scores were similar, with most patients having a CEAP Severity Assessment for the leg to be treated of C_2 (varicose veins), C_3 (edema), or C_4 (skin changes without ulceration). There was slight heterogeneity between Studies 015 and016, with a higher percentage of patients with a C_3 rating (40%) in Study 016 compared to Study 015 (28%), whereas Study 016 had a lower percentage of patients with a C_2 rating (32%) compared to Study 015 (49%). There was a similar percentage of patients with a C_4 rating in Studies 015 and 016 (20% and 23%, respectively). Approximately three-quarters of patients in Studies 015 and 016 (78% and 75%, respectively) reported no previous treatment for varicose veins; the most common previous treatments for varicose veins were liquid sclerotherapy and GSV stripping.

Table 6 Demographic and baseline characteristics

Parameter	Placebo (N=112)	PEM 0.125% (N=114)	PEM 0.5% (N=111)	PEM 1.0% (N=109)	PEM 2.0% (N=63)	PEM (0.5%+1.0% +2.0%) (N=283)
Age, years						
n	112	114	111	109	63	283
Mean	47.9	52.2	49.4	49.7	49.7	49.6
SD	11.05	9.81	10.80	10.09	10.49	10.43
Median	47.0	53.0	49.0	50.0	50.0	50.0
Min, Max	25, 72	25, 73	19, 71	21, 73	24, 74	19, 74
Age Group, years, n (%)						
18 - 40	29 (25.9)	15 (13.2)	26 (23.4)	20 (18.3)	12 (19.0)	58 (20.5)
41 - 64	75 (67.0)	90 (78.9)	76 (68.5)	82 (75.2)	47 (74.6)	205 (72.4)
≥65	8 (7.1)	9 (7.9)	9 (8.1)	7 (6.4)	4 (6.3)	20 (7.1)
Sex, n (%)						
Male	27 (24.1)	29 (25.4)	34 (30.6)	28 (25.7)	16 (25.4)	78 (27.6)
Female	85 (75.9)	85 (74.6)	77 (69.4)	81 (74.3)	47 (74.6)	205 (72.4)
Race, n (%)						
White	105 (93.8)	104 (91.2)	101 (91.0)	102 (93.6)	61 (96.8)	264 (93.3)
Non-White	7 (6.3)	10 (8.8)	10 (9.0)	7 (6.4)	2 (3.2)	19 (6.7)
Black or African American	2 (1.8)	5 (4.4)	4 (3.6)	1 (0.9)	1 (1.6)	6 (2.1)
Native Hawaiian or Pacific Islander	0	0	2 (1.8)	0	0	2 (0.7)
Asian	1 (0.9)	1 (0.9)	0	1 (0.9)	0	1 (0.4)
American Indian or Alaska Native	3 (2.7)	0	0	1 (0.9)	0	1 (0.4)
Other	1 (0.9)	4 (3.5)	4 (3.6)	4 (3.7)	1 (1.6)	9 (3.2)
Ethnicity, n (%)						
Hispanic or Latino	8 (7.1)	10 (8.8)	12 (10.8)	9 (8.3)	3 (4.8)	24 (8.5)
Non-Hispanic or Latino	104 (92.9)	104 (91.2)	99 (89.2)	100 (91.7)	60 (95.2)	259 (91.5)
Height, cm						
n	112	114	111	109	63	283
Mean	170.2	169.0	169.4	169.5	171.0	169.8
SD	9.47	9.95	9.78	9.50	9.32	9.56
Median	169.5	167.6	167.6	167.6	170.2	167.6
Min, Max	147, 201	146, 198	154, 196	147, 193	152, 192	147, 196
Weight, kg						
n	112	113	111	109	63	283
Mean	82.30	84.34	84.37	82.19	82.64	83.14
SD	20.34	19.57	22.56	20.09	16.97	20.43
Median	78.29	81.65	81.65	79.38	82.01	81.19
Min, Max	45.4, 148.1	49.9, 152.4	44.5, 147.4	49.0, 137.0	56.5, 140.6	44.5, 147.4
BMI, kg/m^2						
n	112	113	111	109	63	283
Mean	28.26	29.42	29.14	28.47	28.26	28.68
SD	5.87	5.61	6.24	5.98	5.40	5.95
Median	28.07	29.29	28.87	27.16	27.56	27.81
Min, Max	17.0, 46.2	16.4, 47.7	17.3, 44.6	17.2, 46.0	18.2, 41.5	17.2, 46.0
BMI Group, kg/m^2, n (%)						
<25	36 (32.1)	27 (23.7)	33 (29.7)	32 (29.4)	20 (31.7)	85 (30.0)
25 to <30	38 (33.9)	38 (33.3)	28 (25.2)	37 (33.9)	24 (38.1)	89 (31.4)
≥30	38 (33.9)	48 (42.1)	50 (45.0)	40 (36.7)	19 (30.2)	109 (38.5)
Missing	0	1 (0.9)	0	0	0	0
GSV Diameter, mm						
n	110	110	106	106	63	275
Mean	7.79	7.47	8.19	8.06	7.60	8.00
SD	3.39	3.19	3.33	3.66	3.69	3.54
Median	6.95	6.80	7.60	7.60	6.80	7.40
Min, Max	2.9, 20.1	1.9, 19.3	2.5, 19.4	2.4, 25.9	1.5, 17.3	1.5, 25.9
GSV Diameter Group, mm, n (%)						
<5 mm	20 (17.9)	20 (17.5)	14 (12.6)	18 (16.5)	19 (30.2)	51 (18.0)
5 - <8 mm	52 (46.4)	53 (46.5)	44 (39.6)	40 (36.7)	22 (34.9)	106 (37.5)
8 - <10 mm	17 (15.2)	17 (14.9)	23 (20.7)	24 (22.0)	7 (11.1)	54 (19.1)
10 - <12 mm	6 (5.4)	9 (7.9)	11 (9.9)	10 (9.2)	6 (9.5)	27 (9.5)
≥ 12 mm	15 (13.4)	11 (9.6)	14 (12.6)	14 (12.8)	9 (14.3)	37 (13.1)
Missing	2 (1.8)	4 (3.5)	5 (4.5)	3 (2.8)	0	8 (2.8)

6.1.3 Subject Disposition

A summary of patient disposition for the Integrated Efficacy Population is shown in Table 7. Across treatment groups, 98% to 100% of patients completed the study, and <2% of patients discontinued for any reason. Four patients discontinued early, and all were lost to follow-up: 1 patient (0.9%) in the Vehicle placebo group, 1 (0.9%) in the PEM 0.125% group and 2 (1.8%) in the PEM 1.0% group. The percent of patients who received optional treatment with open label PEM 1.0% was highest in the placebo group (95.5%) and lowest in the PEM 1.0% group (49.5%).

Table 7 Disposition of patients

Status	Placebo (N=112)	PEM 0.125% (N=114)	PEM 0.5% (N=111)	PEM 1.0% (N=109)	PEM 2.0% (N=63)	PEM (0.5%+1.0%+ 2.0%) (N=283)
Completed	111 (99.1)	113 (99.1)	111 (100.0)	107 (98.2)	63 (100.0)	281 (99.3)
Discontinued	1 (0.9)	1 (0.9)	0	2 (1.8)	0	2 (0.7)
Withdrew Consent	0	0	0	0	0	0
Adverse Event	0	0	0	0	0	0
Lost to Follow-up	1 (0.9)	1 (0.9)	0	2 (1.8)	0	2 (0.7)
Death	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0
Investigator Decision	0	0	0	0	0	0
Sponsor Decision	0	0	0	0	0	0
Protocol Violation	0	0	0	0	0	0
Other	0	0	0	0	0	0
Entered Optional OL Treatment Period with PEM 1.0%	107 (95.5)	82 (71.9)	67 (60.4)	54 (49.5)	32 (50.8)	153 (54.1)

6.1.4 Analysis of Primary Endpoint(s)

Individual Study Results: Primary Efficacy Endpoint

The VVSymQ score is a patient-reported outcome (PRO) measure based on daily patient assessment of 5 varicose vein symptoms: heaviness, achiness, swelling, throbbing and itching (HASTI). The VVSymQ was completed by the patient each evening using the e-diary by scoring the duration of each of the 5 symptoms during that day on a 6-point scale ranging from 0 (“None of the time”) to 5 (“All of the time”). The daily VVSymQ score was the sum of the 5 symptom scores and ranged from 0 (no symptoms) to 25 (all 5 symptoms experienced all day). Daily VVSymQ scores were averaged for the 7 days immediately preceding the scheduled visit at Baseline and Weeks 4 and 8. In the ongoing Studies 015 and 016, VVSymQ scores will also be collected at the 1 Year visit.

Table 8 shows the results from Studies 015 and 016 for the primary efficacy analysis comparing the absolute change from baseline to Week 8 in the VVSymQ score for patients treated in Study 015 with PEM 0.5%, 1.0% and 2.0% (pooled), and in Study 016 with PEM 0.5% and 1.0% (pooled), compared to Vehicle placebo.

The pre-specified primary endpoint of the pooled PEM dose concentrations showed a

statistically significantly greater improvement in VVSymQ (symptoms) at Week 8 (LOCF) compared to the Vehicle placebo treated patients (Table 8). For Study 015, the **pooled** PEM 0.5%, 1.0% and 2.0% dose concentrations were statistically significantly (P<0.0001) superior to Vehicle placebo (adjusted mean change from baseline: -5.44 points vs. -2.13 points, respectively). For Study 016, too, the **pooled** PEM 0.5% and 1.0% dose concentrations were statistically significantly (P<0.0001) superior to Vehicle placebo (adjusted mean change from baseline: -5.53 points vs. -2.0 points, respectively). For both studies, **each** of the individual PEM dose concentrations was also statistically significantly (P≤0.0001) superior to Vehicle placebo (Table 8).

Table 8 Primary Efficacy Analysis: Absolute Change from Baseline to Week 8 in VVSymQ Score (LOCF), Efficacy Populations of Studies 015 and 016

Parameter : Study Treatment Group	N[a]	Baseline[b]		Adjusted Mean[c] Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Adjusted Mean	SE	Estimate (95% CI)[d]	*P*-value[e]
VVSymQ: Study 015							
Placebo	55	8.60	0.687	-2.13	0.452		
PEM 0.125% (control)	56	9.01	0.650	-4.63	0.447	-2.49 (-3.72 , -1.27)	0.0001
PEM 0.5%	51	9.30	0.615	-5.68	0.483	-3.54 (-4.80 , -2.29)	<0.0001
PEM 1.0%	50	8.82	0.663	-4.87	0.477	-2.73 (-3.98 , -1.48)	<0.0001
PEM 2.0%	63	9.49	0.625	-5.78	0.425	-3.65 (-4.84 , -2.46)	<0.0001
Pooled PEM (0.5%+ 1.0% +2.0%)	164	9.23	0.366	-5.44	0.287	-3.31 (-4.31 , -2.30)	<0.0001
VVSymQ: Study 016							
Placebo	54	9.26	0.666	-2.00	0.474		
PEM 0.125% (control)	54	9.11	0.618	-5.34	0.476	-3.34 (-4.63, -2.04)	<0.0001
PEM 0.5%	60	9.48	0.573	-6.01	0.454	-4.00 (-5.26, -2.74)	<0.0001
PEM 1.0%	57	7.82	0.568	-5.06	0.463	-3.05 (-4.33, -1.77)	<0.0001
Pooled PEM (0.5% + 1.0%)[f]	117	8.67	0.409	-5.53	0.330	-3.53 (-4.63, -2.42)	<0.0001
VVSymQ: Study 015 & 16 Integrated							
Placebo	109	8.93	0.48	-2.07	0.31		
PEM 0.125% (control)	110	9.06	0.45	-4.92	0.31	-2.85 (-3.72 , -1.98)	<0.0001
PEM 0.5%	111	9.40	0.42	-5.77	0.31	-3.70 (-4.57 , -2.83)	<0.0001
PEM 1.0%	107	8.29	0.43	-4.96	0.32	-2.89 (-3.77 , -2.01)	<0.0001
PEM 2.0%	63	9.49	0.63	-5.93	0.44	-3.86 (-4.92 , -2.79)	<0.0001
Pooled PEM (0.5% + 1.0%)	218	8.85	0.30	-5.36	0.22	-3.29 (-4.05, -2.54)	<0.0001
Pooled PEM (0.5%+ 1.0% +2.0%)	281	9.00	0.27	-5.55	0.21	-3.48 (-4.22 , -2.74)	<0.0001

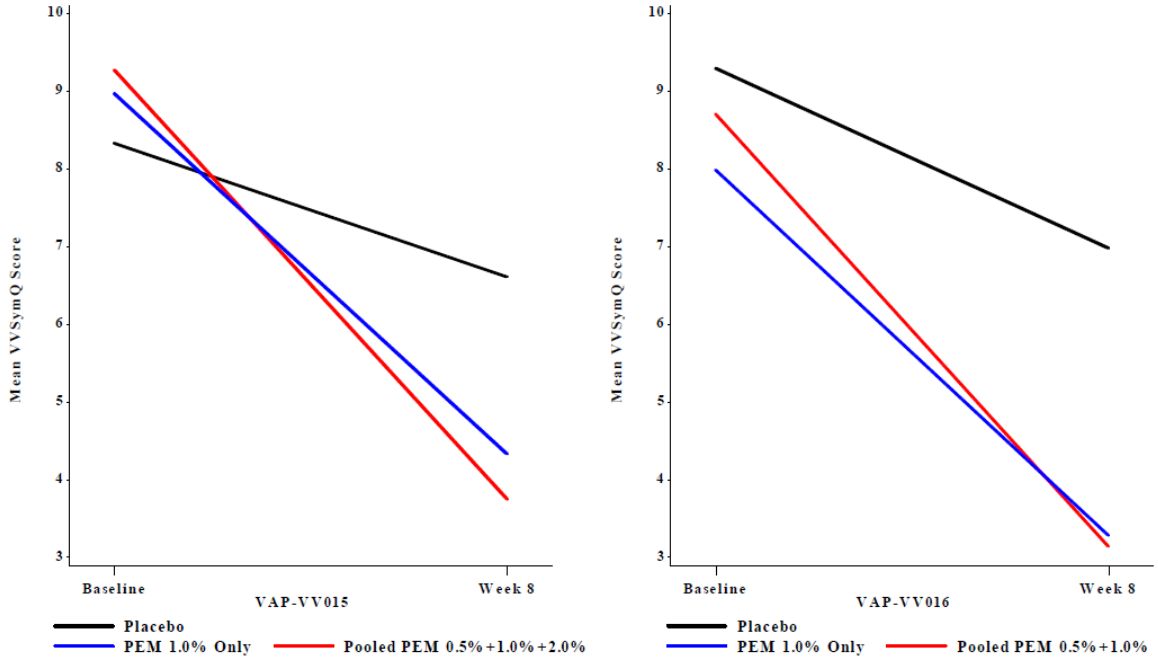
[a] N is the number of patients with both a baseline value and a value at the corresponding visit. [b] Visit 2 (baseline)
[c] Least square means from analysis of covariance (ANCOVA) model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate. [d] 95% Confidence Interval for comparison of PEM vs. Vehicle based on adjusted means (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), unadjusted for multiple comparisons. [e] Two-sided significance level for paired comparisons.
[f] Primary efficacy analysis Note: On the VVSymQ instrument, lower scores and/or negative change scores indicate better outcomes.
{Source: Sponsor's Tables 3 & 4 in Summary of Clinical Efficacy, Table 1 of ISI}

Integrated Efficacy Study Results: Primary Efficacy endpoint

Table 8 also displays the primary efficacy endpoint results for the pooled PEM groups in Studies 015 and 016 combined, which showed significantly (P<0.0001) greater improvement in symptoms at Week 8 (difference between pooled PEM and placebo -3.48 [95% Confidence Interval (CI): -4.22, -2.74]). Each of the individual PEM dose concentrations also showed greater improvement in symptoms than Vehicle placebo.

Figure 3 illustrates these results for the Vehicle placebo, pooled PEM and PEM 1.0% treatment groups for both Studies 015 and 016.

Figure 3 Primary Efficacy Analysis: Daily Diary 7 Day Average VVSymQ Score from Baseline to Week 8 by Dose Concentration and Study, Efficacy Populations of Studies 015 and 016



Note: Patients with both a baseline value and a value at subsequent visit are included. {Source: Sponsor's Figure 1 in Summary of Clinical Efficacy}

Responder analyses for the Primary Efficacy Endpoint

In the first analysis (Responders-I) of a clinically meaningful change in symptom burden, the response threshold was calculated as the mean change in VVSymQ score for all patients who rated their change in symptoms from baseline to Week 8 as "moderately improved" on the PGIC instrument. This mean change in VVSymQ score was similar in both studies; for Study 015, this change was -4.66 points, and for Study 016 it was -4.60 points. In Study 015 (Table 9), patients in the pooled PEM 0.5%, 1.0%, and 2.0% treatment groups had a statistically significant clinically meaningful change in VVSymQ score compared with patients in the Vehicle placebo group (49.7% vs. 14.3%, respectively, P<0.0001). In Study 016 (Table 9) too, patients in the pooled PEM 0.5% and 1.0% treatment groups had a statistically significant clinically meaningful change in VVSymQ score compared with in the Vehicle placebo group (51.7% vs. 23.3%, respectively, *P*=0.0004).

In the second analysis (Responders-II) of a clinically meaningful change in symptom burden, the response threshold was calculated as the mean change in VVSymQ score for patients who rated their change in symptoms from baseline to Week 8 as "moderately improved" or "much improved" on the PGIC instrument. Again, this was

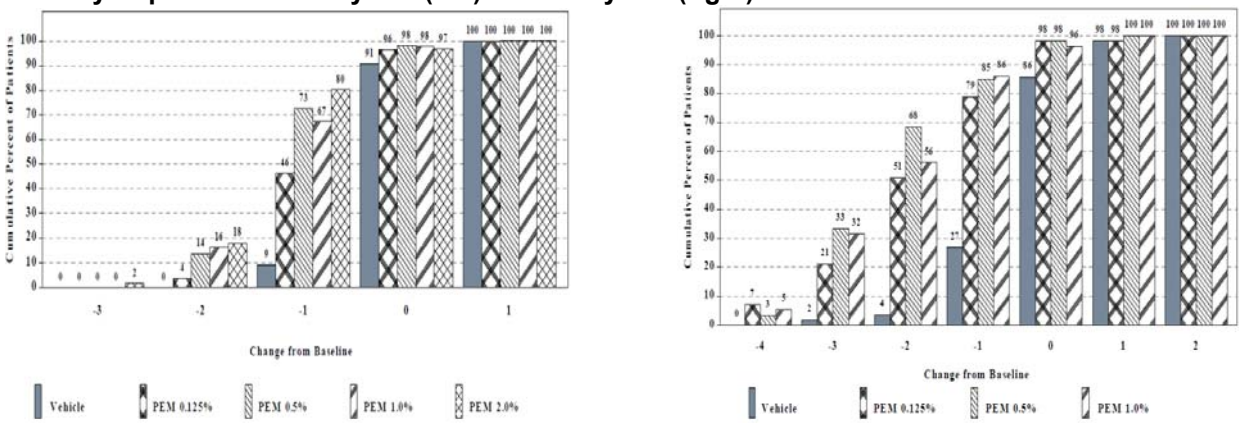
similar in both studies; for Study 015 this change was -6.07 points, and in Study 016 it was -5.99 points. In Study 015 (Table 9), patients in the pooled PEM 0.5%, 1.0%, and 2.0% treatment groups had a statistically significant clinically meaningful change in VVSymQ score versus patients in the Vehicle placebo group (33.3% vs. 7.1%, respectively, *P*<0.0001). In Study 016 (Table 9) too, patients in the pooled PEM 0.5% and 1.0% treatment groups had a statistically significant clinically meaningful change in VVSymQ score versus patients in the Vehicle placebo group (40.7% vs. 12.5%, respectively, *P*=0.0004).

Table 9 Clinically meaningful changes: Number of Patients Achieving a Clinically Meaningful Change from Baseline at Week 8 in VVSymQ – Efficacy Populations of Studies 015 and 016

Parameter Study	Study 015 (Placebo, N = 56) (Pooled PEM 0.5%+1.0%+2.0%, N = 165)		Study 016 (Placebo, N = 56) (Pooled PEM 0.5%+1.0%, N = 118)	
VVSymQ (PGIC in Symptoms)	**Responders-I[a] n (%)**	**Responders-II[b] n (%)**	**Responders-I[c] n (%)**	**Responders-II[d] n (%)**
Placebo	8 (14.3)	4 (7.1)	13 (23.2)	7 (12.5)
Pooled PEM	82 (49.7)	55 (33.3)	61 (51.7)	48 (40.7)
Comparison vs. Vehicle[e]	<0.0001	<0.0001	0.0004	0.0002

[a]Patients who meet the Responders-I threshold = -4.66 (the mean change in VVSymQ in all patients with a response of 'moderately improved' only on the PGIC in Symptoms)
[b]Threshold = -6.07 (the mean change in VVSymQ in all patients with a response of 'moderately improved' or 'much improved' on the PGIC in Symptoms)
[c]Threshold = -4.59 (the mean change in VVSymQ in all patients with a response of 'moderately improved' only on the PGIC in Symptoms)
[d]Threshold = -5.99 (the mean change in VVSymQ in all patients with a response of 'moderately improved' or 'much improved' on the PGIC in Symptoms)
[e]P-values from the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by site.
PGIC: Patient Global Impression of Change; PEM: Polidocanol Endovenous Microfoam; VVSymQ: Varicose Vein Symptoms Questionnaire; {Source: Study 015 CSR Table 14.2.6.1, Table 14.2.6.2, Table 14.2.6.3; Study 016 CSR Table 14.2.6.1, Table 14.2.6.2, Table 14.2.6.3}

Figure 4 Cumulative Distribution of the Change from Baseline for IPR-V3 at Week 8 (LOCF) Efficacy Population in Study 015 (left) and Study 016 (right)



Note: Bars represent the percentage of patients achieving the indicated level of change or better (lower scores indicate better outcomes). Percent labels on each bar are rounded due to space limitations. {Source: Study 015 CSR Figure 2.1; Study 016 CSR Figure 3.1}

In the third analysis, cumulative distribution curves were constructed for the VVSymQ score by plotting the percent of patients demonstrating change at each possible level of

the instrument (Figure 4). For both Studies 015 and 016, the percent of patients with an improvement (i.e. decrease) in VVSymQ score was higher in each of the PEM treatment groups, compared with the Vehicle placebo treatment group, throughout the distribution indicating that regardless of the threshold selected for a meaningful change, the PEM response was superior.

In summary, in all 3 responder analyses that evaluated clinically meaningful changes in VVSymQ score for both Studies 015 and 016, a statistically significantly larger proportion of patients in the pooled PEM treatment group (0.5%, 1.0%, and 2.0% in Study 015; 0.5% and 1.0% in Study 016) achieved a clinically meaningful change as compared to the Vehicle placebo group.

Reviewer's Comment: The placebo responder rates in the analyses of "clinically meaningful changes" in the VVSymQ (Table 9), and IPR-V3 and PAV3 scores (Table 12) are different between Study 015 and Study 016, suggesting some heterogeneity across the studies.

To evaluate inter-study differences with respect to placebo responder rates, the distribution of demographics and baseline patient and disease characteristics were examined for imbalances between the two study populations; these study populations were comparable with minor differences observed in age, sex, weight, CEAP classification, GSV diameter and baseline symptom scores.

A slight heterogeneity between Studies 015 and 016 which was observed as a higher percentage of patients with a C_3 rating (40%) in Study 016 compared to Study 015 (28%), and a lower percentage of patients in Study 016 with a C_2 rating (32%) compared to Study 015 (49%) could have contributed to the difference in placebo responder rates.

The sponsor explained that even though the entry criteria and endpoints were similar, the design of Study 016 differed from that of Study 015 in that an optional second treatment was administered, if indicated, at Week 1 in Study 016, which could have influenced placebo responder rates in that study. This is a plausible explanation. In Section 6.1.8 of this review, it is observed that the proportion of patients in the Placebo group who had "residual visible varicosities" following open-label optional treatment is much lower (45.1%) in Study 016 (Table 19) compared to that (80.0%) in Study 015 (Table 18), which could have influenced the placebo responder rates.

The difference in placebo response rates was not statistically significant.

6.1.5 Analysis of Secondary Endpoints(s)

Individual Efficacy Study Results: IPR-V3

Table 10 shows the results from Studies 015 and 016 for the co-secondary endpoint comparison of the absolute change from baseline in IPR-V^3 score for patients treated with pooled PEM dose concentrations versus Vehicle placebo. PEM treated patients

had a statistically significantly (*P*<0.0001) greater improvement in appearance at Week 8, as measured by the IPR-V^3, compared to the Vehicle placebo group, for both Study 015 (adjusted mean decrease -0.81 points vs. -0.01 points, respectively); and Study 016 (adjusted mean decrease -0.86 points vs. -0.07 points, respectively).

Table 10 Co-Secondary Efficacy Analyses: Absolute Change from Baseline to Week 8 (LOCF) in IPR-V^3 Scores, Efficacy Populations of Studies 015 and 016

Parameter : Study Treatment Group	N[a]	Baseline[b]		Adjusted Mean[c] Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Adjusted Mean	SE	Estimate (95% CI)[d]	*P*-value[e]
IPR-V^3: Study 015							
Placebo	55	1.82	0.10	-0.01	0.08		
PEM 0.125% (control)	56	1.95	0.09	-0.46	0.08	-0.45 (-0.98, -0.23)	0.0001
PEM 0.5%	51	2.12	0.09	-0.77	0.09	-0.76 (-0.98 , -0.53)	<0.0001
PEM 1.0%	49	1.98	0.10	-0.76	0.09	-0.75 (-0.97 , -0.53)	<0.0001
PEM 2.0%	61	2.10	0.10	-0.91	0.08	-0.90 (-1.11 , -0.68)	<0.0001
Pooled PEM (0.5%+ 1.0% +2.0%)	161	2.07	0.06	-0.81	0.05	-0.80 (-0.98 , -0.62)	<0.0001
IPR-V^3: Study 016							
Placebo	56	2.18	0.07	-0.07	0.08		
PEM 0.125% (control)	56	2.27	0.07	-0.74	0.08	-0.66 (-0.88 , -0.45)	<0.0001
PEM 0.5%	60	2.20	0.09	-0.89	0.08	-0.82 (-1.04 , -0.61)	<0.0001
PEM 1.0%	57	2.02	0.10	-0.83	0.08	-0.75 (-0.97 , -0.54)	<0.0001
Pooled PEM (0.5% + 1.0%)[f]	117	2.11	0.07	-0.86	0.06	-0.79 (-0.98 , -0.60)	<0.0001
IPR-V^3: Study 015 & 16 Integrated							
Placebo	111	2.00	0.06	-0.06	0.06		
PEM 0.125% (control)	112	2.11	0.06	-0.60	0.06	-0.54 (-0.70 , -0.38)	<0.0001
PEM 0.5%	111	2.16	0.06	-0.84	0.06	-0.78 (-0.94 , -0.62)	<0.0001
PEM 1.0%	106	2.00	0.07	-0.81	0.06	-0.75 (-0.91 , -0.59)	<0.0001
PEM 2.0%	61	2.10	0.10	-0.97	0.08	-0.91 (-1.10 , -0.71)	<0.0001
Pooled PEM (0.5% + 1.0%)	217	2.08	0.05	-0.82	0.04	-0.76 (-0.90 , -0.62)	<0.0001
Pooled PEM (0.5%+ 1.0% +2.0%)	278	2.09	0.04	-0.87	0.04	-0.81 (-0.94 , -0.68)	<0.0001

[a] N is the number of patients with both a baseline value and a value at the corresponding visit. [b] Visit 2 (baseline)
[c] Least square means from analysis of covariance (ANCOVA) model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate. [d] 95% Confidence Interval for comparison of PEM vs. Vehicle based on adjusted means (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), unadjusted for multiple comparisons. [e] Two-sided significance level for paired comparisons. [f]Co-secondary efficacy endpoint.
Note: Lower scores and/or negative change scores indicate better outcomes. {Source: Sponsor's Tables 5 & 7 in Summary of Clinical Efficacy}

Individual Efficacy Study Results: PA-V^3

Table 11 shows the results from Studies 015 and 016 for the co-secondary endpoint comparison of the absolute change from baseline in PA-V^3 scores. PEM treated patients had a statistically significantly (*P*<0.0001) greater improvement in appearance at Week 8, as measured by the PA-V^3 compared to the Vehicle placebo group for both Study 015 (adjusted mean decreases -1.58 points vs. -0.15 points, respectively) and Study 016, (adjusted mean decreases -1.82 points vs. -0.32 points, respectively).

Integrated Efficacy Study Results: IPR-V^3 and PA-V^3

Table 10 and Table 11 also show the results from the Integrated Efficacy Population of Studies 015 and 016, respectively, for the change from baseline to Week 8 in IPR-V3

and PA-V^3 scores. The pooled PEM group showed statistically significantly greater improvement in appearance at Week 8, as measured by the adjusted mean change from baseline in IPR-V^3 compared to Vehicle placebo (difference between pooled PEM and placebo -0.81 [95% CI: -0.94, -0.68]), and also, as measured by the adjusted mean change from baseline in PA-V^3 compared to Vehicle placebo (difference between pooled PEM and placebo -1.52 [95% CI:-1.74, -1.29]). Each of the individual PEM doses was also superior to Vehicle placebo in reductions of IPR-V^3 and PA-V^3 scores.

Table 11 Co-Secondary Efficacy Analyses: Absolute Change from Baseline to Week 8 (LOCF) in PA-V^3 Scores, Efficacy Populations of Studies 015 and 016

Parameter : Study Treatment Group	N[a]	Baseline[b]		Adjusted Mean[c] Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Adjusted Mean	SE	Estimate (95% CI)[d]	*P*-value[e]
PA-V^3: Study 015							
Placebo	55	3.49	0.11	-0.15	0.14		
PEM 0.125% (control)	56	3.57	0.08	-0.93	0.14	-0.78 (-1.17 , -0.40)	0.0001
PEM 0.5%	51	3.45	0.11	-1.40	0.15	-1.26 (-1.65 , -0.86)	<0.0001
PEM 1.0%	50	3.46	0.10	-1.60	0.15	-1.45 (-1.85 , -1.06)	<0.0001
PEM 2.0%	63	3.68	0.07	-1.75	0.14	-1.60 (-1.98 , -1.23)	<0.0001
Pooled PEM (0.5%+ 1.0% +2.0%)	164	3.54	0.05	-1.58	0.09	-1.44 (-1.75 , -1.12)	<0.0001
PA-V^3: Study 016							
Placebo	56	3.30	0.11	-0.32	0.13		
PEM 0.125% (control)	57	3.53	0.10	-1.55	0.13	-1.23 (-1.59 , -0.87)	<0.0001
PEM 0.5%	60	3.58	0.08	-1.86	0.13	-1.54 (-1.90 , -1.18)	<0.0001
PEM 1.0%	57	3.49	0.10	-1.79	0.13	-1.47 (-1.83 , -1.11)	<0.0001
Pooled PEM (0.5% + 1.0%)[f]	117	3.54	0.07	-1.82	0.09	-1.50 (-1.81 , -1.19)	<0.0001
PA-V^3: Study 015 & 16 Integrated							
Placebo	111	3.40	0.08	-0.21	0.10		
PEM 0.125% (control)	113	3.55	0.07	-1.22	0.10	-1.01 (-1.28 , -0.75)	<0.0001
PEM 0.5%	111	3.52	0.07	-1.61	0.10	-1.40 (-1.66 , -1.14)	<0.0001
PEM 1.0%	107	3.48	0.07	-1.67	0.10	-1.47 (-1.73 , -1.20)	<0.0001
PEM 2.0%	63	3.68	0.07	-1.90	0.14	-1.69 (-2.01 , -1.36)	<0.0001
Pooled PEM (0.5% + 1.0%)	218	3.50	0.05	-1.64	0.07	-1.43 (-1.66 , -1.20)	<0.0001
Pooled PEM (0.5%+ 1.0% +2.0%)	281	3.54	0.04	-1.73	0.06	-1.52 (-1.74 , -1.29)	<0.0001

[a] N is the number of patients with both a baseline value and a value at the corresponding visit. [b] Visit 2 (baseline)
[c] Least square means from analysis of covariance (ANCOVA) model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate. [d] 95% Confidence Interval for comparison of PEM vs. Vehicle based on adjusted means (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), unadjusted for multiple comparisons. [e] Two-sided significance level for paired comparisons.
[f]Co-secondary efficacy endpoint. Note: Lower scores and/or negative change scores indicate better outcomes.
{Source: Sponsor's Tables 6 & 7 in Summary of Clinical Efficacy}

Responder analyses for the Secondary Efficacy Endpoint

For both Studies 015 and 016, assessments of clinically meaningful changes in IPR-V^3 and PAV^3 scores were evaluated in the same 3 ways as for the primary efficacy endpoint (VVSymQ scores): Responders-I, Responders-II, and cumulative distribution of change. Regardless of the method used and/or PEM dose concentration, the percent of PEM-treated patients with clinically meaningful changes in IPR-V^3 and PA-V^3 scores were significantly (P<0.0001) greater than that in the Vehicle group (Table 12).

Table 12 Clinically meaningful changes: Number of Patients Achieving a Clinically Meaningful Change from Baseline at Week 8 in IPR-V^3 and PAV^3 Scores (LOCF) – Efficacy Populations of Studies 015 and 016

Parameter Study	Study 015 (Placebo, N = 56) (Pooled PEM 0.5%+1.0%+2.0%,N=165)		Study 016 (Placebo, N = 56) (Pooled PEM 0.5%+1.0%, N = 118)	
IPR-V^3 (CGIC in Appearance)	**Responders-I[f] n (%)**	**Responders-II[g] n (%)**	**Responders-I[h] n (%)**	**Responders-II[i] n (%)**
Placebo	5 (8.9)	5 (8.9)	8 (14.3)	8 (14.3)
Pooled PEM	119 (72.1)	119 (72.1)	81 (68.6)	81 (68.6)
Comparison vs. Vehicle[e]	<0.0001	<0.0001	<0.0001	<0.0001
PA-V^3 (PGIC in Appearance)	**Responders-I[j] n (%)**	**Responders-II[k] n (%)**	**Responders-I[l] n (%)**	**Responders-II[m] n (%)**
Placebo	2 (3.6)	2 (3.6)	2 (3.6)	1 (1.8)
Pooled PEM	92 (55.8)	92 (55.8)	73 (61.9)	38 (32.2)
Comparison vs. Vehicle[e]	<0.0001	<0.0001	<0.0001	<0.0001

[e]P-values from the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by site.
[f]Threshold = -0.65 (the mean change in IPR-V^3 in all patients with a response of 'moderately improved' only on the CGIC in Appearance)
[g]Threshold = -0.93 (the mean change in IPR- V^3 in all patients with a response of 'moderately improved' or 'much improved' on the CGIC in Appearance)
[h]Threshold = -0.84 (the mean change in IPR- V^3 in all patients with a response of 'moderately improved' only on the CGIC in Appearance)
[i]Threshold = -0.98 (the mean change in IPR- V^3 in all patients with a response of 'moderately improved' or 'much improved' on the CGIC in Appearance)
[j]Threshold = -1.45 (the mean change in PA- V^3 in all patients with a response of 'moderately improved' only on the PGIC in Appearance)
[k]Threshold = -1.9 (the mean change in PA- V^3 in all patients with a response of 'moderately improved' or 'much improved' on the PGIC in Appearance)
[l]Threshold = -1.57 (the mean change in PA- V^3 in all patients with a response of 'moderately improved' only on the PGIC in Appearance)
[m]Threshold = -2.08 (the mean change in PA- V^3 in all patients with a response of 'moderately improved' or 'much improved' on the PGIC in Appearance)
CGIC: Clinician Global Impression of Change CI: confidence interval; GSV: great saphenous vein; IPR- V^3: Independent Photography Review – Visible Varicose Veins; LOCF: last observation carried forward; PA- V^3: Patient Self-Assessment of Visible Varicose Veins; PGIC: Patient Global Impression of Change PEM: Polidocanol Endovenous Microfoam; VVSymQ: Varicose Vein Symptoms Questionnaire
Source: Study 015 CSR Table 14.2.6.1, Table 14.2.6.2, Table 14.2.6.3; Study 016 CSR Table 14.2.6.1, Table 14.2.6.2, Table 14.2.6.3

Reviewer's evaluation of pre- and post-treatment photographs of 32 subjects submitted by the sponsor in response to the IR:

As mentioned earlier in Section 6.1.1 of this review, I requested the sponsor to provide pre- and post-treatment photographs of a sample of 16 subjects each in Study 015 and Study 016, all of whom were found – in a review of line item listing of the IPR-V^3 scores – to have a change in the IPR-V^3 scores by 2 grades. Table 13 summarizes my evaluation of these pre- and post-treatment photographs.

For most of the patients, the IPR-V^3 scores and the change in the IPR-V^3 scores are consistent with the photographic appearances and with the improvement in the appearance of the varicose veins seen in the photographs. In six instances (4 in Study 015 and 2 in Study 016), the site physician made an IPR-V^3 score of 2, but the 3 independent photographic reviewers adjudicated the photographs of these varicose veins as 0. I agree with the 3 adjudicators because varicose veins were not discernible in these photographs (pre-treatment as well as post-treatment); it is doubtful if enrollment of these six subjects was justified.

Table 13 Reviewer's evaluation of pre- and post-treatment photographs of a sample of 16 each subjects in Study 015 and Study 016

Subject ID #	Site IPR-V³ Score	Pre-Treatment IPR-V³ Score†	Post-Treatment IPR-V³ Score†	Treatment	Clinical Reviewer's Comments
Study 015					
21-1017	2	2	0	PEM 2%	Consistent with photographic improvement; good quality photos.
22-1078	3	1	2	PEM 2%	Photographs do not show obvious change; reviewer #1 scored post-treatment photograph worse, which drove the median score.
23-1005	2	Not evaluable	1	PEM 2%	Baseline photograph very poor quality; not possible to assign a score.
27-1025	2	1	2	Vehicle	Photographs do not show obvious change; Reviewer #2 deemed post-treatment photograph worse, and this evaluation drove the median score.
29-1034	3	3	1	PEM 1%	Consistent with photographic improvement; good quality photos.
32-1007	2	0	0	Vehicle	No varicose veins discernible in photos, which are of good quality. *Doubt enrollment was justified.*
33-1004	2	0	1	Vehicle	Photographs do not show obvious change. All 3 reviewers gave different post-treatment scores; varicosities are visible below the ankle only. *Doubt enrollment was justified.*
33-1023	2	2	0	PEM 2%	Consistent with photographic improvement; color in photos do not match.
33-1035	2	2	0	PEM0.5%	Consistent with photographic improvement; acceptable photo quality.
33-1057	2	0	0	PEM 1%	No varicose veins discernible in photos, which have acceptable quality. *Doubt enrollment was justified.*
34-1002	2	2	1	PEM 2%	Consistent with photographic improvement; color in photos do not match.
34-1005	3	2	3	Vehicle	Consistent with photos showing worsening of varicosities; photos have acceptable quality.
36-1024	3	3	3	PEM 0.5%	Both pre- and post-treatment photos show equally extensive varicosities; photos consistent with scores..
37-1006	4	4	2	PEM 2%	Consistent with photographic improvement; photo quality is acceptable.
39-1033	2	2	0	PEM 1%	Consistent with photographic improvement; good quality photos.
39-1091	2	0	1	PEM 2%	No varicose veins discernible in photos, which have acceptable quality. *Doubt enrollment was justified.*
Study 016					
60-1011	2	2	0	PEM 1%	Consistent with photographic improvement; acceptable photo quality.
60-1015	2	0	0	PEM 0.5%	Minimal varicosities discernible in photos, which have acceptable quality. *Doubt enrollment was justified.*
60-1022	2	1	0	PEM 0.5%	Minimal localized varicosities discernible in photos, which have acceptable quality. Photographic improvement present.
60-1041	2	0	0	PEM 1%	Minimal below-ankle varicosities discernible in photos, which have acceptable quality. *Doubt enrollment was justified.*
63-1003	2	1	2	Vehicle	Both pre- and post-treatment photos show equally extensive varicosities.
63-1008	2	3	1	PEM 1%	Consistent with photographic improvement; color in photos do not match.
64-1036	2	3	1	PEM 0.125%	Consistent with photographic improvement; good photo quality.
64-1052	2	1	1	Vehicle	Minimal below-ankle varicosities discernible in photos, which have acceptable quality.
67-1006	3	2	0	PEM 1%	Consistent with photographic improvement; acceptable photo quality.
68-1003	2	2	0	PEM 0.5%	Consistent with photographic improvement; color in photos slightly different.
68-1051	2	1	2	Vehicle	No change in varicosities, acceptable photos, color slightly different.
69-1018	2	2	0	PEM 1%	Consistent with photographic improvement; color in photos slightly different.
72-1018	3	3	1	PEM 0.5%	Consistent with photographic improvement; color in photos slightly different.
75-1005	3	2	3	PEM 0.125%	No change in varicosities, acceptable photos, color slightly different.
75-1025	3	4	2	PEM 1%	Consistent with photographic improvement; color in photos slightly different.
76-1026	2	2	0	PEM 0.5%	Consistent with photographic improvement; color in photos slightly different.

† Median of IPR-V³ scores given by 3 independent photographic reviewers

Correlations between the primary endpoint (VVSymQ score) and (i) secondary endpoint (digital photographic scores) and (ii) tertiary endpoint (Duplex ultrasound response)

The correlations between the VVSymQ score (and individual symptoms) and the IPR-V^3 and PA-V^3 scores and the Duplex ultrasound response statistically significant (Table 14). The correlations among VVSymQ, IPR-V^3, PA-V^3 and Duplex Response were comparable in strength for Kendall's tau and Spearman rank coefficients. Each of the five symptoms comprising the VVSymQ score (heaviness, achiness, swelling, throbbing and itching) correlated positively with the IPR-V^3 score. The correlations were statistically significant or marginally significant, with the exception of itching.

Table 14 Correlation between Duplex Response and change from baseline in VVSymQ, IPR-V3, PA-V3 and Individual VVSymQ Symptoms at Week 8 in Study 015 and Study 016

	Change in VVSymQ	Change in IPR-V^3	Change in PA-V^3	Individual VVSymQ Symptoms				
				Heaviness	Achiness	Swelling	Throbbing	Itching
Study 015								
Kendall's Tau Correlation Coefficient, r (p-value)								
Duplex Response	-0.193 (<0.0001)	-0.299 (<0.0001)						
Change in Daily Diary VVSymQ		0.176 (0.0002)						
Change in IPR-V^3			0.343 (<0.0001)	0.204 (<0.0001)	0.138 (0.005)	0.188 (0.0002)	0.101 (0.043)	0.041 (0.421)
Spearman Rank Correlation Coefficient, r (p-value)								
Duplex Response	-0.235 (<0.0001)	-0.315 (<0.0001)						
Change in Daily Diary VVSymQ		0.227 (0.0002)						
Change in IPR-V^3			0.393 (<0.0001)	0.261 (<0.0001)	0.178 (0.005)	0.235 (0.0002)	0.129 (0.040)	0.051 (0.418)
Study 016								
Kendall's Tau Correlation Coefficient, r (p-value)								
Duplex Response	-0.228 (<0.0001)	-0.364 (<0.0001)						
Change in Daily Diary VVSymQ		0.163 (<0.002)						
Change in IPR-V^3			0.324 (<0.0001)	0.095 (<0.077)	0.126 (0.018)	0.125 (0.020)	0.115 (0.033)	0.102 (0.062)
Spearman Rank Correlation Coefficient, r (p-value)								
Duplex Response	-0.279 (<0.0001)	-0.381 (<0.0001)						
Change in Daily Diary VVSymQ		0.206 (<0.002)						
Change in IPR-V^3			0.383 (<0.0001)	0.121 (0.0755)	0.162 (0.017)	0.161 (0.017)	0.146 (0.031)	0.127 (0.062)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose response based on primary efficacy endpoint:

Table 15 shows that the adjusted mean change at Week 8 from baseline values in VVSymQ for the PEM groups (-5.73 for 0.5%, -5.04 for 1.0% and -5.98 for 2.0%) were greater than for the PEM 0.125% (control) group (-4.93). The linear trend test showed a

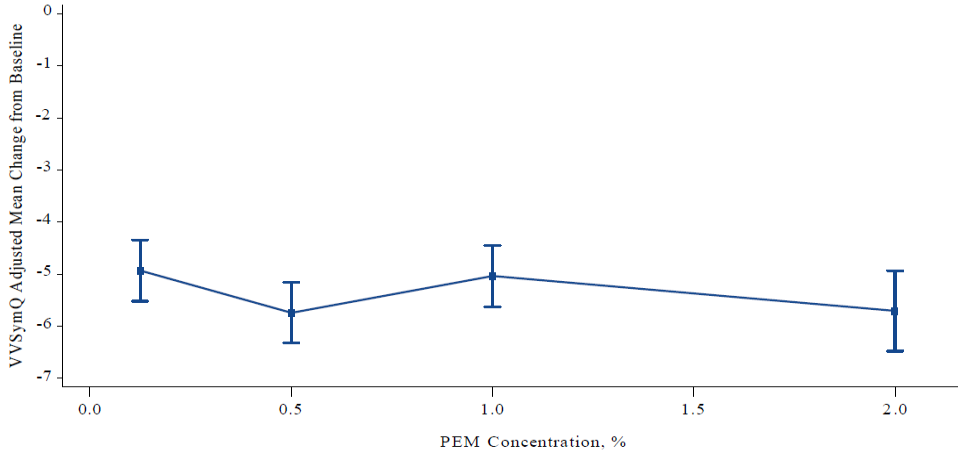
marginal linear trend across PEM concentrations from 0.125% to 2.0% (*P*=0.1303), although the dose response does not appear to be monotonic. The PEM 0.5%, 1.0% and 2.0% dose concentration were not substantially different from one another with regard to improvement in VVSymQ score, with only PEM 2.0% showing a statistically significant (*P*=0.0442) difference from PEM 0.125% (control).

Table 15 Statistical Analysis: PEM Dose Response in VVSymQ 7-Day Average Daily Diary Score Change from Baseline at Week 8 (LOCF): Integrated Efficacy Population

Study Treatment Group	N[b]	Adjusted Mean[a] Change from Baseline		
		Adjusted Mean[c]	SE	(95% CI)
Integrated Studies 015 and 016				
PEM 0.125% (control)	110	-4.93	0.30	(-5.51, -4.35)
PEM 0.5%	111	-5.73	0.30	(-6.31, -5.15)
PEM 1.0%	107	-5.04	0.30	(-5.63, -4.44)
PEM 2.0%	63	-5.98	0.43	(-6.82, -5.14)
Linear Trend Test[d]:	*P* = 0.1303			
All Paired Comparisons - Estimates (95% CI)[e] [*P*-value]				
	PEM 0.125% (control)	PEM 0.5%	PEM 1.0%	PEM 2.0%
PEM 0.125% (control)	-	0.80 (-0.02, 1.63) *P* = [0.0554]	0.11 (-0.72, 0.94) *P* = [0.8018]	1.05 (0.03, 2.07) *P* = [0.0442]
PEM 0.5%	-	-	-0.70 (-1.53, 0.13) *P* = [0.0995]	0.24 (-0.79, 1.27) *P* = [0.6416]
PEM 1.0%	-	-	-	0.94 (-0.10, 1.98) *P* = [0.0750]
PEM 2.0%	-	-	-	-

[a] Least square means from ANCOVA model with treatment group, and study as class variables and the corresponding baseline VVSymQ score as a continuous covariate. Only PEM arms included in model. [b] Number of patients with both a baseline value and a change from baseline.
[c] Based on adjusted means. Unadjusted for multiple comparisons. [d] Linear Contrast from model using coefficients -3 -1 1 3 for the 4 PEM contributions.
[e] Difference in adjusted mean changes [Row Concentration - Column Concentration]. CI: confidence interval; LOCF: last observation carried forward;
Note: VVSymQ Summary Score includes 5 items (1=Heaviness, 2=Achiness, 3=Swelling, 4=Throbbing and 5=Itching) where lower scores and/or negative change scores indicate better outcomes. Dashes (-) indicate that no pair wise comparison was conducted for the treatment groups.
PEM: Polidocanol Endovenous Microfoam; VVSymQ: Varicose Vein Symptoms Questionnaire {Source: Sponsor's Table 12 in Summary of Clinical Efficacy}

Figure 5 Dose-Response Curve: Adjusted Mean Change in VVSymQ at Week 8 (LOCF) with 95% Confidence Intervals by PEM Concentration Efficacy Population



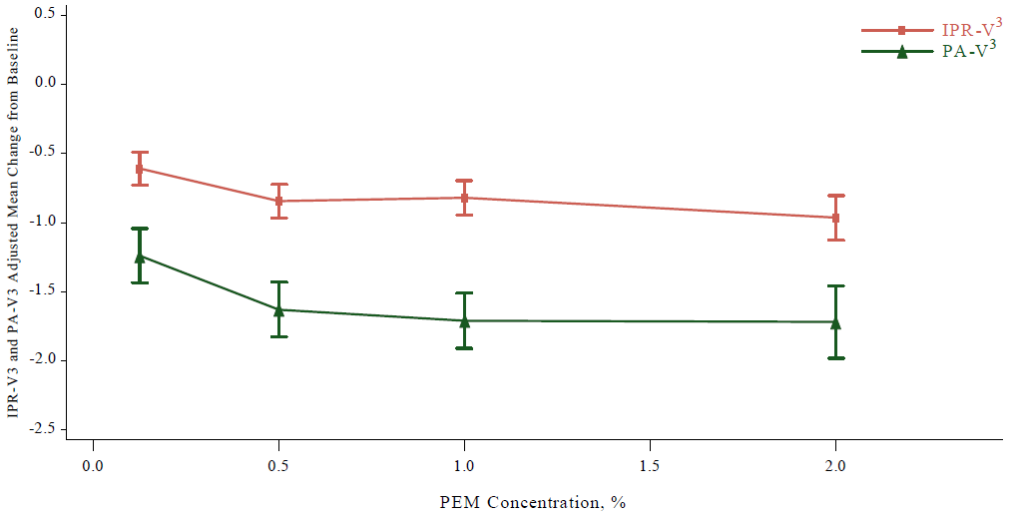
Source: ISE Appendix 12.1.2 Figure 4.1

The dose-response curve for VVSymQ from the Integrated Efficacy Population (Figure 5) shows that the individual PEM dose concentrations were each superior to vehicle placebo and generally showed improvement compared to PEM 0.125%; however, the improvements in VVSymQ scores among the PEM 0.5%, 1.0%, and 2.0% dose concentrations were not different from one another, with only the PEM 2.0% showing a significant difference from PEM 0.125% (control) (*P*=0.0442; Table 15). In the pairwise comparisons of each dose concentration of PEM 0.5%, 1.0% and 2.0% versus PEM 0.125%, statistically significant differences were observed in the formal dose-response analysis in Study 015, but not in Study 016. The explanation is that this difference may be due to the additional blinded treatment allowed in Study 016.

Dose-response based on secondary endpoints:

Figure 6 shows that there were no significant differences in the reduction (i.e., mean change at Week 8 from the baseline values) in the IPR-V^3 or PA-V^3 scores between the PEM 0.5%, 1.0%, and 2.0% dose groups for the Integrated Efficacy Population.

Figure 6 Dose-Response Curves: Adjusted Mean Change in IPR-V3 and PA-V3 Score at Week 8 (LOCF) with 95% Confidence Intervals by PEM Concentration Efficacy Population



NOTE: IPR-V3 score is the median of the 3 qualified individual reviewer scores using the 5-point scale from 0 ("None") to 4 ("Very severe"). Lower scores indicate better outcomes. PA-V3 score has a 5-point scale from 0 ("Not at all noticeable") to 4 ("Extremely noticeable"). Lower scores indicate better outcomes. Least square means and 95% Confidence Interval from ANCOVA model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate. {Source: CSR Study 015, Figure 5.2} Source: ISE Appendix 12.1.2 Figure 4.2

Table 16 shows that the adjusted mean change from baseline values in IPR-V^3 score for each of the PEM groups (-0.85 for PEM 0.5%, -0.82 for PEM 1.0% and -0.99 for PEM 2.0%) were greater than for the PEM 0.125% (control) group (-0.61), with a statistically significant linear trend across PEM concentrations from 0.125% to 2.0% (*P*=0.0011), although the dose response does not appear to be strictly monotonic, tapering between 0.5% and 2.0%. In the paired comparison estimates, the change from baseline for each of the PEM 0.5%, 1.0% and 2.0% groups was significant (*P*≤0.02)

compared to PEM 0.125% control; however, there were no substantial differences in mean change from baseline scores between PEM 0.5%, 1.0% and 2.0% dose groups.

Table 16 PEM Dose Response in IPR-V^3 Change from Baseline at Week 8 (LOCF)

Study Treatment Group	N[b]	Adjusted Mean[a] Change from Baseline		
		Adjusted Mean[c]	SE	(95% CI)
Integrated Studies 015 and 016				
PEM 0.125% (control)	112	-0.61	0.06	(-0.73, -0.49)
PEM 0.5%	111	-0.85	0.06	(-0.97, -0.73)
PEM 1.0%	106	-0.82	0.06	(-0.94, -0.69)
PEM 2.0%	61	-0.99	0.09	(-1.16, -0.81)
Linear Trend Test[d]:	*P* = 0.0011			
All Paired Comparisons - Estimates (95% CI)[e] [*P*-value]				
	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%
PEM 0.125% (control)	-	0.23 (0.07, 0.40) *P* = [0.0066]	0.21 (0.03, 0.38) *P* = [0.0187]	0.38 (0.16, 0.59) *P* = [0.0005]
PEM 0.5%	-	-	-0.03 (-0.20, 0.14) *P* = [0.7411]	0.14 (-0.07, 0.36) *P* = [0.1932]
PEM 1.0%	-	-	-	0.17 (-0.05, 0.39) *P* = [0.1212]
PEM 2.0%	-	-	-	-

[a] Least square means from ANCOVA model with treatment group, and study as class variables and the corresponding baseline IPR-V^3 score as a continuous covariate. Only PEM arms included in model. [b] Number of patients with both a baseline value and a change from baseline.
[c] Based on adjusted means. Unadjusted for multiple comparisons. [d] Linear Contrast from model using coefficients -3 -1 1 3 for the 4 PEM contributions.
[e] Difference in adjusted mean changes [Row Concentration - Column Concentration]. CI: confidence interval; LOCF: last observation carried forward;
Dashes (-) indicate that no pair wise comparison was conducted for the treatment groups. {Source: Sponsor's ISE Table 7.2 and 31}

Table 17 PEM Dose Response in PA-V^3 Change from Baseline at Week 8 (LOCF)

Study Treatment Group	N[b]	Adjusted Mean[a] Change from Baseline		
		Adjusted Mean[c]	SE	(95% CI)
Integrated Studies 015 and 016				
PEM 0.125% (control)	113	-1.24	0.10	(-1.44, -1.05)
PEM 0.5%	111	-1.63	0.10	(-1.83, -1.43)
PEM 1.0%	107	-1.72	0.10	(-1.90, -1.50)
PEM 2.0%	63	-1.93	0.10	(-2.21, -1.64)
Linear Trend Test[d]:	*P* = 0.0001			
All Paired Comparisons - Estimates (95% CI)[e] [*P*-value]				
	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%
PEM 0.125% (control)	-	0.39 (0.11, 0.66) *P* = [0.0062]	0.46 (0.18, 0.74) *P* = [0.0013]	0.69 (0.34, 1.03) *P* = [0.0001]
PEM 0.5%	-	-	0.07 (-0.21, 0.35) *P* = [0.6169]	0.30 (-0.05, 0.65) *P* = [0.1932]
PEM 1.0%	-	-	-	0.23 (-0.12, 0.58) *P* = [0.2033]
PEM 2.0%	-	-	-	-

[a] Least square means from ANCOVA model with treatment group, and study as class variables and the corresponding baseline PA-V^3 score as a continuous covariate. Only PEM arms included in model. [b] Number of patients with both a baseline value and a change from baseline.
[c] Based on adjusted means. Unadjusted for multiple comparisons. [d] Linear Contrast from model using coefficients -3 -1 1 3 for the 4 PEM contributions.
[e] Difference in adjusted mean changes [Row Concentration - Column Concentration]. CI: confidence interval; LOCF: last observation carried forward;
Dashes (-) indicate that no pair wise comparison was conducted for the treatment groups. {Source: Sponsor's ISE Table 7.3 and 32}

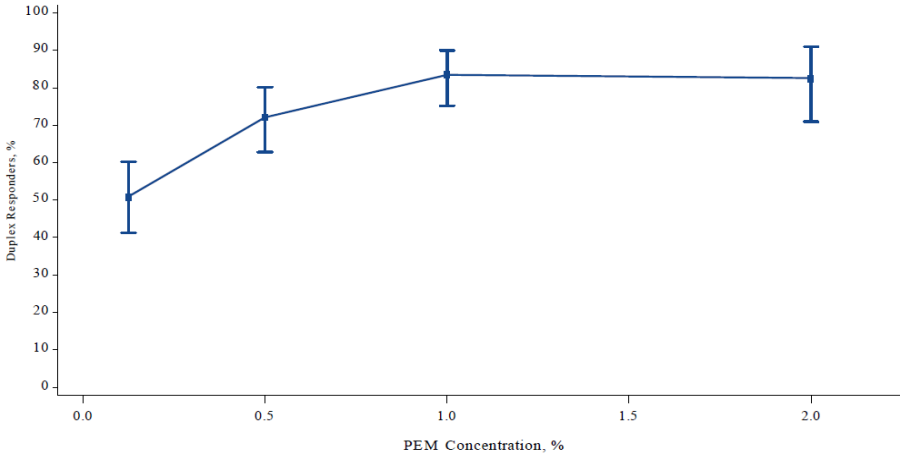
Similarly, the dose response analysis in Table 17 shows that the adjusted mean change from baseline values in PA-V^3 score for each of the PEM groups (-1.63 for 0.5%, -1.70

for 1.0% and -1.93 for 2.0%) were greater than for the PEM 0.125% (control) group (-1.24), with a statistically significant linear trend across PEM concentrations from 0.125% to 2.0% (*P*=0.0001). While the dose response appeared to be monotonic for this endpoint, tapering in dose-response was evident between PEM 0.5% and 2.0% dose concentrations. In the paired comparison estimates, the change from baseline for each of the PEM 0.5%, 1.0% and 2.0% groups was statistically significant compared to PEM 0.125% control (*P*≤0.006); however, the differences in mean change from baseline scores between the individual PEM 0.5%, 1.0% and 2.0% dose groups were less substantial: estimate 0.07 (95% CI: -0.21, 0.35) for PEM 1.0% vs. PEM 0.5%; estimate 0.30 (95% CI:-0.05, 0.65) for PEM 2.0% vs. PEM 0.5%; and estimate 0.23 (95% CI: -0.12, 0.58) for PEM 2.0% vs. PEM 1.0%.

Dose-response based on tertiary endpoint

Figure 7 shows the dose response with the percent of Duplex responders increasing as the PEM dose increases from 0.125% (control; (51% Duplex responders) to 0.5% (72% Duplex responders) and 1.0% (84% Duplex responders). The dose-response trend reached a plateau at PEM 1.0%, as the Duplex responder rate for PEM 2.0% (83%) was nearly identical to that for PEM 1.0%. The sponsor uses this result to support the selection of the PEM 1.0% dose concentration for the treatment of patients with incompetence of the GSV system.

Figure 7 Dose-Response Curve: Proportion of Duplex Responders at Week 8 (LOCF) with 95% Confidence Intervals Efficacy Population



Source: ISE Appendix 12.1.2 Figure 5

Dose-relationship based on treatment failure or need for open-label treatment:

Patients in Study 015 received only one treatment during the blinded phase of the study; after 8 weeks, patients with an inadequate response were able to receive treatment with open-label PEM 1.0% (Table 15). In this setting, a dose-relationship was apparent, as 74% of patients treated with blinded PEM 0.125% (control) required

subsequent open-label PEM 1.0% treatment compared with 63%, 56% and 51% for patients treated with blinded PEM 0.5%, 1.0%, or 2.0%, respectively (Table 18). Patients who required open-label treatment due to failure of the first treatment (i.e., SFJ reflux > 0.5 seconds) comprised 60% in the PEM 0.125% (control) arm compared to 55%, 34% and 39% for PEM 0.5%, 1.0% and 2.0%, respectively. The proportion of patients with residual visible varicosities as the main reason for open-label treatment was 74%, 86% and 83%, respectively, in the PEM 0.5%, 1.0% and 2.0% groups.

Table 18 Optional Open-label PEM 1.0% Treatment at Visit 6, Safety Population of Study 015

	Treatment Group				
Parameter	Placebo (N=56)	PEM 0.125% (control) (N=57)	PEM 0.5% (N=51)	PEM 1.0% (N=52)	PEM 2.0% (N=63)
Treated at Visit 6 (Optional Open-label PEM 1.0%), n (%)[a]	52 (92.9)	42 (73.8)	32 (62.7)	29 (55.8)	32 (50.8)
Met Criteria for Open-label Treatment at Visit 6 (Yes), N	55	52	42	35	41
Criteria Met for Open-label Treatment[b,c]:					
Treatment Failure (SFJ reflux >0.5 second)	53 (96.4)	31 (59.6)	23 (54.8)	12 (34.3)	16 (39.0)
Partial Treatment Failure (GSV incompetence)	29 (52.7)	33 (63.5)	25 (59.5)	13 (37.1)	20 (48.8)
Residual Visible Varicosities	44 (80.0)	41 (78.8)	31 (73.8)	30 (85.7)	34 (82.9)

[a] Percents are based on the number of patients in the Safety Population in each treatment group. [b] If a patient had more than one criteria applied, the patient was counted once in each subcategory. [c] Percents are based on the number of patients who met the criteria in each treatment group.
GSV: great saphenous vein; PEM: Polidocanol Endovenous Microfoam; SFJ: saphenofemoral junction {Source: ISE Table 28}.

Table 19 Additional Study Treatment at Visit 3 and Optional Open-label PEM 1.0% Treatment at Visit 6, Safety Population of Study 016

	Treatment Group			
Parameter	Placebo (N=57)	PEM 0.125% (control) (N=57)	PEM 0.5% (N=60)	PEM 1.0% (N=58)
Received Additional Study Treatment at Visit 3	23 (40.4)	29 (50.9)	20 (33.3)	23 (39.7)
Reason for Additional Treatment at Visit 3				
Failed treatment at Visit 2[a]	16 (28.1)	5 (8.8)	1 (1.7)	2 (3.4)
Incomplete Treatment at Visit 2	2 (3.5)	14 (24.6)	11 (18.3)	6 (10.3)
Treatment of Additional Incompetent Veins	5 (8.8)	10 (17.5)	9 (15.0)	15 (25.9)
Met Criteria for Open-label Treatment with PEM 1.0% at Visit 6, (Yes)	55 (96.5)	40 (70.2)	35 (58.3)	25 (43.1)
Reason for Open-label Treatment at Visit 6[b], N[c]	51	36	34	24
Treatment Failure (SFJ reflux >0.5 second)	50 (98.0)	11 (30.6)	6 (17.6)	3 (12.5)
Partial Treatment Failure (GSV incompetence)	15 (29.4)	11 (30.6)	13 (38.2)	9 (37.5)
Residual Visible Varicosities	23 (45.1)	25 (69.4)	25 (73.5)	16 (66.7)

[a] Reflux present and/or target veins patent/partially occluded despite successful administration of treatment at Visit 2. One Patient (75-1056, Vehicle group) had unsuccessful treatment administration at Visit 2 (failure to cannulate the vein; see Study 016 CSR Appendix 16.2.1.8).
[b] For patients who completed Visit 5/Week 8 CRF according to Protocol Amendment #1 (Study 016 Protocol Version 2.0 dated 04Feb2011). If a patient had more than 1 criterion that applied, the patient was counted in each subcategory. [c] N for each group is based on the number of patients' response to 'Met Criteria for Open-label Treatment with PEM 1.0% at Visit 6' as 'Yes' according to Amendment #1 only in each treatment group.
GSV: great saphenous vein; PEM: Polidocanol Endovenous Microfoam; SFJ: saphenofemoral junction {Source: ISE Table 29}

In Study 016, after 8 weeks, patients inadequately treated were able to receive treatment with open-label PEM 1.0% at Visit 6 (Table 19). In this setting, the dose-relationship was more apparent, as 70% of patients treated with blinded PEM 0.125% (control) received open-label treatments compared with 58% and 43% in patients treated with blinded PEM 0.5% and 1.0%, respectively. The reason for treatment with

open-label PEM 1.0% also varied by dose concentration. Patients who required open-label treatment due to failure of the first treatment (i.e. SFJ reflux > 0.5 secs) comprised 31% in the PEM 0.125% (control) group compared to 18% and 13% for PEM 0.5% and 1.0% dose concentration groups, respectively. The proportion of patients with residual visible varicosities as the predominant reason for open-label treatment was 69%, 74% and 67%, respectively in the PEM 0.125% (control), PEM 0.5% and PEM 1.0% groups.

Dose-relationship based on the frequency of venous thrombus AEs:

Table 20 shows that the frequency of venous thrombus AEs were lowest in patients in the PEM 1.0% and the pooled PEM 1.0% dose groups compared to those in the PEM 0.5% and PEM 2.0% dose groups, which can be considered an additional supportive finding for selecting the PEM 1.0% dose for the proposed indication.

Table 20 Number of patients with venous thrombus AEs in all PEM-treated patients

Vein	Treatment Group, n (All patients)					
	PEM 0.125%[c] N=130	PEM 0.5%[d] N=150	PEM 1.0%[e] N=837	PEM 2.0%[f] N=75	Pooled PEM 1.0%[a] N=1,170	Pooled PEM[b] N=1,333
Number of Patients with Venous Thrombus[g]	6 (4.6)	9 (6.0)	49 (5.9)	8 (10.7)	71 (6.1)	94 (7.1)
Number of Patients with Pulmonary Embolism[g]	0	0	0	0	0	0
Primary Location of Thrombus per Number of Patients in the Treatment Group[g]						
Common femoral vein thrombus extension	3 (2.3)	5 (3.3)	24 (2.9)	4 (5.3)	27 (2.3)	39 (2.9)
Proximal deep vein thrombosis						
Femoral vein	0	1 (0.7)	6 (0.7)	2 (2.7)	13 (1.1)	16 (1.2)
Popliteal vein	0	0	4 (0.5)	1 (1.3)	5 (0.4)	6 (0.5)
Distal deep vein thrombosis						
Posterior tibial vein	0	2 (1.3)	2 (0.2)	1 (1.3)	9 (0.8)	12 (0.9)
Anterior tibial vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Peroneal vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Isolated gastrocnemius and soleal vein thrombosis						
Soleus vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)
Gastrocnemius vein	3 (2.3)	1 (0.7)	10 (1.2)	0	14 (1.2)	18 (1.4)

[a]Studies 013, 014, 015 and 016; [b]Includes all patients treated with PEM; [c]Studies 014, 015, 016; [d]Studies 015, 016 and 017;
[e]Studies COM001, 001, 003, 0005, 008, 011, 012, 013, 015, 016 and 017; [f]Studies 008 and 015;
[g]Percents are based on number of patients (N) in each treatment group. {Source: Sponsor's Table in ISS}

Summary of Dose Response Results

The PEM 2.0% dose is not chosen for the proposed indication because:

- The symptom and appearance results in the PEM 2.0% dose group were only slightly improved compared to the lower PEM dose concentrations, with only a minor added benefit from using twice the concentration of PEM 1.0%.
- For duplex responder endpoint, the results of the PEM 2.0% and 1.0% dose groups were similar.

The PEM 0.5% dose is not chosen for the proposed indication because:

- While the results of the primary (symptom improvement) and co-secondary (improvement in appearance) endpoints suggest that the 0.5% and 1.0% dose concentrations were generally comparable, for the Duplex Responder endpoint, PEM 1.0% was notably more effective compared to PEM 0.5%.

The PEM 1% dose is chosen for the proposed indication because of the following dose response findings:

- The integrated analysis of dose response showed a statistically significant linear trend across PEM concentrations from 0.125% to 2.0% for the response in appearance endpoints of IPR-V^3 (p=0.0011) and PA-V^3 (P=0.0001), and a marginal linear trend in the change in VVSymQ scores (P=0.1303).
- In both Study 015 (Table 18) and Study 016 (Table 19), the percent of patients with treatment failure (SFJ Reflux >0.5 sec) and that of patients with partial treatment failure (GSV incompetence) were lowest in the PEM 1.0% group (34.3% and 37.1%, respectively, in Study 015, and 12.5% and 37.5%, respectively, in Study 016) compared to the other PEM dose groups.
- In the safety analyses, the frequency of venous thrombus AEs was lowest in the PEM 1.0% dose group (Table 20).
- In the Integrated Analyses, the percent of responders as determined by duplex ultrasound was substantially greater in the PEM 1.0% group (83.5%) than in the other PEM dose groups (Table 21 and Figure 7). Table 21 also shows that for Study 015, the percent of duplex responders in the PEM 1.0% groups was 80.4%, and for Study 016 it was 86.2%.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Both Studies 015 and 016 include the following long-term objectives:

(1) Studies 015 & 016: To evaluate the durability of efficacy at 1 year as measured by:
   a. VVSymQ score, based on responses in a daily e-diary;
   b. Improvement of appearance, based on IPR-V3 and PA-V3 scores; and
   c. Response to treatment, based on duplex ultrasound findings.

(2) Study 016: To evaluate the 1-year and long-term 5-year durability of efficacy as measured by annual assessments of:
   a. Improvement of Symptoms (VVSymQ) using the VEINES-QOL/Sym paper questionnaire
   b. Improvement of Appearance based on the site physician's assessment and the patient's self-assessment
   c. Elimination of reflux or occlusion of the target vein(s) using duplex ultrasound

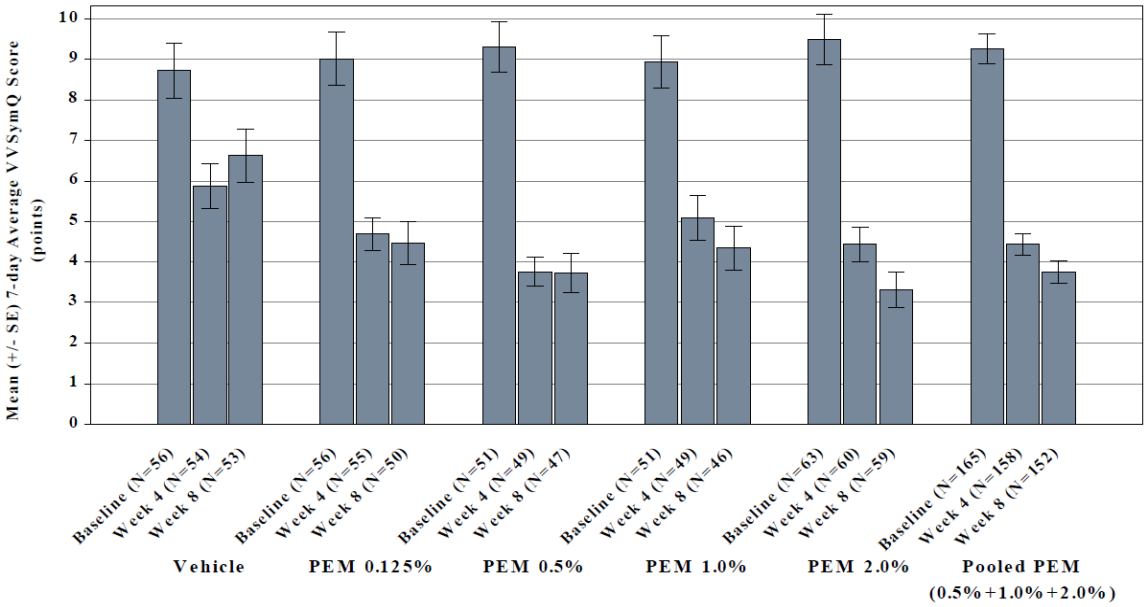
The 1-year and 5-year follow-up studies are currently on-going.

Most of the beneficial effect of treatment with PEM 0.5%, 1.0% and 2.0% is apparent by

4 weeks after treatment, with incremental improvement at 8 weeks in both Studies 015 and 016 where mean and median VVSymQ and PA-V^3 scores and changes from baseline were calculated by visit (baseline, Week 4 and Week 8). For the IPR-V^3 endpoint, only baseline and Week 8 photographs were assessed by the IPR panel; therefore, efficacy at Week 4 were not assessed for the IPR-V^3 endpoint.

For example, Figure 8 shows that in Study 015 at Week 8, patients in the PEM 0.5%, 1.0% and 2.0% treatment groups had a reduction (symptom improvement) the mean VVSymQ score by approximately 60% of the baseline mean value, compared with a decline of approximately 20% in the Vehicle placebo group; much of this decrease in the PEM groups was apparent at Week 4. PA-V^3 scores show the same trend.

Figure 8 Mean (±SE) VVSymQ Scores by Treatment Group and Visit (OC), Study 015 Efficacy Population



{Source: Sponsor's Figure 7 in Clinical Summary of Efficacy}

Similar results were observed in Study 016 with the PEM 0.5% and 1.0% treatment groups. These results demonstrate that most of the beneficial effect of treatment with PEM 0.5%, 1.0% and 2.0% is apparent by 4 weeks after treatment, with incremental improvement at 8 weeks in Studies 015 and 016.

6.1.10 Additional Efficacy Issues/Analyses

The tertiary efficacy variables in Studies 015 and 016 were:

1. Duplex ultrasound response, which was assessed by the study site ultrasonographer. The ultrasound based assessment of venous reflux is considered a measure of the physiological response to treatment, and therefore a measure of efficacy.

2. Change from baseline to Week 8 in the Venous Clinical Severity Score (VCSS), which was assessed by the study physician
3. Change from baseline to Week 8 in the Venous Insufficiency Epidemiological and Economic Study – Quality of Life/Symptoms (VEINES-QOL/Sym) score, which was assessed by the patient

Response to Treatment as Determined by Duplex Ultrasound: Response to treatment, as assessed by duplex ultrasound examination at Week 8 employing LOCF, was compared between treatment groups using the CMH chi-square test stratified by site.

Response was defined as:

- Elimination of reflux through the SFJ, as measured in the GSV 1-3 cm distal to the SFJ, where reflux is demonstrated by retrograde flow of >0.5 seconds following augmentation of flow by calf compression and subsequent release (shown on duplex ultrasound and spectral display); and/or
- Complete occlusion of the GSV and/or other major accessory target veins (AASV, PASV), as measured within 10 cm of the SFJ, where occlusion is defined as the demonstration of incompressibility of the target vein(s) with the absence of any flow by duplex ultrasound.

All trunk veins (i.e., the proximal GSV, AASV or PASV) with findings of reflux at screening, as assessed by a blinded review of screening duplex data by the Sponsor's medical monitor, were designated as target veins and included in this analysis. PEM 0.125% (control) was chosen as the control group for this analysis to minimize the potential for bias.

For both Studies 015 and 016, the pooled PEM groups were statistically superior to PEM 0.125% (control) based on Duplex ultrasound response (Table 21). For Study 015, 75% of patients in the pooled PEM 0.5%, 1.0% and 2.0% treatment group met the criteria for response to treatment compared to 42% of patients in the PEM 0.125% (control) group (P<0.0001). Analysis of the Nonzero Correlation (Linear Trend) showed a dose response (P<0.0001) with the percent of responders increasing as the PEM dose concentration increased. For Study 016, too, 85% of patients in the pooled PEM 0.5% and 1.0% treatment group met the criteria for response to treatment compared to 60% of patients in the PEM 0.125% (control) group (P=0.0002).

The majority of patients from Studies 015 and 016 in the PEM (pooled) group met the response to treatment criteria because they had "both Elimination of SFJ Reflux and Complete Occlusion of All Target Veins" (42% and 46% of patients, respectively). In the PEM 0.125% (control) group for Studies 015 and 016, this criterion was achieved by only 18% and 26% of patients, respectively.

Table 21 Number of Responders to treatment determined by Duplex Ultrasound at Week 8 (LOCF)

	Treatment Group, n (%)						
Study Parameter	Placebo (N=56)	PEM 0.125% (control) (N=57)	PEM 0.5% (N=51)	PEM 1.0% (N=51)	PEM 2.0% (N=63)	-	Pooled PEM (PEM 0.5%+ 1.0%+ 2.0%) (N=165)
Study 015							
Responders[a] n (%)	3 (5.4)	24 (42.1)	30 (58.8)	41 (80.4)	52 (82.5)	-	123 (74.5)
[95% Confidence Interval][b]	[1.1,14.9]	[29.1,55.9]	[44.2,72.4]	[66.9,90.2]	[70.9,90.9]	-	[67.2, 81.0]
Elimination of SFJ Reflux Only	3 (5.4)	10 (17.5)	9 (17.6)	11 (21.6)	8 (12.7)	-	28 (17.0)
Complete Occlusion of All Target Veins Only	0	4 (7.0)	5 (9.8)	9 (17.6)	11 (17.5)	-	25 (15.2)
Elimination of SFJ reflux + complete occlusion of all target veins	0	10 (17.5)	16 (31.4)	21 (41.2)	33 (52.4)	-	70 (42.4)
Comparison vs. Placebo[c]		<0.0001	<0.0001	<0.0001	<0.0001	-	<0.0001
Comparison vs. PEM 0.125% [c]			0.0539	<0.0001	<0.0001	-	<0.0001
P-value for Non-zero Correlation (Linear Trend)	<0.0001						
Study Parameter	Placebo (N=56)	PEM 0.125% (control) (N=57)	PEM 0.5% (N=60)	PEM 1.0% (N=58)	-	Pooled PEM (PEM 0.5% +1.0%) (N=118)	-
Study 016							
Responders[a] n (%)	1 (1.8)	34 (59.6)	50 (83.3)	50 (86.2)	-	100 (84.7)	-
Elimination of SFJ Reflux Only	1 (1.8)	16 (28.1)	22 (36.7)	20 (34.5)	-	42 (35.6)	-
Complete Occlusion of All Target Veins Only	0	3 (5.3)	1 (1.7)	3 (5.2)	-	4 (3.4)	-
Elimination of SFJ reflux + complete occlusion of all target veins	0	15 (26.3)	27 (45.0)	27 (46.6)	-	54 (45.8)	-
Comparison vs. Placebo[c]		<0.0001	<0.0001	<0.0001	-	<0.0001	-
Comparison vs. PEM 0.125% [c]			0.0043	0.0009	-	0.0002	-
Integrated Efficacy Population (Studies 015 & 016)							
Study Parameter	Placebo (N=112)	PEM 0.125% (control) (N=114)	PEM 0.5% (N=111)	PEM 1.0% (N=109)	PEM 2.0% (N=63)	Pooled PEM (PEM 0.5%+ 1.0%) (N=220)	Pooled PEM (PEM 0.5%+ 1.0%+ 2.0%) (N=283)
Responders[a] n (%)	4 (3.6)	58 (50.9)	80 (72.1)	91 (83.5)	52 (82.5)	171 (77.7)	223 (78.8)
[95% Confidence Interval][b]	[0.98,8.89]	[41.35,60.36]	[62.76,80.1]	[75.16,89.9]	[70.90,90.95]	[71.65,83.04]	[73.57,83.41]
Elimination of SFJ Reflux Only	4 (3.6)	26 (22.8)	31 (27.9)	31 (28.4)	8 (12.7)	62 (28.2)	70 (24.7)
Complete Occlusion of All Target Veins Only	0	7 (6.1)	6 (5.4)	12 (11.0)	11 (17.5)	18 (8.2)	29 (10.2)
Elimination of SFJ reflux + complete occlusion of all target veins	0	25 (21.9)	43 (38.7)	48 (44.0)	33 (52.4)	91 (41.4)	124 (43.8)
P-value for Non-zero Correlation (Linear Trend)[c]	<0.0001						

[a] Patients with elimination of reflux through the SFJ or/and complete occlusion of an incompetent GSV, PASV and/or AASV at screening. If a patient fulfilled any of the duplex criteria, the patient was counted only once for this row. [b] Exact 2-sided 95% for proportion based on Clopper-Pearson methodology.
[c] P-value from the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by study.
Note: Percents are based on the number (N) of patients in the Integrated Efficacy Population in each treatment group.
AASV: anterior accessory saphenous vein; GSV: great saphenous vein; LOCF: last observation carried forward; PASV: posterior accessory saphenous vein; PEM: Polidocanol Endovenous Microfoam; SFJ: saphenofemoral junction. {Source: Sponsor's Tables 8 &9 in Summary of Clinical Efficacy}

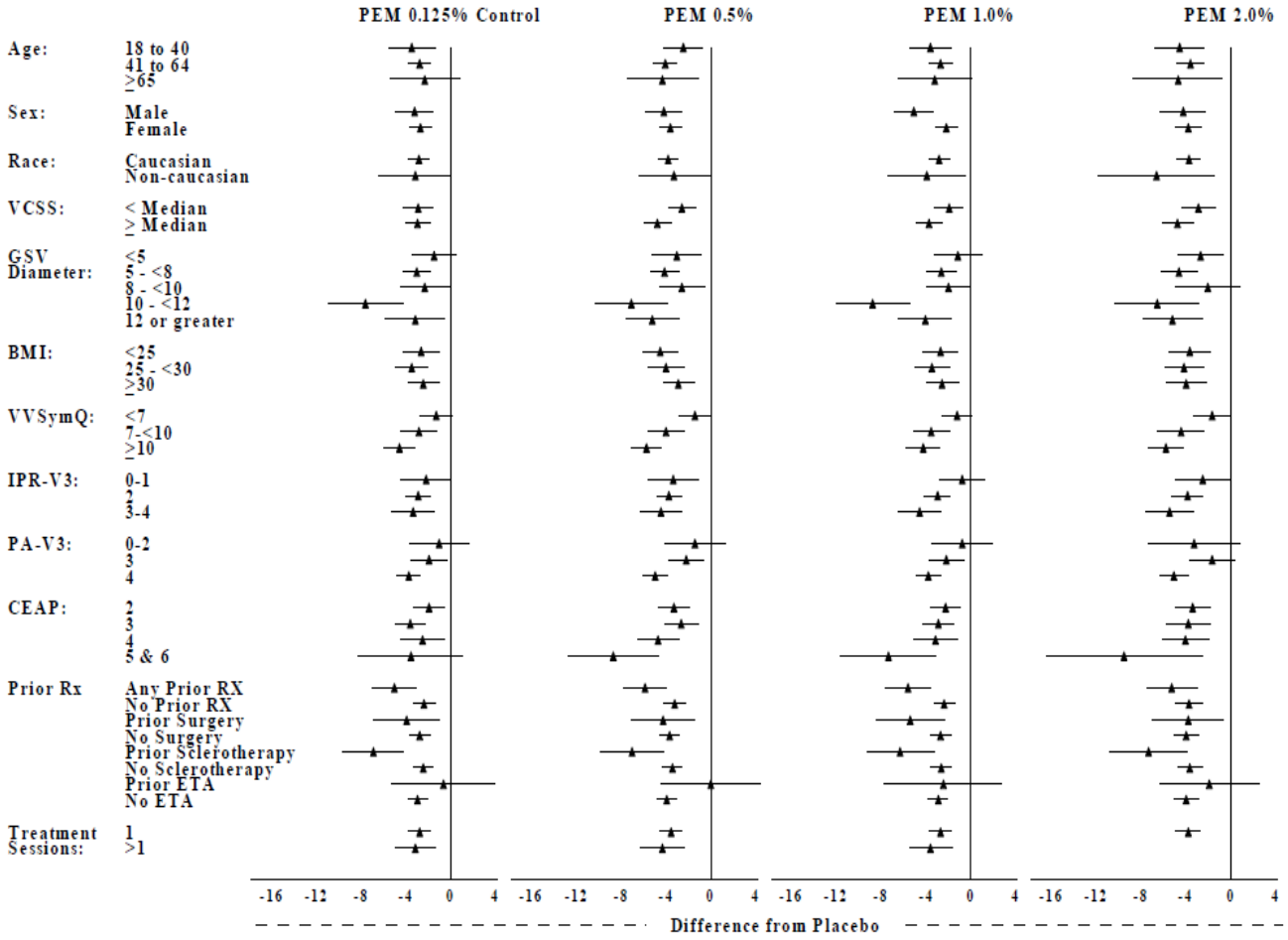
The Integrated Efficacy Population (Table 21) also shows the same findings in duplex ultrasound examination at Week 8 with a higher percentage of patients in the pooled PEM (0.5%, 1.0% and 2.0%) group than the PEM 0.125% (control) group (79% [95%

CI: 73.6, 83.4] vs. 51% [95% CI: 41.4, 60.4]). Each of the individual PEM dose concentrations was also superior to PEM 0.125% (control) based on duplex response (72%-84% vs. 51%). Analysis of the Nonzero Correlation (Linear Trend) showed a dose response (P<0.0001) with the percent of responders increasing as the PEM dose concentration increased.

Comparison of results of subpopulations

Figure 9 is a forest plot showing that the point estimates with 95% confidence intervals of the difference in the VVSymQ scores at Week 8 from baseline for each PEM dose concentration and for all subgroups were consistently better than Vehicle placebo. Similar results were obtained for subgroup analyses of the IPR-V^3 and PA-V^3 co-secondary endpoints.

Figure 9 VVSymQ Treatment Effect at Week 8 (LOCF) by Subgroup: Difference from Vehicle Placebo with 95% Confidence Intervals, Integrated Efficacy Population



NOTE: Horizontal lines for each subgroup factor represent the 95% Confidence Interval for the estimate of the difference (triangle on line) of PEM from Vehicle placebo based on adjusted means from ANCOVA models, unadjusted for multiple comparisons. Source: ISE Appendix 12.1.2 Figure 6

Some of the apparent differences in the PEM treatment effect observed in subgroups were attributable to small sample sizes or variability in placebo response across subgroups, rather than differences in magnitude of PEM treatment response (i.e., men vs. women in VVSymQ). In general, all subgroups benefited from PEM treatment. No sub-group had either substantially greater or lesser differences in outcome, although patients with more severe chronic venous insufficiency at baseline (i.e., subgroups with higher VVSymQ, IPR-V^3, PA-V^3 and VCSS scores) had the largest treatment effects.

Table 22 Primary efficacy endpoint (VVSymQ scores) by CEAP classification (Integrated Efficacy Population)

CEAP Grade	Number PEM treated	Number Placebo treated	Estimate (95% CI)
2 (varicose veins)	122	41	-2.96 (-4.12, -1.79)
3 (edema)	81	43	-3.09 (-4.34, -1.83)
4 (skin changes)	68	20	-3.94 (-5.57, -2.30)
5 & 6 (skin changes with healed and active ulceration)	10	5	-8.48 (-12.34, -4.61)

For all CEAP classification subgroups, the pooled PEM group showed consistently improved VVSymQ scores at Week 8, compared to Vehicle placebo (Table 22). The higher CEAP classifications show the largest improvements in symptoms; however, the sample size for Grade 5 & 6 groups was much smaller than the other groups. Across CEAP classification subgroups the placebo responses were lower with higher CEAP classification, with the Vehicle placebo group adjusted mean change from baseline in VVSymQ score ranging from 2.15 (worsening) in the Grade 5 & 6 group to -2.73 in the CEAP Grade 2 group. The magnitude of the adjusted mean change from baseline for the pooled PEM group was similar across CEAP classification subgroups. The adjusted mean change from baseline values for Grade 2, Grade 3, Grade 4 and Grade 5&6 were as follows: -5.69, -5.15, -5.72, and -6.33, respectively, again suggesting that variations in magnitude of observed treatment effects across CEAP classification subgroups were largely due to variation in placebo responses across subgroups rather than differential PEM treatment effects.

Table 23 Primary efficacy endpoint (VVSymQ scores) by GSV Diameter (Integrated Efficacy Population)

Baseline GSV diameter	Number PEM treated	Number Placebo treated	Estimate (95% CI)
< 5mm	50	20	-2.28 (-3.98 , -0.59)
5 to <8 mm	106	49	-3.79 (-4.91, -2.66)
8 to <10 mm	54	17	-2.17 (-4.03, -0.32)
10 to <12 mm	27	6	-7.45 (-10.36, -4.54)
≥12 mm	37	15	-4.80 (-6.77, -2.83)

For all GSV diameter categories (Table 23), too, the pooled PEM group showed consistently greater improvement in symptoms at Week 8, as measured by the VVsymQ, compared to Vehicle placebo.

In the pooled PEM group when compared to Vehicle placebo, the larger GSV diameter groups of (10 to <12 mm) and (≥12 mm) show the largest improvements in symptoms; however, the sample sizes for both of these groups were the smallest. The treatment effects across GSV subgroups are partly attributable to differences in placebo response in these groups, which was lowest in the 10 to <12 mm group (2.57, i.e. worsening), and highest in the <5 mm group (-3.16), while the magnitude of the adjusted mean change from baseline for the pooled PEM group was similar across GSV diameter subgroups (from <5 up to ≥12 mm) at -5.44, -5.60, -5.29, -4.88, and -6.45, respectively.

Conclusions of Efficacy Results

Table 24 provides a summary of the treatment effects (pooled PEM vs. Vehicle placebo or PEM 0.125%) for each of the endpoints in Studies 015 and 016.

Table 24 Summary of results from the primary, secondary and tertiary efficacy endpoints for Studies 015 & 016

Study Endpoint		Study 015[a]			Study 016[a]		
Change from Baseline to Week 8[b] in:		Treatment Effect	[95% CI]	*P*-value	Treatment Effect	[95% CI]	*P*-value
Primary	VVSymQ (LOCF)	-3.31	[-4.31,-2.30]	<0.0001	-3.53	[-4.63,-2.42]	<0.0001
Co-Secondary	IPR-V^3 (LOCF)	-0.80	[-0.98,-0.62]	<0.0001	-0.79	[-0.98,-0.60]	<0.0001
	PA-V^3 (LOCF)	-1.44	[-1.75,-1.12]	<0.0001	-1.50	[-1.81,-1.19]	<0.0001
Tertiary	Duplex Response (LOCF)[c]	32.4%	not calculated	<0.0001	25.1%	not calculated	0.0002
	VCSS	-3.21	[-3.88,-2.54]	<0.0001	-3.58	[-4.35,-2.80]	<0.0001
	VEINES-QOL	13.50	[9.97,17.02]	<0.0001	14.18	[10.47,17.89]	<0.0001

[a] Results from primary analysis ANCOVA models; Treatment Effect = difference between pooled PEM and Vehicle placebo in adjusted mean.
[b] For duplex response, study endpoint is evidence of response at Week 8 (LOCF).
[c] For duplex response, the difference in percent of responders between pooled PEM and PEM 0.125% (control) is provided as the Treatment Effect, while the reported *P*-value is from the primary analysis CMH chi-square test.
CI: confidence interval; IPR-V^3: Independent Photography Review – Visible Varicose Veins; LOCF: last observation carried forward;
PA-V^3: Patient Self-Assessment of Visible Varicose Veins; VCSS: Venous Clinical Severity Score ; VEINES-QOL: Venous Insufficiency Epidemiological and Economic Study-Quality of Life; VVSymQ: Varicose Vein Symptoms Questionnaire {Source: Summary of Clinical Efficacy Table 10}

The improvement in symptoms from baseline to Week 8 was statistically significantly greater in the pooled PEM treatment group than in the Vehicle placebo group (primary endpoint; *P*<0.0001). Treatment with PEM also resulted in statistically significantly greater improvement in appearance as assessed by the patient using the PA-V^3 instrument (*P*<0.0001), and as assessed by the blinded Independent Photography Review Panel (3 clinicians) using the IPR-V^3 instrument to rate patient photographs (*P*<0.0001). Results for the tertiary efficacy analyses, duplex ultrasound response, improvement in VCSS and improvement in the modified VEINES-QOL, were all highly statistically significant (*P*<0.0001) in favor of PEM versus Vehicle placebo (or for duplex ultrasound response versus PEM 0.125% control). These results show consistently that treatment with PEM leads to an improvement in the symptoms and appearance of varicose veins, duplex ultrasound response, improvement in the clinical severity of venous disease and improvement in patients' quality of life.

7 Review of Safety

Safety Summary

PEM is injected in small volumes at low total doses for a local sclerotic effect, usually only once, and does not reach significant levels in the systemic circulation. Thus, in addition to the conventional safety parameters, the safety review is focused on local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses and pigmentation) and on the following submission-specific safety concerns:

(i) The potential for stroke due to polidocanol microfoam (bubbles) reaching the cerebral circulation via a patent foramen ovale
(ii) Deep vein thrombosis (DVT), and
(iii) Potential allergic or anaphylactic reactions.

The Safety Population is defined as all patients who received at least 1 study treatment (i.e., PEM, saline or Vehicle placebo, or other study treatment) in any of the 12 clinical studies pooled (See section 5.3). Two patients who participated in a clinical study of PEM that was prematurely discontinued, (Study 007 at a single study site in the United Kingdom with open-label PEM 1.0% as part of the study investigator training procedure), were excluded from the Safety Population.

Safety data in the current submission is based on 1,333 patients who received PEM, of which 907 were followed for ≥91 days, 527 for ≥6 months and 483 for ≥1 year.

Saline and Vehicle solutions were used as placebo in the placebo-controlled studies of PEM: both Saline placebo and Vehicle placebo are referred to as "Placebo."

Calculation of the total dose of polidocanol in each volume of PEM administered to patients in the clinical trials suggests that patients were exposed to small doses which contains <19.5 mg of polidocanol (i.e., less than $1/5^{th}$ of the polidocanol contained in the maximal dose of liquid polidocanol (Asclera®)).

No deaths or non-fatal serious adverse events (SAEs) attributed to the study treatment were reported. However, there were four deaths: 3 in patients treated with PEM and 1 patient treated with comparator sclerotherapy. All deaths occurred several months post-treatment. Three deaths were related to comorbid conditions (heart failure, cirrhosis liver and prostate cancer) and one death was from a motor-vehicle accident.

There were 36 patients who experienced 46 SAEs including the 4 deaths, of which 26 patients were treated with PEM and 10 were treated with a comparator. The non-fatal SAEs included spinal osteoarthritis, venous thrombosis limb (3 patients), gastric obstruction, cellulitis (in untreated leg), diverticulitis, sick sinus syndrome, trachea-bronchitis, breast cancer and recurrence of lymphoma.

There were 13 early discontinuations due to an AE (of which 12 were treated with PEM), including the 4 deaths.

Of 797 patients treated with PEM 1%, 56 (7%) had one or more severe AEs including

pain in the extremity (26 patients), headache (10 patients), muscle spasms (4 patients), venous thrombosis limb (3 patients) and inflammation, tenderness, paresthesia, pruritis and vein pain (2 patients each).

The submission-specific AEs included the potential for stroke, neurological events, deep vein thrombosis, anaphylactic reactions and local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses and pigmentation).

Potential for stroke: Among 1,333 patients exposed to PEM, which included 60 patients with confirmed patent foramen ovale (PFO) and micro-bubbles detected in the middle cerebral artery by Transcranial Doppler, only one patient complained of "twinky lights" lasting about 20 seconds about one hour after treatment. Extensive screening for neurological effects with diffusion-weighted MRI at 24 hours and T2 MRI imaging at 28 days post treatment in a study of 82 patients (60 had demonstrable PFO) did not reveal abnormalities in the MRIs on post-treatment scans. One more patient (Patient 022-2297 in Study 001) reported TIA-like symptoms in the hours following treatment; this patient was treated with PEM produced using the original gas mixture containing (b) (4) This patient did not report for medical care and had no sequelae.

While there are individual case reports in the medical literature of neurological events following sclerotherapy, most of these patients recover from stroke with only 4 patients sustaining non-reversible neurological deficits. On the other hand, none of the large studies and randomized clinical trials (totaling > 37,000 treatments of varicose veins) in the medical literature reported any major neurological complications, underscoring the relative infrequency of major neurological complications associated with sclerotherapy.

Thus, in the PEM clinical trials submitted in this NDA, there was no signal that PEM treatment was associated with an increase in neurological adverse events.

Venous thrombosis: In PEM Studies 015, 016, 017 and 008, duplex ultrasound surveillance of the leg veins was made at screening and on a minimum of 3 occasions following the initial study treatment and twice more after optional open-label treatments. The ultrasound images were reviewed by the Venous Thromboembolic Event Review Board (VTERB). 96 of 1,333 (7.2%) patients had venous thrombus detected by ultrasound following PEM treatment; 2 patients had venous thrombus AEs 53 days to 9 months after treatment. Thus, 94 patients (7.1%) had treatment emergent venous thrombus AEs. Of the 1,170 patients treated with PEM 1.0%, 6.1% (71 patients) had venous thrombus AEs, a per-treatment session rate of 5.1%.

The most common type of venous thrombus was asymptomatic, non-occlusive, common femoral vein thrombus observed in 39 (2.9%) PEM-treated patients. The second type of venous thrombosis was the isolated gastrocnemius and soleal vein thrombosis (IGSVT) which were observed in 1.4% (19 patients) during detailed duplex ultrasound evaluations of the calf, and caused no symptoms.

Deep vein thromboses (DVT) were detected by ultrasound in 38 of 1,333 (2.8%) PEM-treated patients: distal DVT in 1.1% and proximal DVTs in 1.7%. One percent of 1,333 PEM-treated patients had proximal, symptomatic thrombi. The venous thrombi AEs

resolved or stabilized rapidly (median of 29 days) irrespective of whether or not the patient was treated with anticoagulants in all but 3 patients. Most patients with DVT (79%) or IGSVT (84%) did not receive anticoagulants.

51 of 97 patients with venous thrombus AEs were treated with anti-coagulants. About 70% of patients with proximal DVT (thrombus in femoral vein or popliteal) received anticoagulants; the median time to stabilization or resolution was 87 days. Most patients with DVT (79%) and most with IGSVT (84%) did not receive anticoagulants; half of the patients with common femoral vein thrombus extensions were managed with ultrasound observation and did not receive anticoagulants.

No patient had a diagnosis of pulmonary embolism.

The venous thrombi that occurred in the PEM studies were small (median thrombus volume = 0.7 cm^3, median length = 24.5 mm, largest thrombus volume = 5.41 cm^3, giving an average Marder scale of 5, compared to much larger thrombus volumes reported in the literature with an average Marder scale of 20).

The male sex was statistically significantly (P=0.021) associated with the occurrence of venous thrombus AEs following PEM treatment. There is an incremental association between increasing volume of PEM administered and incidence of venous thrombus AE; however, this was not statistically significant (P=0.095). There was no increased risk of venous thrombus AEs in patients who received multiple treatment sessions.

Anaphylactic or hypersensitivity reactions: In the 1,333 patients treated with PEM, there were no anaphylactic or major hypersensitivity reactions. Five patients experienced severe possible hypersensitivity events (two experienced localized swelling, and one each reported chest discomfort, cough and pruritus); 2 more patients reported AEs of "allergy." Seventeen (3.9%) of 427 PEM treated patients and 9 (6.0%) of 151 placebo-treated patients experienced possible hypersensitivity reactions (pruritus, edema peripheral, and rash) within 1 day of study treatment. These possible hypersensitivity reactions appeared to increase with the PEM dose-concentration.

The AEs most commonly observed in the clinical studies of PEM are 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. In contrast to endovenous thermal ablation (ETA), no patient required anesthesia or sedation prior to study treatment. Post-procedural pain resolved within 1 week in 80% of the cases reported, and a few PEM-treated patients were treated with opioid analgesics within 10 days of the study treatment procedure (1.3% of PEM-treated patients in the pooled, placebo-controlled studies).

In the pooled clinical studies of PEM, the only signal for a treatment-related change in laboratory parameters was a slight but consistent decrease from baseline in hemoglobin and hematocrit in PEM-treated patients; for hemoglobin, this decrease ranged from 0.1 to 0.3 g/dL, and for hematocrit it ranged from 0.2% to 1.0%. It is possible that they are

related to the mobilization of peripheral fluid due to post-procedural use of compression stockings, or to the hemolysis of red blood cells caused by contact with the microfoam.

With regard to vital signs, there were no clinically important changes in diastolic BP, oral temperature, pulse rate or respiratory rate. Some patients had transient decreases in systolic BP of ≥20 mmHg; none were associated with symptoms or classified as an AE.

In lieu of a formal thorough QT study, confirmation of QT safety was ascertained by obtaining well-standardized ECGs in triplicate at peak plasma concentration during the PK study (VAP.VV008), which showed no dose-related effect of the PEM on QT_{cF}. Also, the results of ECG, Holter monitoring, cardiac enzymes, transthoracic ultrasound, oxygen saturation and end-tidal CO_2 evaluations consistently demonstrate no adverse cardiac or cardiopulmonary effects following treatment with PEM.

My conclusion is that there were no unexpected safety signals.

7.1 Methods

The sponsor submitted that investigators could not be blinded to treatment with PEM versus placebo, because it was not possible to create microfoam using the placebo solution (Saline or Vehicle). Therefore, investigators were not blinded to active treatment vs. placebo when assessing the relationship of an AE to study treatment. In the US Phase 3 studies, investigators were blinded to the PEM dose-concentration patients received during the blinded phase of those studies.

The Safety Population is defined as all patients who received at least 1 study treatment (i.e., PEM, saline or Vehicle placebo, or other study treatment) in any of the 12 clinical studies pooled. AEs were evaluated for five populations:

- Placebo-controlled Studies (the “PCS”) Population;
- All Studies, Excluding Study 017 (the “All Studies”) Population;
- All PEM Treatment Sessions (the “All PEM”) Population;
- All Saphenous Vein Treatments; and
- Long-term Follow-up (the “LTFU” Population).

The Placebo-Controlled Studies Population (PCS Population) is selected as the main population for estimating AE incidence, because they enrolled patients only in the US, and there were uniform standards for AE reporting and similar duration of post-treatment follow-up. In PEM-treated patients in the PCS Population, the SOCs in which AEs assessed as related to study treatment (i.e., possibly, probably or definitely related) occurred in ≥5% of patients were the general disorders and administration site conditions, musculoskeletal and connective tissue disorders, vascular disorders, and skin and subcutaneous tissue disorders SOCs. At the Preferred Term level, the related AEs that occurred in ≥5% of PEM-treated patients in the PCS Population were Pain in extremity (13.0%), Infusion site thrombosis (10.5%), Thrombophlebitis superficial

(8.7%), Limb discomfort (7.1%), and Venous thrombosis limb (5.5%).

In the All Studies Population, only the Study 017 is excluded, and AEs are evaluated for the main treatment period only. Since this population includes open-label studies, and studies that do not have uniform AE reporting procedures (e.g., in Study 001 in Europe, AEs were solicited from patients in the CRF, and AE data was collected using a daily patient diary, leading to a higher incidence of many common AEs) which may distort AE incidence across treatment groups, this is not an appropriate population to compare AE rates among the PEM dose-concentration groups.

The All PEM Population comprises all patients treated with PEM, including those treated with ETA + PEM (0.5% or 1.0%) in Study 017; data from both the main and optional OL treatment periods were evaluated. Compared with the All Studies Population, the All PEM Population includes an additional 220 PEM-treated patients.

The All Saphenous Vein Treatments Population comprises all patients who received treatments to the saphenous vein(s), and who were treated with active comparator (Surgery, sclerotherapy or ETA) or a therapeutic dose-concentration (0.5%, 1.0% or 2.0%) of PEM. AEs are evaluated for the main treatment period only. In this population, the percent of patients with one or more related events was highest in the Surgery treatment group (96%), was similar in the PEM 1.0% and Sclerotherapy groups (78%), and was lowest in the PEM 0.5% (48%), PEM 2.0% (41%) and ETA (29%) groups. Unlike Surgery, PEM and Sclerotherapy, which were used to treat the GSV, its tributaries and visible varicosities, ETA was used only to treat the proximal GSV.

The Long-term Follow-up (LTFU) Population includes data for 824 patients in Studies 001, 012 and 017, in which there was no Optional OL Treatment Period following the Main Treatment Period. The safety data in the LTFU population were limited to information on SAEs; however, in a small number of cases, non-serious AEs were reported. SAEs for 6 patients in Study 001 and 8 patients in Study 016 are not included in the pooled ISS database and therefore are not presented in the summary tables or listings for the LTFU Population.

In most of these studies, AE data were collected based on spontaneous reporting by the patient. However, in Study 001 in addition to spontaneous reporting, two methods of reporting AE data were used: (i) a Patient Diary Card on which patients were asked to record details of any illnesses of unusual feeling, and (ii) the CRF in which the study investigator solicited information on discoloration and bruising for the subjects. Thus, discoloration and bruising are reported more frequently for Study 001. Data from Study 001 are included in All Studies, All PEM Treatment Sessions and All Saphenous Vein Treatments Populations. The safety assessments performed in the clinical studies of PEM are shown in Table 25.

Table 25 By-study summary of safety assessments in PEM studies

Study	Vital Signs	Physical Examination	Venous Duplex Ultrasound	Chemistry and Hematology	Serum or Urine Pregnancy Test	Concomitant Medications	Concomitant Procedures	Magnetic Resonance Imaging	Transcranial Doppler Ultrasound	Precordial Ultrasound	Electrocardiogram	Holter Monitor	O_2 Saturation	Visual & Neurologic Assessments	Adverse Events
Placebo-controlled Studies															
013	X	S	X	S	S	X	-	-	-	-	-	-	-	-	X
015	S	S	X	X	S	X	X	-	-	-	-	-	-	-	X
016	S	S	X	X	S	X	X	-	-	-	-	-	-	-	X
017	S	S	X	X	S	X	X	-	-	-	-	-	-	-	X
Active-controlled Studies															
001	S	S	X	X[a]	S	X	-	-	-	-	-	-	-	-	X
Clinical Pharmacology Studies															
008	S	S	X	X[b]	S	X	-	-	-	-	X	X	-	-	X
Uncontrolled Studies															
COM001	S	S	X	X[a]	S	X	-	-	-	-	-	-	-	-	X
003	X	S	X	X	S	X	-	-	-	X	X	X	X[c]	X	X
0005	X	X	X	X[d]	S	X	-	-	-	-	X	X	X[c]	X	X
011	X	S	X	X[e]	S	X	-	-	S	X	-	-	-	S[f]	X
012	X	X	X	X	S	X	-	X	X	-	X	-	-	X	X
014	X	S	X	S	S	X	-	-	-	-	-	-	-	-	X

[a] On-study hematology and chemistry evaluations were performed only if additional study treatment was planned.
[b] In Study 008, hematology and chemistry evaluations were performed only at Screening; pharmacokinetic sampling and urinalysis were performed at Screening and post-treatment time points.
[c] End-tidal CO2 assessment also performed
[d] In Study 0005, urinalysis, pharmacokinetic parameters, coagulation times, cardiac enzymes and D-dimer were also assessed.
[e] In Study 011, PK sampling was also performed at Screening and on Study Day 0 (treatment day).
[f] Patients were screened for history of visual or neurological events; no examination was performed.
X= evaluation performed at one or more post-treatment time points (may also have been performed at Screening); S = evaluations performed at Screening only (or in the case of pregnancy test, before each study treatment only); "-" = evaluation not performed. [Source: ISS Table 5]

I requested FDA-library for a literature search on the AEs of stroke, venous thrombosis and/or anaphylactic reaction associated with the use of polidocanol foam or microfoam to treat varicose veins of the leg. I used the key words: polidocanol foam, varicose veins, sclerotherapy, saphenous vein, stroke, seizure, syncope, TIA, hemiparesis, embolism, scotoma, numbness, death, deep vein thrombosis, venous thrombosis, anaphylaxis, anaphylactic reaction, allergic reaction, hypersensitivity reaction. This literature search returned 11 articles which I reviewed to supplement this safety review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data reviewed includes data from 12 clinical studies of PEM in patients with varicose veins (Table 26): i.e., 4 placebo-controlled Phase 3 trials, 1 randomized, open-label, active-controlled Phase 3 trial, 1 open-label study of clinical pharmacology and safety, and 6 open-label Phase 2 trials.

Table 26 List of clinical studies for safety evaluation

Study	Treatment	Main Treatment Period Only[a]			Main and OL Treatment Period		
		Placebo-Controlled Studies (N=588)	All Studies (Excluding 017) (N=1264)	All Saphenous Vein Treatments (N=1240)	All PEM Treatment Sessions[b] (N=1333)	All Venous Thrombus Adverse Events[c] (N=97)	Long-Term Follow-Up (N=824)
COM001	PEM 1.0%	0	20 (1.6)	20 (1.6)	20 (1.5)	0	0
001	PEM 1.0%	0	437 (34.6)	437 (35.2)	437 (32.8)	11 (11.3)	416 (50.8)
	Surgery	0	0	94 (7.6)	0	0	90 (10.9)
	Sclerotherapy	0	0	125 (10.1)	0	1 (1.0)	124 (15.1)
003	PEM 1.0%	0	40 (3.2)	40 (3.2)	40 (3.0)	3 (3.1)	0
0005	PEM 1.0%	0	24 (1.9)	24 (1.9)	24 (1.8)	1 (1.0)	0
008	PEM 1.0%	0	9 (0.7)	9 (0.7)	9 (0.7)	1 (1.0)	0
	PEM 2.0%	0	12 (0.9)	12 (1.0)	12 (0.9)	2 (2.1)	0
011	PEM 1.0%	0	35 (2.8)	35 (2.8)	35 (2.6)	0	0
012	PEM 1.0%	0	83 (6.6)	83 (6.7)	82 (6.2)	10 (10.3)	77 (9.4)
013	Placebo	38 (6.5)	38 (3.0)	0	0	0	0
	PEM 1.0%	39 (6.6)	39 (3.1)	39 (3.1)	73 (5.5)[b]	10 (10.3)	0
014	PEM 0.125%	0	16 (1.3)	0	16 (1.2)	0	0
	PEM 1.0%	0	0	0	11 (0.8)[b]	1 (1.0)	0
015	Placebo	56 (9.5)	56 (4.4)	0	0	0	0
	PEM 0.125% (control)	57 (9.7)	57 (4.5)	0	57 (4.3)	2 (2.1)	0
	PEM 0.5%	51 (8.7)	51 (4.0)	51 (4.1)	51 (3.8)	4 (4.1)	0
	PEM 1.0%	52 (8.8)	52 (4.1)	52 (4.2)	210 (15.8)[b]	15 (15.5)	0
	PEM 2.0%	63 (10.7)	63 (5.0)	63 (5.1)	63 (4.7)	6 (6.2)	0
016	Placebo	57 (9.7)	57 (4.5)	0	0	0	0
	PEM 0.125% (control)	57 (9.7)	57 (4.5)	0	57 (4.3)	4 (4.1)	0
	PEM 0.5%	60 (10.2)	60 (4.7)	60 (4.8)	60 (4.5)	2 (2.1)	0
	PEM 1.0%	58 (9.9)	58 (4.6)	58 (4.7)	188 (14.1)[b]	18 (18.6)	0
017	ETA + Placebo	0	0	38 (3.1)	0	1 (1.0)	34 (4.2)
	ETA + PEM 0.5%	0	0	0	39 (2.9)	3 (3.1)	38 (4.6)
	ETA + PEM 1.0%	0	0	0	40 (3.0)	2 (2.1)	40 (4.9)
ALL	Placebo or ETA + Placebo	151 (25.7)	151 (11.9)	38 (3.1)	0	1 (1.0)	34 (4.2)
	Placebo	151 (25.7)	151 (11.9)	0	0	0	0
	ETA + Placebo	0	0	38 (3.1)	0	1 (1.0)	34 (4.2)
	PEM 0.125%	114 (19.4)	130 (10.3)	0	130 (9.8)	6 (6.2)	0
	PEM 0.5% or ETA + PEM 0.5%	111 (18.9)	111 (8.8)	111 (9.0)	150 (11.3)	9 (9.3)	38 (4.6)
	PEM 0.5%	111 (18.9)	111 (8.8)	111 (9.0)	111 (8.3)	6 (6.2)	0
	ETA + PEM 0.5%	0	0	0	39 (2.9)	3 (3.1)	38 (4.6)
	PEM 1.0% or ETA + PEM 1.0%	149 (25.3)	797 (63.1)	797 (64.3)	1170 (87.8)[b]	72 (74.2)	537 (65.2)
	PEM 1.0%	149 (25.3)	797 (63.1)	797 (64.3)	1130 (84.8)[b]	70 (72.2)	497 (60.3)
	ETA + PEM 1.0%	0	0	0	40 (3.0)	2 (2.1)	40 (4.9)
	PEM 2.0%	63 (10.7)	75 (5.9)	75 (6.0)	75 (5.6)	8 (8.2)	0

[a] Patients are summarized according to their initial treatment. These categories exclude data for the Optional OL Treatment Period.

[b] Patients who received PEM in the Main Treatment Period and also received PEM 1.0% in the Optional OL Treatment Period appear in more than one row. However, the column header counts a patient only once regardless of whether PEM was received in the Main Treatment Period, the Optional OL Treatment Period, or both. Therefore, the total of the rows is greater than the total number of patients in the column header.

[c] Includes all PEM-treated patients with venous thrombus AEs in the Main or Optional OL Treatment Periods. The 97 patients with venous thrombus AEs in the ISS database include 94 PEM-treated patients with venous thrombus AEs in the Main or Optional OL Treatment Period; one PEM-treated patient in the LTFU Period (061-6004 in Study 001); one patient treated with Sclerotherapy (Patient 023-2148 in Study 001); and one patient treated with ETA + Vehicle placebo (Patient 45-1009 in Study 017). The pooled ISS database does not include a venous thrombus AE that occurred in Patient 01-101 in Study 0005.

ETA: endovenous thermal ablation; ISS: Integrated Summary of Safety; OL: open-label; PEM: Polidocanol Endovenous Microfoam.

Data are displayed as number of patients (percent of patients). Source: Table 6 of ISS.

7.1.2 Categorization of Adverse Events

AEs and SAEs are reported using MedDRA Preferred Terms and patient-reported Verbatim Terms.

For the venous thrombus AEs (VTAEs), 3 different MedDRA preferred terms were employed, and one of these (MedDRA Preferred Term "Deep vein thrombosis") was further sub-categorized as Proximal or Distal.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data reviewed includes pooled data from the 12 clinical studies of PEM in patients with varicose veins listed in Table 26. These clinical studies were conducted using 2 different PEM formulations (see Section 5.3).

The exposure and safety data are reviewed pooling the effects produced by the two PEM formulations.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 27 Duration of follow-up of all PEM treatment sessions (N=1,333)[§]

Days of follow-up	
Mean (SD)	209.5 (170.0)
Median (min, max)	112.0 (1, 738)
Follow-up group (days)	***N (%) of patients***
≤30	108 (8.1)
31 – 90	318 (23.9)
91 – 180	380 (28.5)
181 – 360	45 (3.4)
>360	482 (36.2)

[§]Includes patients who received PEM in the Main Treatment Period, Optional OL Period or both. (Source: Sponsor's Table 7.6 in ISS.)

Table 27 shows an overall summary duration of follow-up for the 1,333 patients treated with PEM:

- 907 patients were followed for ≥91 days (3 months),
- 527 were followed for ≥181 days (6 months) and
- 482 were followed for ≥360 days (1 year).

This exposure to PEM is roughly consistent with the agreed-upon number of patients

between the Division and the sponsor at the End-of-Phase 2 meeting (29-Jun-2009) which stipulated a total exposure of 1000-1200 patients with about 500 patients followed for 1 year.

In the All Studies Population, 948 of 1,333 PEM-treated patients (85%) had 1 treatment session, 151 patients (14%) had 2 treatment sessions, and 14 patients (1%) had 3 treatment sessions. In the placebo group, 85% of patients had 1 treatment session and 15% had 2 treatment sessions.

The median total volume administered at any treatment session ranged from 12 to 15 mL in the PEM groups, and it was 10 mL in the placebo group. The maximum total volume administered at any treatment session ranged from 11 to 15 mL in the PEM groups and it was 10 mL in the placebo group. The median total volume administered at the first treatment session was 14 or 15 mL in the PEM 0.125%, 0.5%, and 1.0% groups, and it was 10 mL in the PEM 2.0% and placebo groups. In the Pooled PEM group, the median total volume administered at the first treatment session was 15 mL.

In the All Studies Population (i.e., Study 017 excluded, main treatment period only), the duration of the Main Treatment Period was about 50% longer for patients in the PEM 1.0% group than in the other PEM treatment groups (median of 92 days in the PEM 1.0% group and 62-64 days in the other PEM groups) because patients in the PEM 1.0% group were followed for a longer time than patients in the other PEM groups.

In the Open Label (OL) PEM 1.0% group (All PEM Population), the median total volume administered at the first treatment session was 14 mL, the median total volume administered across treatment sessions was 13 mL, and the median maximum total volume at any treatment session was 12 mL. Three hundred and thirty-eight (338) of 387 patients treated with OL PEM 1.0% (87%) had 1 treatment session, 48 patients (12%) had 2 treatment sessions, and 1 patient (0.3%) had 3 treatment sessions.

Table 28 Patient Disposition, PCS Population (Main Treatment Period only)

Status	Placebo[a] (N=151)	PEM 0.125%[b] (N=114)	PEM 0.5%[b] (N=111)	PEM 1.0%[a] (N=149)	PEM 2.0%[c] (N=63)	Pooled PEM (N=437)
Completed	149 (98.7)	113 (99.1)	111 (100)	146 (98.0)	63 (100)	433 (99.1)
Discontinued	2 (1.3)	1 (0.9)	0	3 (2.0)	0	4 (0.9)
Withdrew Consent	1 (0.7)	0	0	0	0	0
Adverse Event	0	0	0	0	0	0
Lost to Follow-up	1 (0.7)	1 (0.9)	0	3 (2.0)	0	4 (0.9)
Death	0	0	0	0	0	0
Pregnancy	0	0	0	0	0	0
Investigator Decision	0	0	0	0	0	0
Sponsor Decision	0	0	0	0	0	0
Protocol Violation	0	0	0	0	0	0
Other	0	0	0	0	0	0
Optional OL PEM 1.0% Treatment	141 (93.4)	82 (71.9)	67 (60.4)	54 (36.2)	32 (50.8)	235 (53.8)

[a] Studies 013, 015 and 016; [b] Studies 015 and 016; PEM 0.125% was a control in these studies.
[c] Study 015; OL: open-label; PEM: Polidocanol Endovenous Microfoam [Source: ISS Table 10]

Table 28 shows a summary of patient disposition for the PCS Population (Main Treatment Period). Across treatment groups, 98% to 100% of patients completed their study, and ≤2% of patients discontinued. One patient in the placebo group (0.7%) withdrew consent; 1 patient in the placebo group (0.7%) and 4 PEM-treated patients (0.9%) were lost to follow up. In the PCS Population studies, the percent of patients who received optional treatment with OL PEM 1.0% was highest in the placebo group (93%) and lowest in the PEM 1.0% group (36%).

7.2.2 Explorations for Dose Response

The **dose-concentrations** studied were: 0.125%, 0.5%, 1.0% and 2.0%.

The maximum **volume** of PEM administered varied across the clinical studies. Early on in Study 001, total volumes of up to 60 mL of PEM per treatment session were allowed; with these higher volumes of PEM, microfoam was more likely to enter non-target veins. Study 001 protocol was then amended to limit the maximum total volume per treatment session to 30 mL in France and 45 mL in all other countries. In subsequent studies, the maximum volume of PEM injected was 30 mL or less. For about half of the patients who participated in the pooled studies of PEM, including placebo-controlled Phase 3 Studies 015, 016 and 017 and PK and safety Study 008, the maximum volume that could be administered in a single treatment session was 15 mL. Because the Phase 3 efficacy and safety data were collected under protocols that limited the maximum volume per treatment session to 15 mL, this is the maximum volume per treatment session that is recommended for general clinical use in the labeling.

Table 29 Polidocanol content of the PEM dose-concentrations administered in the clinical studies

Volume of PEM	Amount of Polidocanol per PEM Dose-concentration			
	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%
1 mL	0.16 mg	0.65 mg	1.3 mg	2.6 mg
Volumes administered in clinical studies				
10 mL	-	-	13.0 mg[a]	26.0 mg[a]
15 mL	2.44 mg[b]	9.75 mg[c]	19.5 mg[d]	39.0 mg[e]
20 mL	-	-	26.0 mg[f]	-
30 mL	-	-	39.0 mg[g,h]	-
45 mL	-	-	58.5 mg[h,i]	-
60 mL	-	-	78.0 mg[h,j]	-

PEM: Polidocanol Endovenous Microfoam; [a] Study 008; [b] Studies 014, 015 and 016 (used as control in Studies 015 & 016)
[c] Studies 015, 016 and 017; administered immediately following endovenous thermal ablation in Study 017
[d] Studies 013, 015, 016 and 017; administered immediately following endovenous thermal ablation in Study 017; Study 008, 013, 014, 015 and 016 optional open-label treatment; [e] Studies 008 and 015 [f] Study 012
[g] Studies 001, 003, 011, 013; [h] Study 001 blinded and optional open-label treatments; during the study, the original 60 mL maximum volume per treatment session was later reduced to 30 mL in France and 45 mL in all other countries
[i] Study COM001 Main Treatment Period and Optional Open-label Treatment Period; [j] Study 0005
Note: In Study 017, PEM 0.5% or PEM 1.0% was administered in visible varicosities and other incompetent areas of the great saphenous vein system immediately following treatment of the great saphenous vein using endovenous thermal ablation (ETA). Source: ISS table 50.

Table 29 shows the total **dose** of polidocanol in each volume of PEM by PEM dose-concentration. Most patients in the clinical studies of PEM had been exposed to small

total doses of polidocanol. The maximum recommended dose of PEM, 15 mL of 1.0% foam, contains 19.5 mg of polidocanol, or less than 1/5th the polidocanol contained in the maximum dose of Asclera® (i.e., 10 mL, which contains 100 mg of polidocanol). The numbers in Table 29 suggest that at similar volumes, the amount of polidocanol contained for each dose-concentration of the foam is 13.3% (i.e., 2/15th or 1/7.5) of that in a similar volume and dose-concentration of polidocanol liquid.

Given the low systemic exposure (mean $AUC_{0-\infty}$ of 82191 ng/min/mL in male patients and 93612 ng.min/mL in female patients in the PEM 2.0% treatment group) and rapid clearance of polidocanol (terminal elimination half-life $T_{½}$ of ~100-150 minutes), it is likely that dose-related AEs would be associated with local effects of polidocanol rather than with increased systemic exposure to polidocanol.

In the All Studies Population, among the groups of patients treated with <11, 11 to 15 and >15 mL of PEM at the first PEM treatment session, patients treated with >15 mL had the highest percent of patients with one or more:

- AEs (70.7%, 69.5% and 88.9%, respectively) and
- severe AEs (2.7%, 4.8% and 9.4%, respectively).

The majority of patients treated with >15 mL at the first treatment session are from Study 001, in which AEs were collected using solicited data from CRFs and a patient diary, as well as via spontaneous patient report, leading to a much higher rate of AEs than in the other pooled clinical studies of PEM.

Because at the first treatment session only 36 placebo-treated patients received 11-15 mL and only 11 placebo-treated patients received >15 mL (2 of the 3 categories in this subgroup analysis), it is not possible to make meaningful comparisons between the PEM- and placebo-treated patients in these volume categories.

Table 30 Treatment-Emergent Adverse Events in ≥5% of patients that increased with higher PEM dose-concentration {in Placebo-Controlled Studies Population (Main Treatment Period only)}

MedDRA Preferred Term	Placebo[a] (N=151)	PEM 0.125%[b] (N=114)	PEM 0.5%[b] (N=111)	PEM 1.0%[a] (N=149)	PEM 2.0%[c] (N=63)	Pooled PEM (N=437)
Infusion site thrombosis	0	6 (5.3)	10 (9.0)	24 (16.1)	6 (9.5)	46 (10.5)
Limb discomfort	5 (3.3)	3 (2.6)	5 (4.5)	18 (12.1)	6 (9.5)	32 (7.3)
Venous thrombosis limb	0	3 (2.6)	5 (4.5)	12 (8.1)	4 (6.3)	24 (5.5)
Pruritus	9 (6.0)	3 (2.6)	4 (3.6)	6 (4.0)	6 (9.5)	19 (4.3)
Injection site pain	3 (2.0)	3 (2.6)	6 (5.4)	6 (4.0)	3 (4.8)	18 (4.1)
Headache	4 (2.6)	2 (1.8)	3 (2.7)	8 (5.4)	3 (4.8)	16 (3.7)
Contusion	3 (2.0)	1 (0.9)	0	14 (9.4)	0	15 (3.4)
Tenderness	2 (1.3)	0	1 (0.9)	11 (7.4)	1 (1.6)	13 (3.0)

[a] Studies 013, 015 and 016; [b] Studies 015 and 016; PEM 0.125% was a control in these studies; [c] Study 015
Notes: Data are displayed as number of patients (percent of patients). Percents are based on the number of patients (N) in each treatment group.
Patients are counted only once for each applicable Preferred Term and/or System Organ Class.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PEM: Polidocanol Endovenous Microfoam; Source: ISS Table 9.1

AEs occurring in at least 5% of patients in the PCS Population which increased with

higher PEM dose-concentration (Table 30) are: infusion site thrombosis, venous thrombosis limb, limb discomfort, injection site pain, headache, contusion, tenderness, and pruritus (for this last AE, the percent of patients in the placebo group with pruritus is also high, suggesting that it may be related to a factor that all treated patients have in common, such as the post-procedure compression protocol).

In the analysis of PEM dose-concentration as a single factor for venous thrombus AE, compared to patients treated with PEM 0.125%, the odds ratios for venous thrombus AE in patients treated with PEM 0.5%, PEM 1.0% and PEM 2.0% were 1.60 (95% CI: 0.52, 4.89), 1.43 (95% CI: 0.56, 3.65) and 2.99 (95% CI: 0.94, 9.49), respectively, suggesting that the odds of venous thrombus AE increase in patients treated with PEM dose-concentrations above 0.125%. A logistic regression analysis of the association of PEM dose-concentration with the occurrence of venous thrombus AE following the first treatment sessions (All PEM Population) was not statistically significant; this was also true when demographic characteristic, baseline characteristic or volume administered at first PEM treatment session were included as factors in the logistic regression.

7.3 Major Safety Results

7.3.1 Deaths

Table 31 Listing of deaths by most recent treatment before event onset, All Studies of PEM

Study/Patient # Age (years)/Sex	Serious Adverse Event (MedDRA Preferred Term) *Verbatim Term*	Onset Study Day / Days from Most Recent Treatment # PEM Sessions	Severity	Relationship to Study Treatment	Action Taken / Treatment	Outcome
Sclerotherapy						
001/024-3137 61/M	Prostate Cancer/ *Prostate Cancer*	38 / 37 NA	Severe	Unrelated	NA/Medication/ Hospitalization/ Prol. Hospitalization	Death
PEM 1.0%						
001/014-1233[a] 25/M	*Patient killed in a road traffic accident (only verbatim term is available)*	NA[b] / 698 1 treatment session	UNKN	Unrelated	NA / UNKN	Death
001/052-5143[a] 69/M	*Heart failure (only verbatim term available)*	NA[b] / 765 1 treatment session	Severe	Unrelated	NA / UNKN	Death
016/76-1025 61/F	Hepatic Cirrhosis *Cirrhosis of Liver*	174 / 111 1 treatment session	Severe	Unrelated	NA / Medication	Death
	Renal Failure Acute *Acute On Chronic Renal Failure*	174 / 111 1 treatment session	Severe	Unrelated	NA / Procedure	Death

[a] SAE(s) identified during review of Study 001 records; event(s) not in pooled ISS database but included in all counts/summaries in the ISS.
[b] Patient completed the Month 12 (i.e., final) visit for the main part of Study 001 and at the time of his death had not signed the consent to participate in the extension phase of the study from the start of Year 2 through the end of Year 5.
F: female; M: male; MedDRA: Medical Dictionary for Regulatory Activities; NA: not applicable; PEM: Polidocanol Endovenous Microfoam; Prol.: prolonged; SAE: serious adverse event; UNKN: unknown Source: ISS Table 28.

Four patients (3 PEM-treated patients and 1 patient treated with sclerotherapy) died during or following participation in clinical studies of PEM (
Table 31). All of these deaths occurred several months following study treatment; in 2 patients, the deaths occurred following completion of the study. Two of the deaths were related to concomitant conditions that pre-dated the patient's participation in the study and one death was accidental (a motor vehicle accident). Brief narratives follow.

Narratives:

i. **Patient 24-3137 (Prostate cancer)**: This was a 61-year-old Caucasian Frenchman with history of prostate enlargement since 1996. His concomitant medications included tamsulosin chlorhydrate for treatment of benign prostatic hypertrophy since 28-Nov-2002. On 09-Dec-2002, the patient received comparator treatment (sclerotherapy) in Study 001. On (b) (6) the patient was hospitalized for a prostatectomy during which prostate cancer and bone metastases were diagnosed. Prostatectomy was performed on (b) (6), followed by radiotherapy, oral cyproterone acetate and subcutaneous triptorelin pamoate. The patient died from complications of prostate cancer, including cachexia and infection, on (b) (6)

ii. **Patient 014-1233 (Verbatim term: Patient killed in a road traffic accident)**: This 25-year old man in the United Kingdom was treated with PEM 1.0% in Study 001 on 22-Jan-2002. He reported no past medical history other than varicose veins. The patient was killed in a motor vehicle accident on (b) (6) At the time of his death, the patient had completed the Month 12 study visit with no ongoing AEs, and he did not consent to participate in the Year 2-5 extension part of the study.

iii. **Patient 052-5143 (Verbatim term: Heart failure):** This 69-year-old Italian man with history of hypertension (on spironolactone) was treated with PEM 1.0% in Study 001 on 26-Apr-2002. On (b) (6) the patient died of heart failure. At the time of his death, he had completed the Month 12 study visit and had not consented to participate in the Year 2-5 extension part of the study.

iv. **Patient 76-1025 (Hepatic cirrhosis, Renal failure acute):** This 62-year-old Caucasian woman in the United States participated in Study 016. The patient had a history of hypertension, hepatitis C since 2009 and heroin addiction since 1977 (on recovery). Her concomitant medications included 25 mg of methadone daily and lisinopril with hydrochlorothiazide for hypertension. Screening laboratory values were within normal limits with the exception of ALT 83 U/L, AST 226 U/L, and total bilirubin 2.4 mg/dL. The patient received study treatment on (b) (6) (Study Day 1: Vehicle), (b) (6) (Study Day 7: Vehicle), and (b) (6) (Study Day 63: open-label PEM 1.0%). On (b) (6) (Study Day 179), she presented to the emergency department reporting jaundice, increasing abdominal girth with discomfort, nausea, cough and generalized weakness for the past 2 to 3 days. She was admitted with diagnoses of ascites secondary to cirrhosis of the liver with worsening hepatic function, acute on chronic renal failure, and right lower lobe pneumonia. She died on (b) (6) Study Day 182 (about 4 months after the most recent treatment with PEM). The death certificate recorded the cause of death as cirrhosis, with chronic renal failure and hypertension listed as other significant conditions contributing to death.

Reviewer's comments: A review of the case report forms of these four subjects who died verifies that in three patients there were coexisting diseases (prostate cancer, hypertensive heart disease and cirrhosis liver with hepatorenal syndrome) to which death could be attributed, and that the fourth patient died from injuries incurred in a motor vehicle accident.

7.3.2 Nonfatal Serious Adverse Events

Through 15-Jul-2012, 36 patients participating in clinical studies of PEM experienced a

total of 46 SAEs. Four patients experienced fatal events (see section 7.3.1), and the remaining 32 patients had non-fatal SAEs. Of the 36 patients with SAEs, 26 patients were treated with PEM and 10 patients were treated with comparator (i.e., 2 patients treated with placebo, 5 patients treated with surgery, and 3 patients treated with sclerotherapy; no patient treated with ETA experienced an SAE).

In the PCS Population (Main Treatment Period only), 13 PEM-treated patients (3.0%) and 1 placebo patient (0.7%) experienced severe AEs (i.e., <5% of patients in all treatment groups). At the Preferred Term Level, severe AEs that occurred in >1 PEM-treated patient were venous thrombosis limb (4 of 437 PEM-treated patients, 0.9%) and DVT (2 of 437 PEM-treated patients, 0.5%); the rest of the severe AEs were in one patient each: pelvic fracture, thrombophlebitis (superficial), pruritus, rotator cuff syndrome, pain in extremity, muscle spasms and arthralgia. The one placebo-treated patient experienced migraine (1 of 151 placebo-treated patients, 0.7%) as severe AE. Overall, severe AEs occurred in 3% of PEM-treated patients in the PCS Population, <6% of PEM-treated patients in the All Studies Populations (higher in the pooled PEM group compared to the placebo group), and <4% of pooled PEM-treated groups (being 7% in PEM 1.0% group) in the All Saphenous Vein Treatments Population (compared to 16.5 in surgery group, 6% in sclerotherapy group and 2.6% in ETA group).

Fatal SAEs: Two patients died during participation in PEM studies and 2 patients died in the period after participation in a study of PEM. See Section 7.3.1 for details.

Occurrence of SAEs Relative to Date of Most Recent PEM Treatment: Of the 26 PEM-treated patients who experienced SAEs, 3 patients had SAEs with onset **within 7 days** of the most recent study treatment:

> Patient 011-1005 and Patient 012-1100 in Study 001 (both patients had Venous thrombosis limb AEs and were hospitalized, per institutional protocol, for initiation of anticoagulant medication), and Patient 61-1007 in Study 016 (Obstruction gastric). For all of these patients, the most recent study treatment prior to onset of the event was PEM 1.0%.

An additional 4 PEM-treated patients had SAEs that occurred **within 30 days** of the most recent study treatment:

> Patient 011-1021 in Study 001 (Appendicitis), Patient 001-1018 in Study 003 (Cellulitis [*of untreated leg*]), Patient 13-1322 in Study 013 (Sick sinus syndrome), and Patient 68-1037 in Study 16 (Diverticulitis). For all of these patients, the most recent study treatment prior to onset of the event was PEM 1.0%.

Three (3) PEM-treated patients had SAEs that occurred **between 30 and 90 days** after the most recent study treatment:

> Patient 041-4041 in Study 001 (Tracheobronchitis), Patient 68-1048 in Study 016 ([*recurrence of*] Lymphoma) and Patient 72-1003 in Study 016 (Breast cancer). For all of these patients, the most recent study treatment prior to onset of the event was PEM 1.0%. All other SAEs in PEM-treated patients occurred **91 to 180 days** after the most recent study treatment (6 patients), or **>180 days** (6 months) following the most recent study treatment (10 patients); one of these patients was treated with PEM 0.5%, all others were treated with PEM 1.0%.

7.3.3 Dropouts and/or Discontinuations

SAEs Leading to Withdrawal: Seven patients experienced SAEs that led to withdrawal; these include 3 PEM-treated patients with non-fatal SAEs and 4 patients with fatal events (3 treated with PEM and 1 treated with sclerotherapy – see Section 7.3.1). Narratives of the 3 non-fatal SAEs follow:

- Patient 025-2248 in the PEM 1.0% group of Study 001 experienced severe **Spinal osteoarthritis** 188 days after the most recent study treatment; the patient withdrew from the study due to the event.
- Patient 011-1005 and Patient 012-1100 in the PEM 1.0% treatment group in Study 001 both experienced **Venous thrombosis limb** AEs that were diagnosed 7 days after the most recent study treatment and led to withdrawal from the study. In both cases, the event was serious because the investigator, per institutional policy, was required to hospitalize the patient in order to begin treatment with anticoagulant medication.

  (Note: In all of the clinical studies of PEM, patients with venous thrombus AEs were precluded per protocol from receiving further study treatment but were to be followed for safety and efficacy for the remainder of their respective studies. However, only patients who left their study (the above 3 patients) due to a venous thrombus AE (not those who were ineligible for further PEM treatment but continued to be followed for safety) were considered to have withdrawn from the study due to an AE.)

Table 32 By-Patient Listing of Patients who withdrew Due to a non-fatal AE (All Studies of PEM)

Study/Patient # Age (years)/Sex	Date of Withdrawal	Study Day of Withdrawal / Days from Last Study Treatment	Comments on Reason for Withdrawal (CRF, Verbatim) / Sponsor Comments	Adverse Event(s) (MedDRA Preferred Term)	Days from First Study Treatment to AE Onset	Grade
Adverse Events						
PEM 1.0%						
001/011-1005 54 / Male	(b) (6)	Day 8 / 7	None / The venous thrombus event caused hospitalization and withdrawal	Venous thrombosis limb (SAE)	8	Mild
001/012-1100 74 / Male	(b) (6)	Day 8 / 7	None / The venous thrombus event caused hospitalization and withdrawal	Venous thrombosis limb (SAE)	8	Mild
001/025-2246 54 / Female	25-Feb-2002	Day 7 / 6	None / Patient was withdrawn due to venous thrombus	Venous thrombosis limb	7	Moderate
001/025-2248 52 / Male	30-Sep-2002	Day 203 / 196	None / Patient was withdrawn due to SAE Spinal osteoarthritis	Spinal osteoarthritis (SAE)	189	Severe
001/041-4008 45 / Female	17-Jan-2002	Day 9 / 8	None / Patient was withdrawn per protocol due to extravasation of PEM	Extravasation	1	Mild
001/041-4013 48 / Female	24-Oct-2002	Day 288 / 287	None / Patient was withdrawn due to superficial thrombophlebitis	Thrombophlebitis superficial	288	Moderate
001/041-4017 44 / Female	10-Jan-2002	Day 1 / 0	None / Patient was withdrawn due to microfoam entering the deep venous system	Therapeutic agent toxicity	1	Mild
012/01-1065 35 / Female	24-Jul-2008	Day 65 / 64	None / Patient was withdrawn due to extravasation of 11 mL of microfoam	Extravasation	1	Mild
003/001-1004 27 / Female	UNKN	UNKN	None / AE listed in CSR as severe and causing withdrawal; patient/event do not appear in ISS listing of withdrawals	Injection site pain	4	Severe

Table 32 is a by-patient summary of patients who withdrew due to an AE, excluding the 4 patients (3 PEM-treated patients and 1 patient treated with Sclerotherapy) who had fatal events (i.e., not shown in Table 32). A total of 13 patients withdrew from their respective studies due to an AE, including 1 patient treated with Sclerotherapy in Study 001 and 12 patients treated with PEM 1.0%. Of the 12 PEM-treated patients who withdrew due to an AE, 7 patients (58%) were female and 5 patients (42%) were male; 3 patients (25%) were 18 to 40 years of age, 7 patients (48%) were 41 to 64 years of age, and 2 patients (17%) were ≥65 years of age.

Of the 12 PEM-treated patients who withdrew:

- 5 patients had AEs occurring **≤7 days** after the first study treatment;
- 1 patient had an AE occurring **8-30 days** after the first study treatment;
- 1 patient had an AE occurring **30-90 days** after the first study treatment;
- 4 patients had AEs occurring **>180 days** after the first study treatment (including 2 patients who withdrew after the Month 12 study visit in Study 001); and
- 1 patient had an AE that led to withdrawal after an unknown number of days.

A total of 36 patients in the clinical studies of PEM withdrew from their respective studies early due to a reason other than AE. Of these:

- 18 patients were lost to follow-up, including 15 of 1,333 PEM-treated patients (1.1%) and 3 patients treated with control (i.e., placebo or surgery);
- 9 patients withdrew consent, including 5 PEM-treated patients (0.4%) and 4 patients treated with control (i.e., placebo or surgery);
- 1 patient was withdrawn after study treatment due to investigator decision; this patient was treated with ETA + placebo in Study 017;
- For 8 patients, including 6 patients treated with PEM, 1 patient treated with ETA + placebo, and 1 patient treated with Surgery, the reason for withdrawal was “Other.”

7.3.4 Significant Adverse Events

Of the 797 patients treated with PEM 1.0% in the All Studies Population, 56 patients (7.0%) had one or more severe AEs. The severe AEs that occurred in more than one patient in the PEM 1.0% treatment group were:

- Pain in extremity (26 patients, 3.3%),
- Headache (10 patients, 1.3%),
- Muscle spasms (4 patients, 0.5%),
- Venous thrombosis limb (3 patients, 0.4%),
- Inflammation, Tenderness, Paraesthesia, Pruritus, and Vein Pain (2 patients, or 0.3%, each).

Across treatment groups, severe events occurred in 3% of PEM-treated patients in the PCS Population and <6% of PEM-treated patients in the All Studies Population; the

percent of patients with severe AEs is higher in the Pooled PEM group than in the placebo group.

In the All Saphenous Vein Treatments Population, the percent of patients with severe AEs was more than twice as high in the surgery group (16% of patients), compared with the highest percent in the PEM treatment groups (7% in the PEM 1.0% group).

The most common severe AEs in PEM-treated patients across ISS populations were Pain in extremity, Headache, Muscle spasms, and Venous Thrombosis Limb.

7.3.5 Submission Specific Primary Safety Concerns

Unlike drugs which have to be taken daily for a long time or life-long, the safety concerns for PEM – which is injected in small volumes, and usually once only, without reaching any significant systemic levels – are:

(i) The potential for stroke due to polidocanol microfoam (bubbles) reaching the cerebral circulation via a patent foramen ovale,

(ii) Deep vein thrombosis (DVT), and whether concomitant use in patients treated with endovenous thermal ablation increased the risk of DVT, and

(iii) Potential allergic or anaphylactic reactions.

(i) Concern for the potential for stroke due to polidocanol microfoam (bubbles) reaching the cerebral circulation via a patent foramen ovale

The potential for stroke due to polidocanol microfoam bubbles reaching the cerebral circulation by paradoxical embolization via a patent foramen ovale is an important safety concern. The initial IND protocol, VAP.VV012, submitted to the Division of Dermatology and Dental Products (DDDP), was placed on complete clinical hold on 14-Nov-2003 because micro-bubbles were detected by echocardiography in the right heart (in 10 of 10 patients) and in the left heart and right internal carotid artery in 1 patient with a patent foramen ovale (PFO) who became symptomatic with visual changes and diminished cognitive testing in picture recognition.

The basis for this concern is the relatively high prevalence in the population of PFO at 27.3% (34% during the first 3 decades of life, 25% during the fourth to eight decades, and 20% during the ninth and tenth decades) and the increase in the average diameter of PFO (usually 4.9 mm) with increasing age[8].

On the other hand, clinical studies of thousands of patients with varicose veins who had been treated with microfoam sclerosants did not report any occurrence of pulmonary embolism[8,**Error! Bookmark not defined.**,40,41,42,43,] or scotoma.

A historical perspective of the steps taken by DCRP to guide the sponsor in the course of drug development to address this concern for the potential for stroke due to paradoxical embolization by polidocanol micro-bubbles via a PFO is summarized below:

(1) On 11-Mar-2005, the sponsor submitted a revised protocol VAP.VV012 to DDDP

proposing to monitor subjects during the Varisolve® procedure (sclerotherapy of varicose veins by injection of polidocanol endovenous microfoam) using Transcranial Doppler (TCD) to detect micro-bubbles in the middle cerebral artery (MCA), and to perform baseline and post-treatment (Day 1 and Day 21) diffusion-weighted image magnetic resonance imaging (DWI MRI) of the brain on patients in whom micro-bubbles are detected in the MCA by TCD. The primary objective of this study was to determine whether patients with micro-bubbles detected in the MCA during the Varisolve® procedure experienced any sub-clinical, safety-related events such as abnormalities in DWI MRI, neurologic examination, cardiac enzymes or other symptoms or signs, compared with untreated controls.

On 24-Mar-2005, DDDDP consulted the Div. of Neuropharmacological Products, the Div. of Medical Imaging and Radiopharmaceutical Products, and the Div. of Cardiovascular and Renal Drug Products, for our opinion on the adequacy and appropriateness of the proposed approach in the revised protocol.

On 10-Apr-2005, this reviewer recommended (*for details, please refer to my review (dated 10-Apr-2005) of the consult in DARRTS*) that:

(i) the study be restricted to 50 events (of micro-bubbles in the MCA detected by TCD) in patients with severe varicose veins who must be hospitalized for 24 hours post-treatment,

(ii) TCD monitoring be done throughout the procedure and for one additional hour, and,

(iii) the 50 subjects who are positive for micro-bubbles in MCA by TCD must have:

a. the first post-treatment DWI MRI performed within 8 hours (7-24 hr. window) of the Varisolve® procedure,
b. the second post-treatment DWI MRI on day 7 (4-7 day window),
c. the third post-treatment DWI MRI at 3 weeks (19-23 days window), and
d. perfusion-weighted imaging (**PWI**) MRIs at the same time points to obtain information regarding PWI/DWI mismatch that would indicate an evolving lesion.
e. neurological examinations, fundoscopy and visual field examinations.

The recommendations were incorporated in a continued clinical hold letter (dated 19-Apr-2005) issued by DDDP as "information needed to resolve clinical hold deficiencies." Subsequently, the IND was transferred to DCRP in May 2005.

(2) The sponsor submitted a revised protocol (serial # 052) on 16-May-2005 which incorporated these recommendations, with the modification that PWI MRI would not be performed together with DWI MRI for all patients with bubbles detected in TCD, but PWI MRI using a single dose of gadolinium contrast agent would be performed only in patients with DWI lesions (within 6 hours), and that the revised protocol would include ADC mapping, axial T2, axial T2* and axial T2 FLAIR.

DCRP's consult to the Div. of Medical Imaging and Radiopharmaceutical Products was responded on June 7, 2005, by Dr. Ramesh Raman who noted that none of the

currently marketed gadolinium agents have an indication for PWI MRI for the evaluation of stroke although such use occurs in clinical practice, and that he deferred to DNP as to what would be considered standard clinical practice for the evaluation of stroke. These suggestions were incorporated in a continued clinical hold letter (dated 09-Jun-2005) issued by DCRP to the sponsor with a description of the "information needed to resolve clinical hold deficiencies." In response to this FDA letter, the sponsor submitted a revised protocol on 16-Jun-2005 with the amendments that PWI/DWI MRIs will be performed in accord with the FDA's recommendations and two recent publications[9,10] in support of the rationale for using gadolinium for PWI MRI.

(3) In a FDA letter dated 11-July-2005, the clinical hold was removed to allow the initiation of a study restricted to 50 events of micro-bubbles in the MCA. The sponsor was also required, after completion of the first 5 patients with micro-bubbles in the MCA detected by TCD, to submit the findings in these 5 patients to FDA for review and to discuss any changes in the schedules of the brain MRIs.

At a Type C meeting on 11-Apr-2006, the Division advised the sponsor regarding the need for screening patients for right-to-left shunt, and that upon completion of 50 patients with micro-bubbles detected in the MRI study, FDA will permit the exclusion criteria for patients for right-to-left shunt to be removed.

On 31-Aug-2006, sponsorship of the IND was transferred to BTG International Ltd (which owns Provensis, the current sponsor). The proposed clinical study has not yet been initiated.

(4) On 27-Jan-2007, the sponsor contacted this reviewer via e-mail to inform that a newly recognized potentially fatal adverse effect, *nephrogenic systemic fibrosis*, has been associated with gadolinium-based MR contrast agents used for PWI MRI, and that FDA had issued a Public Health Advisory on this topic in December 2006. No patients had yet been enrolled in the proposed study. I advised the sponsor to exclude PWI MRI, which uses gadolinium-based contrast agents, and to submit a protocol amendment excluding PWI MRI from the study. On 15-Mar-2007, the sponsor submitted Protocol Amendment #1 excluding the PWI MRI procedure that uses gadolinium-based contrast agents. All other aspects of the protocol remained unchanged, including the imaging studies and the neurological tests that will be performed on the 50 patients with micro-bubbles in the MCA.

(5) In Aug-2007, the sponsor submitted data on the first 5 patients with micro-bubbles in the MCA detected by TCD, and a DSMB letter recommending that (i) the 7-day MRI be discontinued, and (ii) the final MRI time point be changed from 3 weeks to 28 days based on the following rationale: "DWI MRI reliably identifies ischemic tissue (edema) within hours after onset of ischemia. As the ischemic lesion evolves, tissue edema resolves and a fibrotic lesion becomes visible on traditional T2 MRI. During this process of evolution, 'pseudonormalization' of MRI findings can occur, i.e., the lesion disappears from DWI, and may not be seen in early T2 MRI. This may happen as early as 5-10 days after the insult, so that the time period between 5 days and 3

weeks is considered relatively unreliable to assess ischemic cerebral lesions. The 7-day MRI scans could appear completely normal despite the existence of a significant lesion. Thus, the DWI MRI at 24 hours and T2 imaging at 28 days are robust tests, but the 7-day MRI may not be reliable." The sponsor requested that this 7-day MRI be dropped.

(6) The sponsor submitted the DSMB report dated 31-Aug-2007 which showed that 16 patients (9 "bubble-positive" during the Varisolve® procedure) had been treated and had completed ≥7 days follow-up, of which 11 patients (7 "bubble-positive" during Varisolve® procedure) had completed 28-days follow-up.

The absolute number of bubbles detected during the Varisolve® procedure (maximum = 13 bubble emboli (Spencer Grade 2) according to the TCD core lab) was ***less than*** that detected during the diagnostic procedure (>150 bubble emboli, Spencer Grade 5) using 1 ml room air in 10 ml agitated saline injected intravenously and monitored for 15 cardiac cycles after injection (done twice: (i) without Valsalva maneuver and (ii) with Valsalva maneuver).

No new MRI lesions were identified on post-Varisolve® procedure scans. In all but one patient (#2016), the 3 sequential MRIs were normal with no evidence of cerebral lesions of vascular or other etiology. Patient #2016 had an abnormal 24-hr MRI which corresponded to that present at baseline (but was not detected by the site initially), with no change in the MRIs at 24 hours, 7 days and 28 days.

Three patients had variations from the norm:

(1) Patient #2002: negative for right-to-left shunt, and no MCA bubbles detected by TCD during Varisolve® procedure, but the TCD core lab detected MCA bubbles during the Varisolve® procedure

(2) Patient #2026: determined as "bubble-positive" by site, but the TCD core lab classified as "bubble-negative"

(3) Patient #2034: diagnostically shunt negative, but had bubbles detected during the Varisolve® procedure and confirmed by the TCD core lab.

No patients had post-treatment neurological or visual symptoms or visual field abnormalities. One SAE reported was an asymptomatic DVT in a 49-yr old man.

Based on the sponsor's proposal and the supportive data in the DSMB report, the Division accepted the proposed protocol amendment to discontinue the MRIs at day-7. The sponsor submitted Protocol Amendment #2 in which the Day-7 MRI procedure was deleted from the protocol.

(7) On 24-Dec-2008, the sponsor submitted a clinical study report (CSR) of protocol VAP.VV0012, including:

(i) a CD-ROM containing MRI images from a sample of two study images as an example of the sequence of images examined for all patients by the independent third party neuro-radiologist,

(ii) interpretations of MRI images by the independent neuro-radiologist for individual

patients,

(iii) handwritten case report forms from the independent reviewer for all patients with lesions that existed pre-treatment.

The clinical study report states that patients were screened at 6 centers in the US, but only 5 centers treated subjects. Of 6,235 patients who responded to media advertisement (radio, television or newspaper), 3,978 did not pass preliminary screening questions. Of the 2,257 patients who passed screening questions, 242 patients chose not to be referred, and 1,470 did not give consent. Of the remaining 545 patients who consented, 460 failed screening procedures (182 patients had no SFJ/GSV (Sapheno-Femoral Junction/Greater Saphenous Vein) incompetence, 104 patients had no right-to-left shunt, 25 withdrew consent, 20 had abnormal MRI within 5 days of procedure, etc.).

Only 85 patients were enrolled. For 2 of these patients, GSV's could not be cannulated, and one patient had extravasation of microfoam with no microfoam entering the GSV. Thus, 82 patients had microfoam injected into the GSV.

Of the 82 patients who received GSV treatment, 22 had no MCA emboli identified on TCD. Of 60 patients who had MCA emboli detected by TCD, 57 patients had 24-hr MRI (3 patients missed 24 hr. MRI), 22 patients had 7-day MRI (before Protocol Amendment#2), and 58 patients had 28-Day MRI (1 was lost to follow up and 1 refused 28-Day MRI).

Efficacy results: The efficacy endpoint was the frequency and proportion of elimination of reflux in the GSV 2 – 5 cm distal to its point of termination at the SFJ or complete occlusion of the GSV immediately distal to significant tributaries and within 10 cm of the SFJ. Eighty-one patients who received endovenous polidocanol microfoam had at least one post-treatment duplex assessment of efficacy.

Elimination of reflux or complete occlusion was reported as follows:

- at Day 7 80/81 (98%), and
- at Day 28 74/81 (91%).

At Day 28, 71/81 patients (88%) had complete occlusion of GSV, and 73/78 (94%) had elimination of reflux (3 subjects did not have reflux times recorded at Day 28).

Safety results**:** Of 83 patients who had polidocanol microfoam injected (including one patient who had extravasation) into GSV, **MCA micro-emboli were detected by TCD during the Varisolve® procedure in 60 (72.3%) patients**, and no emboli was detected in 22 patients.

In patients who had right-to-left shunt, **89%** of patients had microbubbles detected during the Varisolve® procedure; in those negative for right-to-left shunt, **29%** of patients had microbubbles detected during the procedure.

The number of microbubbles ranges from 1 to 382 per subject: 34/60 (57%) patients had ≤ 5 microbubbles in MCA, and 56/60 (93%) had ≤50 microbubbles in MCA.

The most common AEs were pain in the treated extremity and hematoma. Four patients experienced post-ablation superficial thrombus extension (PASTE).

One 51-year old white female patient complained of "twinkly lights" in her peripheral vision one hour after treatment, lasting about 20 seconds. Ophthalmologic and visual field examinations performed immediately after this AE were reported normal.

One 43-year old white female patient reported syncope, but the patient had reported feeling faint during the insertion of the intravenous cannula *before* the study drug was injected; this subjected recovered spontaneously within minutes and completed the Varisolve® procedure.

The SAEs comprise DVTs reported in six patients. Review of case narratives of the six patients showed that all resolved without requiring hospitalization and with no clinical sequelae. Four were treatment with enoxaparin followed by warfarin, one patient was treated with 81 mg aspirin, and one resolved spontaneously.

No abnormalities in ECGs or cardiac markers were found post-Varisolve® procedure.

No abnormalities were reported in MRI (with one exception), neurological examinations, fundoscopy or visual field examinations.

There was good agreement in the MRI evaluations between the radiologists at the clinical sites and the core laboratory independent neurologist with the exception of one patient (#8037): the site interpreted a new lesion in a 24-hour scan which was characterized by BOTH the core laboratory neuro-radiologist and the DSMB neuro-radiologist as normal. A repeat scan 4 days later was interpreted as normal by the site. The submission contained CRFs (together with annotated images) which documented the fact that the "lesion" reported by the radiologist at the site was considered by the DSMB to be a "phase wrap artifact."

In addition, 10 patients had subtle abnormalities in their MRI at baseline according to the independent core neuro-radiologist, but were enrolled into the study because the radiologists at the clinical sites determined them to be normal. The CRFs documented the core neuro-radiologist's description of these baseline lesions.

This clinical study report was the basis of the sponsor's request to discontinue screening for right-to-left shunt, and to allow patients with patent foramen ovale to enroll in ongoing and future protocols under this IND. Based on the finding that in patients with demonstrated cerebral arterial gas bubble embolization with Varisolve® microfoam, no patients developed clinically apparent neurological symptoms or radiologic evidence of cerebral injury, the Division did not object to the sponsor's request to discontinue screening for right-to-left shunt, and to allow patients with known patent foramen ovale to enroll in ongoing and future protocols under this IND.

One more patient (Patient 022-2297 in Study 001) reported TIA-like symptoms in the hours following treatment; this patient was treated with PEM produced using the original gas mixture (b) (6) This patient did not report for medical care and had no sequelae.

Thus, in the PEM clinical program there was no signal that PEM treatment was associated with an increase in neurological adverse events.

Reports in the literature of neurological or visual events associated with use of polidocanol foam to treat varicose veins:

Table 33 Neurological events reported with foam sclerotherapy in clinical trials and case reports

Year	Study (ref)	Total number Treated	Transient neuro-deficit TIA	Visual	Migraine	Stroke	Left-to-Right shunt
2008	Sponsor's IND study (with TCD and MRI evaluations)	83	-	1	-	-	60
2008	Sponsor's Phase 2 and Phase 3 studies (1333-83)	1,250	1	-	-	-	Not studied
2005	French Polidocanol Registry[7] (Guex et al, *Dermatol Surg* 2005; 31: 123-8)	12,173 (6,739)*	-	-	-	-	Not studied
2012	Literature review study[3] (Sarvanathan et al, *J Vasc Surg* 2012; 55:243-251)	10,819	9		29	12	11
2002	Air-based polidocanol foam study[11] (Henriet et al, *Phlebologie* 2002; 52: 277-282)	10,000	1	8	7	-	Not studied
2011	Ultrasound-guided foam therapy[12] (Beckett et al, *Euro J Endovasc Surg* 2011;42:11-19)	2,500	-	4	-	-	Not studied
2002	Air-based foam therapy[13] (Frullini et al, *Dermatol Surg* 2002; 28: 11-15)	(Monfreux) 257 (Tessari) 196	3 -	3 1	- -	-	Not studied
2004	Reticular veins treatment[14] (Kern et al, *Dermatol Surg* 2004; 30: 367-372)	150 (51)*	-	2	-	-	Not studied
2001	Air-based STS foam treatment[15] (Tessari et al, *Dermatol Surg* 2001;27(1):58-60)	77	-	2	-	-	Not studied
2008	Large volume air-based foam therapy[16] (Morrison et al, *J Vasc Surg* 2008;47(4):830-6)	100	-	2	-	-	Not studied
	Total neurological events in clinical trials	37,605	14	23	36	12	71
	Case report studies						
2011	Three ischemic strokes with STS foam[17] (Ma et al, *Phlebology* 2011 Oct; 26(7):280-284)	3	3				3
2010	One case of cerebral infarct[18] (Picard et al *J Neurol Neurosurg Psych* 2010;81:582-3)	1				1	1
2010	One case of reversible ischemic stroke[19] (Hahn et al, *Vasa* 2010; 39:108-110)	1	1				1
2001	Two cases of amaurosis fugax[20] (Ramelet, AA. *Venous Digest* 2001; 8:2-3)	2		2			---
2003	Four cases of visual migraine[21] (Ratinahirana et al, *Cephalalgia*, 2003; 23:850-851)	4			4		---
2006	One case of ischemic stroke[5] (Forlee et al, *J Vasc Surg* 2006; 43(1):162-164)	1				1	1
2004	One case of stroke[22] (Hanisch et al, *Eur J Med Res* 2004; 9:282-284)	1				1	1
2008	Two neurologic reactions - air-based foam[4] (Bush et al, *Phlebology* 2008;23(4):189-192)	2	1			1	1
1994	One TIA with elevated Coagulation factors[23] (Van der Plas et al, *Lancet* 1994; 343:428)	1	1				No PFO
2004	Seizure after air-based STS therapy[24] (Kritzinger, PM. *Canadian Soc Phlebol* 2004, oral presentation)	1	1	1			--
2009	Reversible aphasia after foam sclerotherapy[25] (Hartmann K et al, *Eur J Vasc Endovasc Surg* 2009; 38(5):648-9)	1	1				1
	Total neurological events in case report studies	18	8	3	4	4	9

*number of patients who were foam-treated

Table 33 summarizes the neurological events associated with sclerotherapy for varicose veins reported in the medical literature.

In the following literature reports of large and small series of patients treated with sclerotherapy, neurological and visual events associated with the use of polidocanol foam sclerotherapy are reported rarely:

(i) In the French Polidocanol Registry[7] of 12,173 sclerotherapy treatments in France including 5,434 sessions with liquid sclerosants and 6,739 sessions with foam sclerosants, almost all of the transient neurological and visual events were associated with foam sclerosants, and none led to long term effects.

(ii) A major literature review of 10,819 patients in 41 studies of varicose vein sclerotherapy[3] (STS used in 5,990 patients, polidocanol in 3,999 patients, chromated glycerin in 52 cases, sodium morrhuate in 1 case, and the rest unknown) revealed rare yet serious neurological complications. There were 97 (0.9%) reports of neurological events including 9 cases of transient ischemic attack [TIA] and 12 cases were reported as cerebrovascular accident [CVA] with confirmatory brain imaging, visual and speech disturbances, and 29 (0.27%) cases of migraine. Eleven patients with TIA or CVA had PFO or other right to left cardiac shunt. However, all of the 12 cases of CVA and 3 of 9 TIAs were reported as case reports.

(iii) In another large series[11] of 10,000 treatments of varicose veins with air-based polidocanol foam, (i) 8 patients reported several minutes of blurred vision with one patient experiencing monocular blindness lasting 2 hours, (ii) 7 patients experienced migraine, and (iii) 1 patient had symptoms of expressive aphasia, malaise, and pins and needles in the left arm lasting 5 minutes (which resolved without sequelae in 90 minutes, and an MRI showed findings consistent with multiple sclerosis).

(iv) In a report of a series of 2,500 patients treated with ultrasound-guided foam sclerotherapy[12], four patients reported "scotoma with or without migraine (in all cases mimicking the patients' previous migrainous aura)" and no cases of neurological deficit.

(v) In a series of 257 patients treated with air-based sclerosing foam (polidocanol or STD)[13] generated by the *Monfreux technique* (which produces larger bubbles than the other techniques), 3 patients reported transient visual disturbances and 3 patients reported transient confusional states.

(vi) In a series of 196 patients treated with sclerosing foam generated by the *Tessari method* [13], one patient reported a transient visual disturbance.

(vii) In a series of 150 consecutive patients[14] treated for telangiectasias and reticular leg veins who were randomized single-blind to receive polidocanol air-based foam, polidocanol solution or chromated glycerin solution, transient visual disturbances (described as "transitory, lasting no longer than 2 hours, always bilateral, and without neurological defect on physical examination") were reported in 3 of 51 patients treated with polidocanol foam, and none in those treated with liquid sclerosant.

(viii) In a pilot study of 77 varicose vein patients treated with air-based STS foam[15], two patients reported transient scotoma. One of these patients had a recurrence of scotoma upon subsequent treatment with STS *solution*, suggesting that the sclerosant rather than the microfoam induced the symptoms.

(ix) In another series of 100 patients treated with large volumes of microfoam (defined as up to 52 mL) generated in the clinical setting using 1% polidocanol solution and room air[16], visual disturbances occurred in 2 patients and lasted up to 6 hours. Chest pain and dry cough were also reported. No other details are provided.

The following case reports in the medical literature describe the ischemic neurological events following sclerotherapy in patients without and with a PFO as:

(i) One report[17] detailed 3 female patients who experienced ischemic stroke after ultrasound-guided

foam sclerotherapy with STS with concurrent ambulatory phlebectomy, and all 3 patients were later found to have a PFO.

(ii) A case report described a 33-year old male patient who developed a cerebral infarct 4 hours post treatment with polidocanol foam sclerotherapy[18]; this patient had a PFO.

(iii) A case report described a patient with a PFO received foam sclerotherapy with polidocanol who experienced reversible symptoms approximately 5 days later[19].

(iv) A clinician reported that a patient he had treated with polidocanol (presumed to be polidocanol foam, although not explicitly stated) developed amaurosis fugax on two consecutive occasions[20].

(v) A case report described four patients in whom injection of polidocanol foam in non-saphenous veins or telangiectasias triggered a typical attack of visual migrainous aura[21].

(vi) A case report described an ischemic stroke manifested as right hemiparesis which developed shortly following polidocanol foam sclerotherapy of the great saphenous vein in a patient with PFO[5]. Power in the right upper limb normalized over the course of 2 weeks, although fine motor coordination remained mildly impaired at last follow-up.

(vii) A case report[22] described a 51-year old, otherwise healthy female patient who experienced stroke several days following sclerotherapy with polidocanol liquid, manifested as an acute onset of motor aphasia and brachio-facial right hemiparesis. A CT scan showed a left striatal ischemic infarction. A PFO was present, and as no other potential risk factors for stroke was identified the presumptive diagnosis was paradoxical embolism from an unidentified thrombotic source. She was treated with anticoagulation and discharged with residual speech difficulties and mild right-sided hemiparesis.

(viii) Two severe neurologic alterations were reported after foam sclerotherapy using room air[4]:

(a) A 72-year-old woman with no significant medical history was found slumped in her chair 25 minutes after foam sclerotherapy treatment. She was unable to move her extremities. A CT scan of the head revealed air in the vertebral artery. The patient's neurological deficits resolved within three hours.

(b) A 35-year-old woman was unconscious for about 30 seconds after striking her head when she attempted to sit up in bed following foam sclerotherapy treatment. When she became responsive, her left leg and arm were immobile and her right hand was spastic. She exhibited seizure activity in the right upper extremity upon arrival at the emergency room. A CT scan of her head showed air in the right venous circulation. After several hours of hyperbaric oxygen therapy, the patient's left hemiparesis improved, with residual numbness on the left side. An echocardiogram revealed a secundum-type of atrial septum deficit with atrial septal aneurysm.

(ix) A reversible ischemic neurological deficit was reported 1 hour after injection of 2 mL of 3% polidocanol solution and 1 mL of 1% polidocanol solution; the patient reported a warm sensation and an unpleasant taste[23]. She then developed paresthesia in the right half of the body and loss of the right upper quadrant of the visual field. A neurological examination revealed paresis of the right arm with normal tone and reflexes, hypoesthesia of the ulnar side of the right hand and forearm, and a right temporal quadrant anopia demonstrated with Goldman perimetry. Neurological symptoms and signs resolved spontaneously within 2 days. The presumptive diagnosis was a lacunar-type lesion of the left cerebral hemisphere in the area of the left middle cerebral artery. CT of the brain 5 days after the event did not show an ischemic lesion. A transthoracic ultrasound did not reveal a right-to-left shunt. Coagulation factors (fibrin monomer, prothrombin fragment 1+2, thrombin-antithrombin III, and D-dimer) were elevated. The authors believed the most likely explanation was a systemic activation of thrombosis resulting in ischemic brain injury.

(x) A case report describes a 70-year-old man treated with sodium tetradecyl sulfate (STS) air-based microfoam who developed scintillating scotomas, headache, stupor and a grand mal seizure within the first hour after treatment[24]. He recovered after three days of intensive care. Electrocardiogram (ECG), transthoracic echocardiogram (without contrast), CT and MRI of the brain and arterial blood

gases were all normal, and investigations for DVT, pulmonary embolism, and sepsis were negative.

(xi) A 37-year old man with a PFO treated with 9 ml of 3% polidocanol foam reported immediate photopsiae lasting a few minutes without migraine, and, 2 hours later, speech disturbance for a few minutes[25]. No other abnormality was found.

Reviewer's comments on the literature review findings: In the treatment of varicose veins, a condition that is commonly perceived as benign, there is an enormous concern for the major and potentially fatal neurological complications that have been reported with sclerotherapy. However, the current medical literature articles above highlight their relative infrequency when taking into consideration that millions of sclerotherapy injections have been carried out to date. For example, more than 50,000 varicose vein operations are performed each year in England and Wales[26].

While there are individual case reports of strokes after foam sclerotherapy in the medical literature, none of the large studies and randomized trials reported any major neurological complications (Table 33, with the exception of the literature review study by Sarvanathan 2012[3], which contained case reports that accounted for all 12 cases of CVAs and 3 of 9 cases of TIA). While it is possible that neurological complications have been under-reported and that the true incidence of neurological complications after sclerotherapy is unknown, most of these patients recover from stroke in the case reports, and only 4 patients have been reported to have non-reversible deficits.

The precise mechanism behind the occurrence of neurological symptoms is poorly understood. In the majority of patients with CVA or TIA, a PFO or other right to left cardiac shunt has been identified, and the symptoms are thought to occur as a consequence of particles of sclerosant arriving in the cerebral circulation through a right-to-left cardiac shunt. However, foam bubbles in the MCA have been observed on TCD in the absence of neurological complications[27] in up to 42% of patients undergoing foam sclerotherapy.[28] Despite the relatively high prevalence of PFO in general population (of 26%)[8], the incidence of neurological complications after foam sclerotherapy is exceedingly low. It is, therefore, highly likely that other factors are involved in the occurrence of neurological symptoms following foam sclerotherapy.

The relationship between PFOs and SGV incompetence with varicose veins is not simple. In a study of 221 men and women 18-60 years with symptomatic varicose veins (CEAP C_{3-5}) demonstrated by duplex ultrasound imaging and tested for right-to-left shunt using TCD of the MCA (to detect the presence of bubble emboli after an injection of agitated saline and air mixture as contrast at rest and with the Valsalva maneuver)[29], a total of 130 patients (58.8%) were positive {with 85 (38.5%) positive at rest and 114 (51.8) positive after the Valsalva maneuver}. This is significantly higher than the reported 26% prevalence of PFO in the general population[8]. The reason for this link between right-to-left shunt and varicose veins is not known. TCD does not differentiate between intracardiac shunts (PFO) and intrapulmonary shunts.

The method for foam creation may also be an influencing factor for the development of neurological symptoms due to the varying size of bubbles produced. The Monfreux method generates foam via the use of a glass syringe that contains liquid sclerosing

solution; this method has higher rates of side effects such as dizziness and states of confusion[27] thought to be due to the creation of larger air bubbles. However, the majority of the above studies utilized the Tessari technique, which is distinguished by creating a mixture of fine-bubbled sclerosant in air or gas using two syringes and a three-way tap. In the context of this NDA, it is noteworthy that most cases of the neurological events in the literature were associated with sclerosant (polidocanol or sotradecol) foam created using room air. The replacement of air mixture, containing high percentages of relatively insoluble nitrogen with carbon dioxide, which is highly soluble, has been shown to reduce side effects such as dizziness and chest tightness, but no statistically significant reduction was noted in the occurrence of visual disturbances or other neurological side effects.[30]

The use of large amounts of foam, such as the 20 mL used in the case report[5] of a case of ischemic stroke reported by Forlee et al is unsafe. However, the role of the injected volume as a contributing factor for neurological events has been questioned as in many reported cases, the total volume was <10 mL of foam.[4,18,23]

It has also been suggested that an inflammatory reaction to the sclerosant may cause vasospasm resulting in symptoms.[31]

It is possible that the pathologic mechanism resulting in CVA is different than that occurring in patients reporting transient visual, speech, and motor disturbances and symptoms of migraine. The majority of the neurological side effects seen are considered unlikely to be related to true CVAs, which are very rare. The majority of symptoms occurred within minutes to hours after the injection of sclerosant, although there are cases of symptoms occurring up to 5 days afterward.[19]

Patients known to suffer from migraine with aura appear to be a greater risk of developing visual disturbances,[31] and it has been suggested that these visual disturbances correspond to migraines with aura. An association between migraines with aura and PFO has been quoted by many observational studies and may offer a plausible explanation for the occurrence of visual disturbances after sclerotherapy. 71.4% of patients reporting visual disturbances, migraines with aura, or chest tightness following foam sclerotherapy were found to have PFO.[44]

From a mechanistic perspective, one explanation for transient neurological symptoms may be the release of endothelin induced by microfoam bubbles acting on the endothelium or as they pass through a PFO. The endothelin quickly flows into the cerebral cortex and initiate one of the pathways leading to cortical spreading depression – a depolarizing waveform occurring in the cerebral cortex, and shown to be associated with migraine with aura, including visual, speech, and motor disturbances.[7] Levels of endothelin measured in rats following foam sclerotherapy appear to be significantly higher than in those who have been treated with liquid sclerosants in the minutes following the procedure[32], which may provide an explanation as to why neurological symptoms appear to occur more frequently following foam sclerotherapy.

(ii) Deep Vein Thrombosis and whether concomitant use in patients treated with endovenous thermal ablation (ETA) increased the risk of DVT:

Deep vein thrombosis is also considered an important submission-specific safety concern. For this safety issue, too, the method of evaluating venous thrombus AE data evolved over the course of the PEM clinical development program. In the earlier studies of PEM, data on venous thrombus AEs were reported to the Sponsor via SAE forms and were subsequently recorded on the AE case report forms.

In the studies of PEM, duplex ultrasound surveillance of the deep veins was required per protocol at screening, on a minimum of 3 occasions following the initial study treatment, and twice after optional OL treatments. These assessments continued throughout the patient's participation in the study, and all patients with venous thrombus AEs were followed and received regular duplex ultrasound examinations per protocol, and were not eligible for further study treatment.

In the US Phase 3 Studies 015, 016, 017 and the PK Study 008, Venous Thrombus Event Forms (VTE worksheets) were developed in collaboration with the Venous Thromboembolic Event Review Board (VTERB). These VTE worksheets were used by the study sites to promptly report details on each venous thrombus AE to the Sponsor and the VTERB. The VTE worksheets were completed by the investigator at the time of venous thrombus diagnosis and at each follow-up visit, and were used in the preparation of narratives for patients with venous thrombus AEs.

All venous thrombus AEs in the studies of PEM were reviewed by the VTERB who examined detailed data collected on venous thrombus AEs as they occurred in Studies 008, 015, 016 and 017, and retrospectively reviewed the data on venous thrombus AEs that had occurred in all other clinical studies of PEM. Treatment for venous thrombus AEs, while at the investigator's discretion, was made in accord with ACCP Guidelines.

Table 34 Coding of thrombi in or distal to the common femoral vein

Medical Terminology Used in the ISS	Location	Colloquial	MedDRA Preferred Term	N (%) PEM-treated patients (n=1333)	Total %
Common femoral vein thrombus extension	Common femoral vein	eHIT 1-3[a] (non-occlusive)	*Venous thrombosis limb*	41 (3.1%)	3.1%
Proximal Deep vein thrombosis	Common femoral vein	eHIT 4 (occlusive)	*Deep vein thrombosis*	0	2.9%
	Femoral vein	Proximal DVT	*Deep vein thrombosis*	14 (1.1%)	
	Popliteal vein	Proximal DVT	*Deep vein thrombosis*	8 (0.6%)	
Distal Deep vein thrombosis	Posterior tibial vein	Distal DVT	*Deep vein thrombosis*	13 (1.0%)	
	Anterior tibial vein	Distal DVT	*Deep vein thrombosis*	1 (0.08%)	
	Peroneal vein	Distal DVT	*Deep vein thrombosis*	2 (0.15%)	
IGSVT	Gastrocnemius vein	Calf muscle vein	*Thrombosis*	17 (1.3%)	1.4%
	Soleal vein	Calf muscle vein	*Thrombosis*	1 (0.08%)	

[a] Of note, a Class 1 eHIT does not meet the criteria specified in the Sponsor's coding convention for the MedDRA Preferred Term Venous thrombosis limb, because it does not extend into the deep venous system. However, because there is no better MedDRA Preferred Term for this event, the single Class 1 eHIT that occurred in the studies of PEM was coded to this term.
DVT: deep vein thrombosis; eHIT: endovenous heat-induced thrombus; IGSVT: isolated gastrocnemius and soleal vein thrombosis
Source: ISS Coding Conventions and Venous Thrombus AE Classification Document, which is located in ISS Appendix K.

In Table 34, thrombi at or distal to the common femoral vein were coded to the MedDRA Preferred Term by the sponsor as follows:

1. *Venous thrombosis limb*: This refers to non-occlusive thrombi extending from the GSV into the common femoral vein; it is also known as 'common femoral vein thrombus extension.' The thrombus originates in the treated superficial vein and exists in both the superficial and the deep venous systems. It is qualitatively different from thrombi that arise in other locations in the leg in that this is a non-occlusive thrombus phenomenon following PEM treatment of the GSV. This was the most common type of venous thrombus, occurring in 3.1% of PEM-treated patients.

Table 35 Thrombus characteristics in patients with venous thrombosis events in placebo-controlled PEM studies

Duplex Ultrasound Parameter	Placebo[a] (N=113)	PEM 0.125%[a] (N=114)	PEM 0.5%[a] (N=111)	PEM 1.0%[a] (N=110)	PEM 2.0%[b] (N=63)	Pooled PEM (N=398)
Thrombus thickness when compressed, mm						
n	0	5	6	13	5	29
Mean		4.14	6.78	5.18	6.50	5.56
SD		2.76	1.54	2.82	3.39	2.73
Median		2.90	6.90	4.80	7.00	5.30
Min, Max		1.5, 8.6	4.3, 8.5	2.0, 11.0	1.0, 10.0	1.0, 11.0
Length of thrombus, mm						
n	0	5	6	16	6	33
Mean		56.42	26.48	56.49	38.87	47.82
SD		58.70	20.28	71.17	40.76	57.26
Median		40.00	22.40	25.70	22.00	24.50
Min, Max		3.0, 150.0	7.0, 62.5	1.7, 240.0	4.4, 100.0	1.7, 240.0
Volume of thrombus, cm^3						
n	0	5	6	13	5	29
Mean		0.63	0.84	1.75	1.74	1.36
SD		0.40	0.46	1.89	2.24	1.60
Median		0.72	0.79	0.69	0.61	0.69
Min, Max		0.01, 0.99	0.20, 1.45	0.04, 4.75	0.03, 5.41	0.01, 5.41
Free floating tail						
Yes	0	2 (33.3%)	3 (50.0%)	0	2 (33.3%)	7 (20.6%)
No	0	4 (66.6%)	3 (50.0%	16 (100%)	4 (66.7%)	27 (79.4%)
Length of free floating tail, mm						
n	0	1	3	0	2	6
Mean		7.70	16.30	-	7.90	12.07
SD		-	5.52	-	0.14	5.81
Median		7.70	18.60	-	7.90	9.00
Min, Max		7.7, 7.7	10.0, 20.3	-	7.8, 8.0	7.7, 20.3

[a] 015, 016: PEM 0.125% is a control; [b] 015; [c] Percents are based on the number (N) of patients in each treatment group; [d] All that apply.
NOTE: Unless otherwise footnoted, percents are based on the number (N) of patients with Venous Thrombosis in each treatment group.
NOTE: 013 study was excluded because no detailed VT data collected in the database. Source: ISS Tables 47.1.1 - 47.2.1 (Pages 1524 – 1547).

2. *Deep vein thrombosis (DVT)*: Deep vein thrombi were quantified by thrombus volume (Table 35) using venography and scored as Marder scales[33], on which a score of 0 signifies no thrombus and a score of 40 signifies thrombus occupying all veins of the leg (with the exception of the veins of the calf muscle, which could not be viewed reliably

using venography). In a study of 24 symptomatic patients with venographically established DVT, the average Marder scale score was 20[33], illustrating extensive DVT. In placebo-controlled studies of PEM, however, smaller thrombi were observed: the largest thrombus (volume of 5.41 cm^3) scored 5 on the Marder scale, the median thrombus volume was 0.69 cm^3 and the median length 24.5 mm (Table 35).

3. *Thrombosis*: This includes thrombi in the gastrocnemius or soleal veins referred to as isolated gastrocnemius and soleal vein thrombosis (IGSVT) in the literature[34,35]. IGSVT were coded separately in order to distinguish them from venous thrombi in other parts of the leg, because their clinical importance is not established[36]. IGSVT were not reported frequently following venography, but were observed during detailed duplex ultrasound interrogation of the calf. Unless there is generalized activation of coagulation, isolated thrombi of the gastrocnemius and/or soleal veins rarely progress[34,36]. Therefore, these thrombi are either never discovered or managed conservatively.

Table 36 Number of patients with venous thrombus AEs in all PEM-treated patients compared to patients in Study 017 (ETA followed by PEM treatment)

Vein	Treatment Group, n (All patients)						Treatment Group, n (Study 017)		
	PEM 0.125%[c] N=130	PEM 0.5%[d] N=150	PEM 1.0%[e] N=837	PEM 2.0%[f] N=75	Pooled PEM 1.0%[a] N=1,170	Pooled PEM[b] N=1,333	ETA + Vehicle N=38	ETA + PEM 1.0% N=40	All ETA + PEM N=79
Number of Patients with Venous Thrombus[g]	6 (4.6)	9 (6.0)	49 (5.9)	8 (10.7)	71 (6.1)	94 (7.1)	1 (2.6)	2 (5.0)	5 (6.3)
Number of Patients with Pulmonary Embolism[g]	0	0	0	0	0	0	0	0	0
Primary Location of Thrombus per Number of Patients in the Treatment Group[g]									
Common femoral vein thrombus extension	3 (2.3)	5 (3.3)	24 (2.9)	4 (5.3)	27 (2.3)	39 (2.9)	0	0	0
Proximal deep vein thrombosis									
Femoral vein	0	1 (0.7)	6 (0.7)	2 (2.7)	13 (1.1)	16 (1.2)	0	0	0
Popliteal vein	0	0	4 (0.5)	1 (1.3)	5 (0.4)	6 (0.5)	0	0	0
Distal deep vein thrombosis									
Posterior tibial vein	0	2 (1.3)	2 (0.2)	1 (1.3)	9 (0.8)	12 (0.9)	1 (2.6)	0	2 (2.6)
Anterior tibial vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	0
Peroneal vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	-	-	-
Isolated gastrocnemius and soleal vein thrombosis									
Soleus vein	0	0	1 (0.1)	0	1 (0.1)	1 (0.1)	0	0	0
Gastrocnemius vein	3 (2.3)	1 (0.7)	10 (1.2)	0	14 (1.2)	18 (1.4)	0	2 (5.0)	3 (3.8)

[a]Studies 013, 014, 015 and 016; [b]Includes all patients treated with PEM; [c]Studies 014, 015, 016; [d]Studies 015, 016 and 017; [e]Studies COM001, 001, 003, 0005, 008, 011, 012, 013, 015, 016 and 017; [f]Studies 008 and 015; [g]Percents are based on number of patients (N) in each treatment group. {Source: Sponsor's Table in ISS, and Table 28 in CSR VAP-VV017}

The frequencies of venous thrombus AEs observed in the PEM-treated patients overall and in patients treated with PEM after endovenous thermal ablation (ETA) in Study 017 are compared in Table 36. In the PEM clinical studies, 98 (7.4%) patients (96 PEM-treated patients and 2 patients not treated with PEM) had venous thrombus AEs detected by ultrasound. In Study 017, 6 of 117 (5.1%) patients (5 PEM-treated patients

and 1 patients treated with vehicle) experienced venous thrombus AEs, the only locations of the thrombi being in the posterior tibial and gastrocnemius veins. The data suggests that treatment with PEM after ETA does not increase the risk of venous thrombus AEs.

No patient in any PEM study had a diagnosis of pulmonary embolism.

The 96 PEM-treated patients with venous thrombus AEs comprise:

- 94 (7.1%) of 1,333 PEM-treated patients had treatment-emergent venous thrombus AEs in the treated leg during participation in the Main or Optional OL Treatment Period of their respective studies.
- One PEM-treated patient in Study 001, Patient 61-6004, had a venous thrombus AE (coded to DVT) in the study treated leg about 9 months after study treatment.
- One PEM-treated patient in Study 0005, Patient 01-101, had a venous thrombus AE (coded to DVT) in the study treated leg that was detected 53 days after treatment and 43 days after the patient completed the study.

Note: One patient in Study 012, Patient 02-2004, was treated with PEM and developed a non-occlusive thrombus in the common femoral vein (coded to Venous thrombosis limb; included in the 94 PEM-treated patients with venous thrombus AEs). During the Long-term Follow-up Period of Study 012, this patient was treated with laser heat ablation in the contralateral (non-study) leg and again developed a venous thrombus AE (coded to Venous thrombosis limb) in the non-study leg (not included in safety database).

Two patients received non-PEM treatments and developed venous thrombus AEs:

- Patient 45-1009 was treated with ETA + Vehicle in Study 017 and had a venous thrombus AE (coded to Deep vein thrombosis) in the study leg.
- Patient 023-2148 was treated with alternative sclerotherapy (not PEM) in Study 001 and had a venous thrombus AE (coded to Thrombosis).

Of the 98 patients with venous thrombus AEs, 87 patients (89%) had a venous thrombus in only one vein location; 11 patients (11%) had venous thrombus AEs in more than one vein location. For 9 of these 11 patients, the 2 thrombus locations were detected at the same study visit.

In the PEM treated population, venous thrombus AEs (VTAEs) were least frequent in the PEM 0.125% dose-concentration group (4.6%), similar in the PEM 0.5% and 1.0% groups (6.0% and 5.9%, respectively) and highest in the PEM 2.0% group (10.7%); a logistic regression model showed no statistically significant association between the PEM dose-concentration and the occurrence of VTAEs (P=0.095).

VTAEs were significantly (P=0.021) more frequent in male patients.

The VTAEs were asymptomatic in 77%, non-occlusive in 56% and resolved rapidly (median time 29 days).

Half of all patients with VTAEs (51 of 97) were treated with anti-coagulants with 20 treated for ≤2 weeks (Table 37). Most patients with DVT (79%) and most with IGSVT (84%) did not receive anticoagulants. About 70% of patients with proximal DVT (thrombus in femoral vein or popliteal) received anticoagulants; the median time to stabilization or resolution was 87 days. About half of the patients with common femoral

vein thrombus extensions were managed with ultrasound observation and did not receive anticoagulants; of 23 who were anticoagulated, 19 were treated for ≤6 weeks.

Table 37 Treatment for venous thrombosis events

	Observation / Stockings only	NSAIDS; ASA	Anticoagulation (<1 month)	Anticoagulation (long term)	Total
Proximal Symptomatic					
Venous thrombosis limb	0	0	0	3	3
DVT	0	0	3	7	10
Proximal Asymptomatic					
Venous thrombosis limb	11	5	13	8	37
DVT	2	1	4	4	11
Distal Symptomatic					
Thrombosis	2	1	1	0	4
DVT	1	3	2	1	7
Distal Asymptomatic					
Thrombosis	8	4	2	0	14
DVT	8	0	1	2	11
Total	32	14	26	25	97

The time to resolution of venous thrombus AEs in the PEM studies are shown in Table 38. All vein thrombus events resolved or became stable with the exception of 1 patient with proximal DVT and 2 with IGSVT.

Table 38 Time to resolution of venous thrombus AEs

Venous Thrombus AE Location	N	Resolved or Stable		Resolved		Stable		Not Resolved or Stable
		N	Median Days (Range)	N	Median Days (Range)	N	Median Days (Range)	N
Common femoral vein thrombus extension	39	39[a]	21 (4, 103)	39[a]	21 (4, 103)	0	NA	0[a]
Proximal deep vein thrombosis[b]	22	21	87 (16, 380)	15	90 (16, 380)	6	69.5 (23, 197)	1[c]
Distal deep vein thrombosis[d]	14	14	49 (14, 99)	9	50 (19, 99)	5	49 (14, 93)	0
Isolated gastrocnemius & soleal vein thromboses	19	17	36 (8, 337)	14	33.5 (8, 337)	3	50 (22, 50)	2[e]

[a] Patient 012-1100 in Study 001 had a venous thrombus of the common femoral vein that resolved 77 days after diagnosis. This patient's resolution information is updated information provided in the narrative for this patient following the cut-off for the 3 Month CSR and is therefore not in the pooled ISS database.
[b] Includes venous thrombi of the femoral and popliteal veins.
[c] Patient 081-8028 in Study 001
[d] Includes thrombi of the posterior tibial, anterior tibial, and peroneal veins
[e] Patient 01-116 in Study 0005 and Patient 11-1114 in Study 013
AE: adverse event; OL: open-label; PEM: Polidocanol Endovenous Microfoam
Source: Sponsor's ISS Tables 38 and 47.2.3.1

In the French Polidocanol Registry[7] of 12,173 sclerotherapy treatments in France (including 5,434 sessions with *liquid* sclerosants and 6,739 sessions with *foam* sclerosants), 14 DVTs were associated only with foam sclerosants of which 8 were noted in relation to polidocanol *foam*.

Two DVTs were associated with liquid sclerosants (sotradeol), with no DVT reported in any patient treated with polidocanol liquid.

In the medical literature, there was a case report of a 67-year old male who experienced delayed atrial embolism of a floating thrombus after ultrasound-guided foam sclerotherapy (UGFS) with 3% polidocanol.[37]

There are more reports in the peer-reviewed literature of embolic events potentially related to the use of UGFS, including some cases where polidocanol was used in a setting of foam generated by hand in the clinic. A prospectively-gathered case database review of 1,252 limbs treated with UGFS using air and STS (not PEM) revealed 3 episodes of DVT and one patient, a 65-year-old female smoker, who experienced a pulmonary embolus and responded to anti-coagulant therapy.[38]

(iii) Potential allergic or anaphylactic reactions

No anaphylaxis or life-threatening hypersensitivity reactions occurred in the PEM clinical studies.

No AE possibly representing a hypersensitivity reaction to PEM was assessed by a study investigator as a serious event.

Five PEM-treated patients experienced severe possible hypersensitivity events.

- Patient 011-1024 experienced a severe 'edema peripheral' event (verbatim term: Swelling L knee) during the long-term follow-up period of Study 001, 125 days following a single treatment session with PEM 1.0%. This event was not discussed further.
- Patient 012-1091, a 71-year-old man in Study 001, experienced non-serious, severe events of Swelling (location not specified; verbatim term: Swelling) and Erythema (verbatim term: Redness) on 30-Mar-2002, 10 days following the 4th treatment with PEM 1.0%. No change was made to the study treatment; the events were treated with diclofenac and resolved without sequelae 4 days after onset.
- Patient 014-1227, a 71-year-old man in Study 001, experienced a non-serious, severe event of Chest discomfort (verbatim term: Tight chest) on 13-Feb-2002, 7 days following a single treatment session with PEM 1.0% on 06-Feb-2002. No change was made to the study treatment. No treatment for the event was recorded. The event decreased to moderate severity on 14-Feb-2002, and resolved without sequelae on 15-Feb-2002. This patient also experienced a non-serious possible hypersensitivity event of mild Pruritus (verbatim term: Itchy leg), which began 2 days after treatment with PEM and resolved 4 days later.
- Patient 014-1244, a 70-year-old woman in Study 001, experienced a non-serious, severe AE of Cough (verbatim term: Dry cough) on 05-Apr-2002, 1 day following a single treatment session with PEM 1.0% on 04-Apr-2002. The event co-occurred with an event of acute chest pain. No change was made in the study treatment. This event was treated with paracetamol and resolved without sequelae on the day of onset.
- Patient 69-1010, a 43-year-old woman in Study 016, experienced a non-serious, severe AE of Pruritus (verbatim term: Severe Itching (Lt Leg)) on 04-May-2011, 1 day after a single treatment session with PEM 1.0% on 03-May-2011.. No change was made in the study treatment. No treatment for the event was reported. The event resolved on 08-May-2011.

Adverse Events with the Preferred Term Hypersensitivity: Two PEM-treated patients had non-serious AEs with the Preferred Term Hypersensitivity.

- Patient 041-4013 in Study 001 experienced an event (verbatim term: Allergy of unknown cause) 85 days following a single treatment session with PEM 1.0% in Study 001; this patient was not discussed

further.

- Patient 052-5136 was a 25-year-old woman in Study 001 who was treated with PEM 1.0% on 26-Apr-2002. On 13-May-2002, 17 days following study treatment, the patient experienced the non-serious AE Hypersensitivity (verbatim term: Allergy). No change was made in the study treatment for this event, which was treated with an unspecified homeopathic medication and resolved without sequelae on the day of onset.

Possible Hypersensitivity Events Occurring within 1 Day of PEM Administration: In each of the studies of PEM, patients were observed for a minimum of 10 minutes following each treatment session for adverse reactions, including events possibly representing hypersensitivity reactions to the study treatment. Therefore, in addition to the summaries of all event terms related to possible hypersensitivity reactions, summaries of only those AEs possibly representing hypersensitivity reactions that occurred within 1 day of (i.e., the day of or the day after) a PEM treatment session were produced for the Placebo-Controlled Studies (PCS) and All Studies Populations.

In the PCS Population, 17 of 427 PEM-treated patients (3.9%) and 9 of 151 placebo-treated patients (6.0%) experienced possible hypersensitivity reactions within 1 day of study treatment.

The overall percent of patients with possible hypersensitivity reactions increased with PEM dose-concentration, from 2.6% in the PEM 0.125% (control) group to 3.6%, 4.7% and 4.8% in the PEM 0.5%, 1.0% and 2.0% groups, respectively. However, the numbers of patients with these events are too small to allow for meaningful conclusions to be drawn based on the available data.

The possible hypersensitivity events that occurred within 1 day of study treatment in the PEM group were: Pruritus (11 patients, 2.5%, versus 4.0% of patients in the placebo group), edema peripheral (4 patients, 0.9%, versus 1.3% of patients in the placebo group), and Rash (2 patients, 0.5%, compared with no patient in the placebo group). The number of events occurring in each treatment group was too small for meaningful comparisons of the incidence of individual events by PEM dose-concentration.

In the All Studies Population, possible hypersensitivity events and their frequencies were nearly identical to the PCS Population (4.0% and 6.0% for PEM-treated patients versus placebo, respectively.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common events (Preferred Terms) that occurred in ≥5% of patients in any PEM treatment group in the PCS Population are shown in Table 39. The common AEs that occurred more frequently in the Pooled PEM treatment group, compared with the placebo group, with a difference of ≥5%, were Infusion site thrombosis (10.5% vs. 0%),

Thrombophlebitis superficial (9.2% vs. 1.3%), Pain in extremity (14.9% vs. 9.3%), and Venous thrombosis limb (5.5% vs. 0%). About 5% of patients in the Pooled PEM group and 7% of patients in the placebo group (PCS Population) reported “Pain in extremity” at baseline. These common AEs in PEM-treated patients in the PCS Population are those that would be expected following a procedure for treatment of the GSV.

Table 39 Treatment-emergent Adverse Events occurring in ≥5% of Patients in Any PEM Treatment Group, by MedDRA SOC and Preferred Term, Placebo-controlled Studies Population (Main Treatment Period only)

MedDRA System Organ Class Preferred Term	Placebo[a] (N=151)	PEM 0.125%[b] (N=114)	PEM 0.5%[b] (N=111)	PEM 1.0%[a] (N=149)	PEM 2.0%[c] (N=63)	Pooled PEM (N=437)
Number of Patients with at Least 1 AE	71 (47.0)	61 (53.5)	66 (59.5)	110 (73.8)	37 (58.7)	274 (62.7)
Musculoskeletal and connective tissue disorders	25 (16.6)	28 (24.6)	22 (19.8)	49 (32.9)	17 (27.0)	116 (26.5)
Pain in extremity	14 (9.3)	20 (17.5)	14 (12.6)	25 (16.8)	6 (9.5)	65 (14.9)
Limb discomfort	5 (3.3)	3 (2.6)	5 (4.5)	18 (12.1)	6 (9.5)	32 (7.3)
General disorders and administration site conditions	21 (13.9)	20 (17.5)	24 (21.6)	55 (36.9)	16 (25.4)	115 (26.3)
Infusion site thrombosis	0	6 (5.3)	10 (9.0)	24 (16.1)	6 (9.5)	46 (10.5)
Injection site haematoma	6 (4.0)	3 (2.6)	8 (7.2)	9 (6.0)	3 (4.8)	23 (5.3)
Injection site pain	3 (2.0)	3 (2.6)	6 (5.4)	6 (4.0)	3 (4.8)	18 (4.1)
Tenderness	2 (1.3)	0	1 (0.9)	11 (7.4)	1 (1.6)	13 (3.0)
Vascular disorders	5 (3.3)	20 (17.5)	23 (20.7)	31 (20.8)	11 (17.5)	85 (19.5)
Thrombophlebitis superficial	2 (1.3)	11 (9.6)	13 (11.7)	8 (5.4)	8 (12.7)	40 (9.2)
Venous thrombosis limb	0	3 (2.6)	5 (4.5)	12 (8.1)	4 (6.3)	24 (5.5)
Skin and subcutaneous tissue disorders	14 (9.3)	12 (10.5)	7 (6.3)	20 (13.4)	9 (14.3)	48 (11.0)
Pruritus	9 (6.0)	3 (2.6)	4 (3.6)	6 (4.0)	6 (9.5)	19 (4.3)
Infections and infestations	14 (9.3)	10 (8.8)	9 (8.1)	15 (10.1)	4 (6.3)	38 (8.7)
Nervous system disorders	13 (8.6)	4 (3.5)	8 (72)	11 (7.4)	6 (9.5)	29 (6.6)
Headache	4 (2.6)	2 (1.8)	3 (2.7)	8 (5.4)	3 (4.8)	16 (3.7)
Injury, poisoning and procedural complications	12 (7.9)	3 (2.6)	3 (2.7)	18 (12.1)	3 (4.8)	27 (6.2)
Contusion	3 (2.0)	1 (0.9)	0	14 (9.4)	0	15 (3.4)

[a] Studies 013, 015 and 016. [b] Studies 015 and 016; PEM 0.125% was a control in these studies. [c] Study 015. Source: Table 9.1
Notes: Data are displayed as number of patients (percent of patients). Percents are based on the number of patients (N) in each treatment group. Patients are counted only once for each applicable Preferred Term and/or System Organ Class. All System Organ Classes meeting the selection criteria for this table are displayed, even if no individual Preferred Term within that System Organ Class met the selection criteria for the table.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PEM: Polidocanol Endovenous Microfoam; SOC: System Organ Class

AEs that occurred in ≥5% of patients in the **PEM 0.5%** treatment group and in a higher percent than in the placebo group were Pain in extremity, Thrombophlebitis superficial, Infusion site thrombosis, Injection site haematoma, and Injection site pain.

AEs that occurred in ≥5% of patients in the **PEM 1.0%** treatment group and in a higher percent than in the placebo group were Pain in extremity, Infusion site thrombosis, Limb discomfort, Contusion, Venous thrombosis limb, Tenderness, Injection site hematoma, Headache, and Thrombophlebitis superficial.

AEs that occurred in ≥5% of patients in the **PEM 2.0%** group and in a higher percent of patients than in the placebo group were Thrombophlebitis superficial (12.7% vs. 1.3%), Infusion site thrombosis (9.5% vs. 0%), Venous thrombosis limb (6.0% vs. 0%), Limb discomfort (9.5% vs. 3.3%) and Pruritus (9.5% vs. 6.0%).

A higher rate of **Headache AEs** was found in the All Studies Population, compared with the PCS Population (incidence of Headache in the Pooled PEM group: 3.7%; Table 39). One explanation is that half (58) of the Headache AEs in the All Studies Population (115 patients) come from patients in Study 001, in which AE data were solicited using a patient diary. Secondly, 90 of the 115 patients in the All Studies Population with Headache AEs (78%) were treated with the original PEM formulation, which was produced with a gas mixture that contained (b) (4) Forty (40) of these 90 patients experienced the Headache AEs within 1 day of (i.e., the day of or the day after) a PEM treatment session. It is possible that for some of these 40 patients (i.e., those with right-to-left cardiac shunt), the nitrogen content of the PEM resulted in persistence of circulating gas bubbles, which contributed to the development of Headache AEs.

Adverse Events, Long-term Follow-up (LTFU) Population: In Studies 001 and 012, data on non-serious AEs were collected during the LTFU Period for 711 patients, of which 214 patients were in Study 001 Surgery/Sclerotherapy arm, 420 patients were in Study 001 PEM 1.0% group, and 77 patients were in Study 012 PEM 1.0% group.

Forty-three (43) of 214 patients in the Study 001 Surgery/Sclerotherapy arm (20.1%), 81 of 420 patients in Study 001 PEM 1.0% group (19.3%), and 22 of 77 patients in Study 012 PEM 1.0% group (28.6%) had one or more non-serious AEs in the LTFU Period.

The SOCs in which ≥5% of patients in the LTFU Population had AEs were Surgical and medical procedures (24.7% of patients in the Study 012 PEM 1.0% group), Infections and infestations (5.1% of patients in the Surgery/Sclerotherapy arm of Study 001), and Musculoskeletal and connective tissue disorders (6.9% of patients in the Study 001 PEM 1.0% group).

At the Preferred Term level, a few AEs occurred in ≥5% of patients only in the Study 012 PEM 1.0% group. These were: Thrombectomy (7.8% of patients), Endovenous ablation (6.5% of patients), Phlebectomy and Sclerotherapy (5.2% of patients, each).

Conclusion: In the PCS Population, the SOCs in which patients most commonly experienced AEs (i.e., occurring in ≥5% of patients) were the Musculoskeletal and connective tissue disorders, General disorders and administration site conditions, Vascular disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, Injury, poisoning and procedural complications, and Infections and infestations SOCs.

At the Preferred Term level, the most common AEs in PEM-treated patients in the PCS Population were Pain in extremity (14.9%), Infusion site thrombosis (10.5%), Thrombophlebitis superficial (9.2%), Limb discomfort (7.3%), Venous thrombosis limb (5.5%), and Injection site hematoma (5.3%).

7.4.2 Laboratory Findings

In the pooled clinical studies of PEM, the only signal for a treatment-related change in laboratory parameters was a slight but consistent decrease from baseline in hemoglobin and hematocrit in PEM-treated patients. Median decreases from baseline to Week 1 in hemoglobin for PEM-treated patients in the placebo-controlled studies ranged from 0.1 to 0.3 g/dL, and for hematocrit ranged from 0.2% to 1.0%. The mechanism of these decreases in hemoglobin and hematocrit in PEM-treated patients is unknown, but it is possible that they are related to the mobilization of peripheral fluid due to post-procedural use of compression stockings, or to the hemolysis of red blood cells caused by contact with the microfoam.

Two PEM-treated patients had treatment-emergent abnormalities in hemoglobin and/or hematocrit values reported as AEs.

- Patient 01-1018 in Study COM001 was a 48-year-old woman who had an AE of Anemia on study Day 29 (28 days after a single treatment with PEM 1.0%).
- Patient 001-1003 in Study 003 was a 44-year-old woman who had an AE of Microcytic anemia on study Day 22 (21 days after a single treatment with PEM 1.0%).

In this patient population, no clinically meaningful post-treatment changes in mean or median values were noted for any biochemistry parameter (i.e., glucose, potassium, sodium, chloride, carbon dioxide, blood urea nitrogen [BUN], creatinine, creatinine clearance, bilirubin, aspartate aminotransferase [AST], or alanine aminotransferase [ALT]):

- Five patients had serum creatinine increased >1.5 times their baseline values (2 were treated with surgery, 2 with 1% PEM and 1 with placebo).
- 12 patients had potentially clinically significant abnormalities in hepatic enzymes and/or bilirubin, of which 11 had elevated baseline values and the 12th had a baseline value at the upper limit of the normal range. Thus, the changes observed are not clinically meaningful.
- Two patients had AEs of hypothyroidism 75-82 days after treatment session, 1 patient with an AE of progesterone decrease and one had an AE of testosterone decrease.
- Two PEM-treated patients (and no patient treated with placebo or other control) had AEs related to abnormalities in clotting times.

Blood samples for D-dimers were collected from all patients in study 0005, patients who participated in Study 016 D-dimer substudy, and all patients with venous thrombus AEs in Studies 008, 015, 016 and 017. Seventeen patients had AEs related to abnormal D-dimer values; all were treated with PEM 1% in Study 0005 and none had venous thrombus AEs. It was likely that PEM treatment itself caused elevated D-dimer levels, irrespective of whether the patient had a venous thrombus or not.

7.4.3 Vital Signs

Detailed vital sign data were collected in Study 003 (at screening and for at least 10 post-treatment time points (1, 2 and 24 hours following the first treatment session and on days 4, 7, 14, 21, 28, 35 and 56) through Week 8 after the last study treatment

session), and in Studies 0005, 012, 013 and 014. In the remaining studies, vital signs were assessed only at screening or (pre-treatment) baseline.

There were no changes of clinical interest in diastolic BP, oral temperature, pulse rate or respiratory rate. One or more patient had transient decreases in systolic BP of ≥20 mmHg; none were associated with symptoms or classified as an AE.

7.4.4 Electrocardiograms (ECGs)

At the end-of-Phase-2 meeting between the Division and the sponsor (22-Jul-2009), it was agreed that in lieu of a formal thorough QT study, confirmation of QT safety could be ascertained by obtaining well-standardized ECGs in triplicate at peak plasma concentration during the PK study (VAP.VV008). In this study, a 12-lead ECGs was taken (i) at screening, and 3 serial 12-lead ECGs were downloaded 1-minute apart from the H-12+ flash card of a Kortara Instrument which made continuous digital records of ECGs at (ii) 30 minutes before treatment and at (iii) 30 minutes following initial injection of PEM. Apart from a slight increase in heart rate (mean change +1.1 bpm in the PEM 1.0% group and +1.3 bpm in the PEM 2.0% group) at 4 to 6 hours after administration of PEM, there was:

(i) no signal of any effect on atrioventricular conduction or cardiac depolarization, as measured by the PR and QRS interval durations,

(ii) no significant effect on cardiac repolarization as measured by the lack of a significant change in QTcF, and

(iii) no new morphological changes. This ECG study showed no evidence of a dose-related effect of PEM on QTcF.

Also, Studies 0005, 003 and 012 included pre- and post-treatment ECG, cardiac enzymes, Holter monitoring, transthoracic ultrasound and oxygen saturation and end-tidal CO_2 evaluations; there were no clinically significant changes in ECG parameters from baseline. One exception was a patient (#1011) in Study 003 who showed isolated pre-ventricular contractions from the pre-treatment time period until 1 hour post-treatment on Holter Monitoring; this patient was asymptomatic and the event resolved spontaneously without sequelae.

The results of ECG, Holter monitoring, cardiac enzymes, transthoracic ultrasound and oxygen saturation and end-tidal CO_2 evaluations consistently demonstrated no adverse cardiac or cardiopulmonary effects following treatment with PEM.

7.5 Other Safety Explorations

7.5.3 Drug-Demographic Interactions

Most patients in the PCS Population were white (91% to 97%), female (69% to 78%) and non-Hispanic/Latino (70% to 95%). Drug-demographic interactions were examined in Study 008 (a safety and PK study of polidocanol following treatment with 10 mL of

PEM 1.0% or PEM 2.0% as two 5 mL injections administered 10 minutes apart). PK and safety parameters (i.e., ECGs, duplex ultrasound evaluations for venous thrombus AEs, and occurrence of AEs and SAEs) were analyzed by treatment and gender.

In Study 008, plasma polidocanol concentration (C_{max} and AUC) appeared to increase with higher PEM dose-concentration, being higher in female patients than in male patients and appears to be related to weight. When weight-normalized data were analyzed, no consistent differences in C_{max} and AUC values between male and female patients treated with PEM 1.0% and PEM 2.0% were noted. Polidocanol was rapidly detected in the plasma of all patients following injection into the GSV or other major accessory vein, and C_{max} was reached within 15 minutes of the 1st injection and 5 minutes of the 2nd injection. Bioavailability, terminal elimination half-life ($T_{1/2}$), volume of distribution (V_d) and rate of clearance (CL) were similar in male and female patients.

Male patients in Study 008 had a higher rate of AEs (100% in PEM 1.0% group and 50% in PEM 2.0% group, compared with 16.7% in PEM 1.0% group and 33% in PEM 2.0% group for female patients). The 3 patients in Study 008 with venous thrombus AEs were male. The numbers of male and female patients in this study were small (9 and 12, respectively), so it is not possible to draw conclusions based on the available data.

Table 40 Potential Predictive Factors by Demographic Data for Venous Thrombosis Events – All PEM Treatment Sessions

Predictive Factor					PEM Dose				
Factor	**Levels**	**Odds Ratio[a]**	**95% CI[b]**	**P-Value[c]**	**PEM Dose**	**Odds Ratio[d]**	**95% CI[b]**	**P-Value[c]**	**Interaction P-Value[e]**
Age	18 to 40			0.650	**0.125%**			0.225	0.811
	41 to 64	1.00	[0.57, 1.77]		**0.5%**	1.58	[0.52, 4.85]		
	≥65	1.41	[0.61, 3.27]		**1.0%**	1.42	[0.56, 3.63]		
					2.0%	2.99	[0.94, 9.51]		
Sex	Male			0.021	**0.125%**			0.248	0.503
	Female	0.57	[0.35, 0.92]		**0.5%**	1.54	[0.50, 4.72]		
					1.0%	1.39	[0.54, 3.54]		
					2.0%	2.89	[0.91, 9.20]		
Race	Caucasian			0.914	**0.125%**			0.233	0.553
	Non-Caucasian	0.94	[0.28, 3.09]		**0.5%**	1.59	[0.52, 4.88]		
					1.0%	1.43	[0.56, 3.65]		
					2.0%	2.97	[0.93, 9.47]		
BMI, Kg/m^2	<25			0.662	**0.125%**			0.257	0.756
	25-<30	1.25	[0.73, 2.13]		**0.5%**	1.60	[0.52, 4.91]		
	≥30	1.27	[0.67, 2.40]		**1.0%**	1.53	[0.59, 3.95]		
					2.0%	3.02	[0.95, 9.62]		

[a] Relative to the level of predictive factor in the top row (categorical) or increase by 5 (continuous) [BMI, GSV Diam and Volume]. From model VT(Y/N) = FACTOR + PEM DOSE, with FACTOR and PEM DOSE as class variables in one model, and separately in another, FACTOR as a continuous covariate and PEM DOSE as class variables. [b] Wald confidence limit. [c] Wald Chi-Square.
[d] Relative to lowest dose. From models as detailed in footnote "a".
[e] Wald Chi-Square for interaction term from model VT(Y/N) = FACTOR + PEM DOSE + FACTOR*PEM DOSE, with FACTOR and PEM DOSE as class variables in one model, and separately in another, FACTOR as a continuous covariate and PEM DOSE as class variables.
NOTE: "By patient analysis" is according to PEM dose at first PEM session (Main Study or Optional Treatment Period in those on Vehicle in Main Treatment Period). Treatment sessions (and any corresponding VTs) after the first PEM dose are excluded.

Table 40 shows the occurrence of AEs by the demographic characteristics of sex, age

group (i.e., 18-40, 41-64 or ≥65 years of age), race (i.e., white or non-white) and BMI group (i.e., <25, 25-29, ≥30 kg/m^2) in the All PEM Treatment Sessions Population.

AEs by gender: Male subjects constitute 29% of PEM-treated patients in the All Studies Population. There was no notable difference between men and women in the proportion of patients with one or more AEs, severe AEs, or serious AEs, with the following exceptions:

(i) more male patients treated with PEM had higher risk for AEs in the general disorders and administration site conditions SOC and nervous system disorders SOC;

(ii) more female patients treated with PEM had higher risk for contusion AEs; and

(iii) PEM-treated male patients had a higher rate of AEs, compared with female patients, with a statistically significant association between male sex and occurrence of venous thrombus AE following the first PEM treatment session (*P*=0.0021).

AEs by age: Older PEM-treated patients ≥65 years of age had a higher overall rate of AEs than younger patients, though this association was not statistically significant. There was a general trend for younger patients treated with PEM to have increased risk for AEs in the nervous system disorders SOC and AEs pain in extremity, headache and infusion site thrombosis compared with older patients, and, on the other hand, have lowest risk for vascular disorders SOC. Older patients generally tend to have higher risk for events in the injury, poisoning and procedural complications, and subcutaneous tissue disorders SOCs, and for the AEs skin discoloration and thrombophlebitis (superficial) compared with patients 18 to 40, and 41 to 64 years age.

AEs by race: The small number of non-white patients (47 PEM-treated and 7 placebo-treated) in the pooled ISS database made it difficult to compare event rates across white and non-white patients. There was no statistically significant association between race and the occurrence of venous thrombus AEs following the first PEM treatment session, and of AEs, serious AEs, and severe AEs.

AEs by Body Mass Index: PEM-treated patients with BMIs ≥30 kg/m^2, compared with patients in the lower BMI groups, have a higher risk for the event of Infusion site thrombosis, but no statistically significant association between BMI and the occurrence of thrombosis was found. There was no notable difference in the percent of patients with one or more SAEs.

AEs by Creatinine Clearance: The percents of patients in the Pooled PEM group with calculated creatinine clearance of <60 mL/minute and ≥60 mL/minute who had severe AEs (6.1% and 5.9%), SAEs (0% and 0.3%), and AEs leading to withdrawal (0% and 0.7%) were similar. In the placebo group, of the 2 patients with a calculated creatinine clearance of <60 mL/minute, 1 patient had one or more AEs. The number of patients with baseline calculated creatinine clearance of <60 mL/minute was too small to make meaningful comparisons of event rates between this group and patients with baseline calculated creatinine clearance ≥60 mL/minute.

7.5.4 Drug-Disease Interactions

Table 41 shows that there is no clear interaction between CEAP Clinical Class (i.e., C_2, C_3, C_4 and $C_{5\&6}$) and most AEs that occurred following treatment with PEM, although patients with CEAP Clinical Class $C_{5\&6}$ disease appear to have a higher risk of Thrombosis events compared to patients with lower CEAP Clinical Class disease at baseline. However, because of the relatively small number of patients with CEAP Clinical Class $C_{5\&6}$ disease, it is not possible to draw meaningful conclusions. There was no statistically significant association between CEAP Clinical Class and occurrence of venous thrombus AE following the first PEM treatment session.

Table 41 Potential Predictive Factors by CEAP Class for Venous Thrombosis Events – All PEM Treatment Sessions

Predictive Factor					PEM Dose				
Factor	Levels	Odds Ratio[a]	95% CI[b]	P-Value[c]	PEM Dose	Odds Ratio[d]	95% CI[b]	P-Value[c]	Interaction P-Value[e]
CEAP	C2			0.198	**0.125%**			0.417	0.715
	C3	1.69	[0.99, 2.88]		**0.5%**	1.58	[0.51, 4.85]		
	C4	1.36	[0.65, 2.83]		**1.0%**	1.56	[0.61, 3.99]		
	C5 & C6	2.44	[0.69, 8.57]		**2.0%**	2.84	[0.83, 9.74]		

[a] Relative to the level of predictive factor in the top row (categorical) or increase by 5 (continuous) [BMI, GSV Diam and Volume]. From model VT(Y/N) = FACTOR + PEM DOSE, with FACTOR and PEM DOSE as class variables in one model, and separately in another, FACTOR as a continuous covariate and PEM DOSE as class variables.
[b] Wald confidence limit. [c] Wald Chi-Square. [d] Relative to lowest dose. From models as detailed in footnote "a".
[e] Wald Chi-Square for interaction term from model VT(Y/N) = FACTOR + PEM DOSE + FACTOR*PEM DOSE, with FACTOR and PEM DOSE as class variables in one model, and separately in another, FACTOR as a continuous covariate and PEM DOSE as class variables.
NOTE: "By patient analysis" is according to PEM dose at first PEM session (Main Study or Optional Treatment Period in those on Vehicle in Main Treatment Period). Treatment sessions (and any corresponding VTs) after the first PEM dose are excluded.

7.5.5 Drug-Drug Interactions

In the All Studies Population, as in the PCS Population, the percent of patients reporting one or more concomitant medical conditions was similar in the Pooled PEM (88.4%) and placebo (82.1%) groups. Nearly all of the patients in every treatment group reported at least one concomitant medication (range: 99.1% to 100%), with the most commonly-reported concomitant medications being similar to those in the PCS Population.

No drug interaction studies were performed with PEM because: (i) the active agent in PEM, polidocanol, is marketed in the US and other countries, (ii) the target population of patients undergoing treatment with PEM is likely to be generally healthy and receiving few concomitant medications, (iii) treatment with PEM is episodic, not chronic, (iv) the product is administered via catheter into a target vein, which subsequently becomes occluded in a controlled medical setting so that the exposure to PEM is brief ($T_{½}$: 102-153 minutes) making drug interactions unlikely, and (v) PEM is not to be mixed or administered with any other product. The sponsor's explanation appear reasonable.

7.6 Additional Safety Evaluations

There were many SOCs and Preferred Terms for which the difference between the Pooled PEM and placebo groups was ≥5% or ≥3%, respectively; however, there is no clear pattern of increased risk among most of the sub-groups examined for most of the events and types of events examined.

A greater percent of patients aged ≥65 years, male patients, and patients with baseline calculated creatinine clearance of <60 mL/minute had one or more AEs, compared with younger patients, female patients, and patients with baseline calculated creatinine clearance of ≥60 mL/minute, respectively.

Patients with body mass indexes >30 kg/m^2 may have a higher risk of events in the Vascular disorders SOC and of the AEs Infusion site thrombosis and Thrombophlebitis superficial; this may be related to difficulty ensuring adequate post-procedure compression of the treated leg.

Because of the small numbers of patients in many subgroups, it is not possible to draw further conclusions about risk for AEs based on the available data.

7.6.4 Overdose, Drug Abuse Potential / Withdrawal and Rebound

No formal studies of withdrawal or rebound were conducted, and withdrawal or rebound effects are not anticipated following administration of PEM.

7.7 Additional Submissions / Safety Issues

7.7.1 Risk Management Plan

The sponsor submitted a risk management plan to mitigate the risks of proximal DVT and common femoral vein thrombus extension, pulmonary embolism, hypersensitivity and anaphylactic reactions, neurological events and accidental intra-arterial injection.

In this NDA, there is no finding of an increased risk of neurological or visual events, pulmonary emboli, or anaphylactic reactions. DVTs and venous thrombus AEs were detected by ultrasound evaluations only, and were mostly asymptomatic and resolved or stabilized rapidly. Intravenous injection of PEM under ultrasound guidance prevented intra-arterial injection. Thus, there is NO reason to recommend a REMS for this NDA.

The purpose of a REMS is to help the patient and/or the physician reduce the risks of a potentially fatal or serious adverse event.

In the case of PEM treatment for varicose veins, a Medication Guide will not serve this purpose because this drug is not taken by the patient. PEM is injected to a maximal volume of 15 mL per treatment session, performed under visual ultrasound guidance by a qualified and trained physician. At the low total doses (19.5 mg maximum) used,

polidocanol does not reach significant levels in the systemic circulation.

A physician communication plan does not help the patient or the physician because the application-specific safety issues of neurological events, deep venous thromboses or anaphylactic reactions are exceedingly rare with this drug product.

In >55 million sclerotherapy exposures to polidocanol injections (including various foam forms of polidocanol) spanning half a century of treatment in different clinical settings in many countries reported in the medical literature, there is no evidence that neurologic events, venous thromboembolic events and anaphylactic reactions are more frequent than one would expect with any other parenteral drug for cosmetic purposes (e.g., botulinum toxin (Botox) to treat glabellar lines) which do not require a REMS.

Based on the clinical data in the application and comprehensive safety data reported in the medical literature, my opinion is that a REMS is not necessary for approval.

7.7.2 Postmarket Requirements and Commitments

The sponsor will submit to FDA a complete training manual and video that will be used to provide education and training to health care providers (physicians and clinical staff).

Only physicians who have completed this training will be able to order PEM from the designated distributor to administer or supervise administration of the PEM.

The sponsor will conduct an assessment of spontaneous reports of death, stroke, neurological or visual event, pulmonary embolism, deep vein thrombosis, and anaphylactic reaction in patients treated with PEM, and submit them in periodic safety update reports / periodic adverse drug event reports (PSURs/PADER).

8 Postmarket Experience

There is no post-marketing experience for the drug product submitted for approval in this application.

9 Appendices

9.1 Literature Review/References

Sclerosing microfoam

Many methods for the production of sclerosing foam have been described[13]:

- The Monfreux (MUS) method (1995): The foam is produced in a "glass" syringe filled with 0.3 – 0.5 ml of sclerosing liquid. The tip of the syringe is closed with a sterile plug, and tension on the piston is exerted until 2-3 ml of foam are generated. This foam is long-lasting (3 hr. *in vitro*, 20 min *in vivo*), but has relatively large-diameter bubbles, is difficult to standardize, and is associated with a high rate of side effects (because the large bubbles spread easily along vessels).
- The Cabrera Method (1997) used CO_2 or physiologic gas to make a foam with a sclerosing agent.
- The Benigni-Sadoun method used repeated and fast pulling and release actions of the piston of a plastic syringe to generate a short-lasting, medium quality foam.
- The Garcia Mingo method produces a sclerosing foam using a special device that generates compressed air.
- The Tessari method (1999) uses two disposable syringes and a three-way tap to produce a high-quality foam with purified sodium tetradecylsulfate (STS). The foam produced is very compact with very small-diameter bubbles.
- The Frullini method (2000) applies the same turbulence effect of the Tessari method to generate the foam. A small connector is inserted to a 5 ml vial of STS with a rubber cap; a 2.5 or 5 ml disposable syringe filled with a pre-determined volume of air is connected to the system, and, after positioning the vial upside down, quick injections/aspirations of the solution are performed.

A comparison of patients' response to sclerosing foam[13,39] produced by the MUS method (257 patients) and Tessari method (196 patients) showed less adverse events with the Tessari method. However, there was no randomized allocation of patients, and the patients were not matched for disease severity. This study[13] indicated that the volume of foam injected per session should not exceed 3 ml, and reported three cases of thrombus propagation in the deep vein system.

A classification of sclerosing foams has been proposed as follows[39]:

Froth: Bubbles with diameters in mm (Orbach method of simple mixing of air with a detergent solution)

Foam: Bubbles with a diameter >100μ (Monfreux method)

Minifoam: Bubbles with diameter 50 - 100μ

Microfoam: Bubbles with diameter <50μ.

Treatment of varicose veins using sclerosing microfoam

Cabrera et al in Granada, Spain, reported patients treated during 1993 through 1999 with sclerosing microfoam[40]. Some of these patients were followed up for 4-6 years. Of 415 patients with incompetent long saphenous vein (LSV) of diameter >9 mm, 80% had LSVs obliterated, with disappearance of all superficial branches in 95% of legs. Of 265 patients with recurrence after surgical treatment, 81% of recurrent veins were obliterated, and 90% of the branches had disappeared. Of 72 patients with venous ulcers, 77% of patients had their LSVs closed after 2.5 years post-treatment; recanalization of perforating veins caused recurrence in the remainder. Of 31 patients with venous malformations, all were reduced in size, and 9 had disappeared completely. The study reported transient adverse events such as cough, inflammation and photopsia. There were no occurrences of DVT or pulmonary embolism or scotoma.

Cabrera's group reported another study of 50 patients[41] (19 with limited venous malformations, 16 with infiltrating venous malformations, and 15 with Klippel-Trenaunay syndrome) treated with 0.25% to 4% polidocanol microfoam (CO_2 micro-bubbles with a small diameter) injected under duplex ultrasound guidance. 46 patients were adjudicated as responders, among whom 18 showed disappearance of the malformations, 15 showed >50% reduction in size of the malformation, and 13 showed ≤ 50% reduction in size. Of 39 patients presenting with pain, the pain disappeared in 25 patients, and was reduced in 14. The only adverse events reported were 4 cases of transient skin pigmentation and 3 cases of skin necrosis.

Two studies were reported by Barrett's group in Auckland, New Zealand, working together with a dermatology clinic in La Jolla, California. The first study[42] reported an analysis of 100 randomly chosen legs with varicose veins treated with ultrasound-guided foam sclerotherapy. The mean duration of follow up was 22.5 months. An average of 2.1 treatments using an average of 8.7 ml of sclerosing foam were required to close incompetent varicose veins. 31% of legs required a second treatment at 3 months. 100% of patients reported that they "felt" their legs were successfully treated, with resolution of symptoms in 85% and of varicose veins in 92%.

The second study by Barrett's group compared the results of treatment with ultrasound-guided foam sclerotherapy[43] in a subgroup of 17 saphenous veins with diameter ≥10 mm at the sapheno-femoral or sapheno-popliteal junction to that of a subgroup of 98 saphenous veins with a diameter <10 mm. A mean of 2.15 treatments using an average of 8.37 ml of sclerosing foam were required to close all incompetent veins in the <10-mm group, versus a mean of 2.8 treatments and 13.9 ml foam for the ≥10-mm group. At 3 months, a second treatment was required in 27.5% of saphenous veins <10 mm, and 37.5% of saphenous veins ≥10 mm. At 2 year follow up, improvement in quality of life was reported by 94% of patients in the <10-mm group and 100% in the ≥10-mm group.

A prospective, multicenter trial of sclerosing foam (using the double syringe method and 3% polidocanol) vs. sclerosing liquid (3% solution of polidocanol) to determine the rates of elimination of reflux in the GSV and of recanalization[44] randomized 88 patients to

treatment with sclerosing foam (45 patients) or sclerosing liquid (43 patients). Follow-up after 3 weeks showed 84% elimination of reflux in the GSV with sclerosing foam versus 40% with sclerosing liquid (P<0.01). At 6 months, there were 2 recanalizations in sclerosing foam group vs. 6 in sclerosing liquid group. No additional recanalization was observed in either group at one year. Side effects did not differ between groups.

Medical literature related to neurological events associated with foam sclerosants

A thorough review of the medical literature related to neurological events that occur in association with treatment of varicose veins using foam sclerosants is presented in Section 7.3.5 (page 75 to 79) of this review.

9.2 Labeling Recommendations

9.2.1 Indications and usage

The indication and usage section of the label appears appropriate. The educational qualification and training of physicians and their staff who will be administering PEM, the process of commercial distribution (whether to be restricted to centers with specially trained care givers), and patient counselling (to keep the post-treatment bandages dry for (b) (4), to keep compression stockings on for 2 weeks continuously and to walk for >10 minutes immediately after the procedure as well as daily for the next month) needs to be further defined in detail.

9.2.2 Dose considerations

As stated in Section 6.1.8 of this review, there is no clear dose-response, but the PEM 1.0% appears to be the most appropriate to recommend for approval based on this dose being associated with (i) highest duplex ultrasound responder (i.e., closure of GSV) rate after which it plateaus off, (ii) lowest rate of treatment failure (SFJ reflux >0.5 sec), (iii) lowest rate of patients with partial treatment failure (GSV incompetence), and, (iv) from the safety perspective, the lowest rate of venous thrombus AEs. The sponsor is manufacturing only the 1.0% formulation.

9.2.3 Contraindications

This section in the label appears appropriate.

9.2.4 Warnings and Precautions

This section should be modified to be consistent with that of other drugs in class such as the Asclera® label and the Sotradecol® label as follows:

Severe allergic reactions have been reported following polidocanol use, including anaphylactic reactions, some of them fatal. Severe reactions are more frequent with use of larger volumes. Be prepared to treat anaphylaxis appropriately.

Severe adverse local effects, including tissue necrosis, may occur following extravasation; therefore, care should be taken in intravenous needle placement and the smallest effective volume at each injection site should be used.

After the injection session is completed, apply compression with a stocking or bandage, and have the patient walk for 15-20 minutes. Keep the patient under supervision during this period to treat any anaphylactic or allergic reaction

Varithena® should only be administered by a physician familiar with venous anatomy and the diagnosis and treatment of conditions affecting the venous system and familiar with proper injection technique. Severe adverse local effects, including tissue necrosis, may occur following extravasation; therefore, extreme care in intravenous needle placement and using the minimal effective volume at each injection site are important.

Emergency resuscitation equipment should be immediately available. Allergic reactions, including fatal anaphylaxis, have been reported. As a precaution against anaphylactic shock, it is recommended that 0.5 mL of Varithena® be injected into a varicosity, followed by observation of the patient for several hours before administration of a second or larger dose. The possibility of an anaphylactic reaction should be kept in mind, and the physician should be prepared to treat it appropriately.

Under Precautions for use, the following should be added to be consistent with the Sotradecol® and Asclera® labels:

Extreme caution must be exercised in the presence of underlying arterial disease such as marked peripheral arteriosclerosis or thromboangiitis obliterans (Buerger's Disease).

9.3 Advisory Committee Meeting

Not applicable.

9.4 Detailed description of individual studies

The submission contains 12 clinical studies of PEM in patients with varicose veins, which were conducted using 2 different PEM formulations:

(i) The original formulation (Varisolve OF) used a gas mixture that contained (b) (4) and was administered in Studies COM001, 001, 003 and 0005, and to some patients in Study 011, and

(ii) A new formulation (polidocanol endovenous microfoam or PEM, which used a low-nitrogen gas mixture and was intended for licensure) was used in some patients in Study 011 (for comparison), and in all subsequent clinical studies of PEM, namely, Studies 008, 012 and 014, and in Phase 3 Studies 013, 015, 016 and 017 (and 2 patients treated in the prematurely-discontinued Study 007).

In this section, brief clinical review of clinical study reports of the pivotal studies 015 and 016, as well as studies 008, 012, 013, 014 and 017 are presented.

9.4.1 Clinical classification of varicose veins

CEAP- Classification[45] of chronic venous disorders according to Eklöf et al., 2004
C_0: No visible or palpable signs of venous disease.
C_1: Telangiectases (spider veins) or reticular veins.
C_2: Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more.
C_3: Edema.
C_4: Changes in skin and subcutaneous tissue secondary to CVD, now divided into 2 subclasses to better define the differing severity of venous disease:
C_{4a}: Pigmentation or eczema. C_{4b}: Lipodermatosclerosis or atrophie blanche.
C_5: Healed venous ulcer. C_6: Active venous ulcer.
S: Symptomatic (ache, pain, tightness, skin irritation, heaviness, muscle cramps); A: Asymptomatic

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

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

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

Example: For the patient who has painful swelling of leg, varicose veins, and acute ulceration with duplex scan showing reflux of great saphenous vein above and below the knee, incompetent calf perforator veins, and axial reflux in femoral and popliteal veins, the classification is: **C**6,s**, E**p**, A**s,p,d**, P**r

Reticular veins
- Dilated bluish subdermal veins, usually 1 mm to less than 3 mm in diameter. Usually tortuous.
- Excludes normal visible veins in persons with thin, transparent skin.
- Synonyms include blue veins, subdermal varices, and venulectasies.
- In this study the term “reticular veins” or “reticulars” was used.

Telangiectases
Confluence of dilated intradermal venules less than 1 mm in caliber. Synonyms include spider veins, hyphen webs and thread veins. In this study the term “spider veins” or “spiders” is used.

9.4.2 Study 015

Title: A randomized, blinded, multi-center study to evaluate the efficacy and safety of Varisolve® Polidocanol Endovenous Microfoam (PEM) 0.5%, 1.0% and 2.0% compared to vehicle for the treatment of saphenofemoral junction (SFJ) incompetence (Study 015 CSR).

Objectives:
- **Primary:** to evaluate the efficacy at Week 8 of Polidocanol Endovenous Microfoam (PEM) 0.5%, 1.0% and 2.0% (pooled), compared with Vehicle placebo, in the improvement of symptoms as measured by a disease-specific symptom questionnaire, the Varicose Vein Symptom Questionnaire (VVSymQ), as administered using an electronic daily diary (e-diary).
- **Secondary:** The co-secondary objectives of this study are to evaluate the efficacy at Week 8 of PEM 0.5%, 1.0% and 2.0% (pooled), compared with Vehicle placebo, in the improvement of appearance of visible varicosities according to:
  1. An Independent Photography Review (IPR) panel using the Independent Photography Review –

Visible Varicose Veins (IPR-V^3) appearance assessment instrument, and
2. A patient self-assessment of varicose vein appearance using the Patient Self-assessment of Visible Varicose Veins (PA-V^3) instrument.

Study subjects: Study subjects were male and female adult patients who were age of consent up to and including 75 years. Eligible patients had SFJ incompetence associated with incompetence of the GSV or other major accessory vein and superficial venous disease manifested by both symptoms and visible varicosities, where SFJ incompetence was the predominant source of reflux. Study patients were also required to have a paper screening VVSymQ instrument score ≥7 points; a PA-V^3 score of moderately noticeable, very noticeable, or extremely noticeable in leg to be treated; and an IPR-V^3 score of moderate, severe, or very severe in leg to be treated. In order to have 225 evaluable patients for the primary efficacy analysis, 250 patients were planned to be randomized.

Treatments: Patients who met the study entry criteria were randomized 1:1:1:1:1 to receive PEM 0.125% (control), PEM 0.5%, PEM 1.0%, PEM 2.0%, or Vehicle placebo (maximum volume per treatment session: 15 mL). Randomization using an Interactive Voice Response System (IVRS) occurred the day before or on the day of Visit 2 (baseline) and was stratified by site and by baseline VVSymQ score (≤14 or >14 on a scale of 0 to 25). Following treatment, all patients were to comply with a 14-day compression therapy protocol.

All patients had a treatment session with blinded study product on Study Day 1 (Visit 2). Following Visit 5/Week 8, patients could opt for an open-label (OL) treatment session with PEM 1.0% (Visit 6). All patients in this ongoing study were followed through Year 1. The total duration of the study was 15 months; this included a screening period of up to 60 days (2 months) before Visit 2.

Primary efficacy endpoint: The primary efficacy endpoint of this study was the absolute change from baseline in the 7-day average e-diary VVSymQ score at Week 8 in patients treated with PEM 0.5%, 1.0% and 2.0% (pooled), compared with Vehicle placebo.

Co-secondary efficacy endpoints: The co-secondary efficacy endpoints of this study were the absolute changes from baseline to Week 8 in patients treated with PEM 0.5%, 1.0% and 2.0% (pooled), compared with Vehicle placebo, in:
1. Independent Photography Review – Visible Varicose Veins (IPR-V^3) score (as assessed by a panel of 3 trained, blinded physician reviewers), and
2. Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V^3) score (an assessment made by the patient).

Tertiary efficacy endpoints: The tertiary efficacy endpoints of this study were:
1. Response to treatment at Week 8 as determined by duplex ultrasound, which was defined as the elimination of reflux through the SFJ and/or complete occlusion of the target vein(s), assessed by the site sonographer;
2. Absolute change from baseline to Week 8 in Venous Clinical Severity Score (VCSS), assessed by the study physician;
3. Absolute change from baseline to Week 8 in the modified Venous Insufficiency Epidemiological and Economic Study – Quality of Life (VEINES-QOL) score, assessed by the patient.

Safety assessments: Safety assessments include duplex scanning for presence of venous thrombus, monitoring of AEs, collection of concomitant medication data, pregnancy testing for women of childbearing potential, clinical laboratory testing (complete blood count [CBC] and serum chemistry) and neurological assessments for patients with neurological and/or visual signs or symptoms within 24 hours following study treatment.

Exposure: 284 patients were randomized, and 279 patients received at least one study treatment.

Analysis sets: The Safety Population was defined as all patients who received at least 1 injection of PEM or Vehicle placebo. This population was to be used in all safety summaries.

The Efficacy Population was defined as all patients in the Safety Population who provided data for at least

1 post-baseline assessment for either the primary efficacy endpoint or a secondary efficacy endpoint.

Demographic and Baseline Characteristics: The study population was representative of the population that would be expected to receive treatment with PEM. Baseline characteristics were similar across treatment groups: the majority of patients were Caucasian women, the mean age of study patients was 49 years and the mean body mass index (BMI) was 28 kg/m^2. Over 90% of patients had venous disease that was CEAP Class C2, C3, or C4 at study baseline, and a few patients had CEAP Class C5 or C6.

Efficacy Results: *See Section 6 of this review for detailed review of efficacy results.*

Blinded treatment with PEM 0.5%, 1.0% and 2.0% (pooled) was statistically significantly superior to Vehicle placebo in the primary efficacy analysis, decrease in varicose vein symptoms as measured by the absolute change in VVSymQ score from baseline to Week 8 (P<0.0001). Treatment with PEM 0.5%, 1.0% and 2.0% (pooled) led to a more than 2-fold higher decrease (i.e., improvement) in VVSymQ score, compared with Vehicle placebo (-5.44 vs. -2.13 points).

Treatment with PEM 0.5%, 1.0% and 2.0% (pooled) was also statistically significantly superior to Vehicle placebo in the co-secondary efficacy analyses, improvement in the appearance of visible varicose veins, as measured on the IPR-V^3 and PA-V^3 instruments (both *P*<0.0001). Treatment with pooled PEM led to a large decrease (i.e., improvement) in IPR-V^3 score, compared with virtually no change in Vehicle placebo (-0.81 vs. -0.01 points), and an about 11-fold greater decrease in PA-V^3 score (-1.58 vs. -0.15 points).

In the tertiary endpoint analyses, patients treated with PEM 0.5%, 1.0% and 2.0% (pooled) had higher rates of response to treatment as determined by the duplex ultrasound at 8 weeks, compared with those treated with PEM 0.125% (control), and a clear dose response was evident among the PEM-treated groups. Patients treated with PEM 0.5%, 1.0% and 2.0% (pooled) also had greater improvement from baseline to Week 8 in VCSS and VEINES-QOL scores, compared with patients treated with Vehicle placebo (P<0.0001 for all comparisons).

Safety Results: *See Section 7 of this review for detailed review of safety results.*

No deaths, serious adverse events (SAEs), or AEs leading to withdrawal were reported in this study. One patient became pregnant while on-study (75 days after study treatment) and birthed a baby boy at 40-weeks' gestation on (b) (6) without complications.

No PEM-treated patient was referred for evaluation of visual or neurological symptoms.

The percent of patients with treatment-related AEs was similar across PEM dose concentrations. The treatment-emergent adverse events (TEAEs) that occurred with the highest incidence in the 223 patients treated with PEM, compared with the Vehicle placebo group, were Thrombophlebitis superficial, Pain in extremity, Injection site haematoma, Venous thrombosis limb, Infusion site thrombosis and Upper respiratory tract infection. The TEAEs that increased in incidence with higher PEM dose concentration were Infusion site thrombosis, Limb discomfort, Venous thrombosis limb and Deep vein thrombosis, all of which are expected events for the PEM procedure.

Twenty-seven patients treated with PEM had venous thrombus AEs in a non-target vein. Venous thrombus AEs were detected on protocol-scheduled duplex ultrasound evaluations; no patient presented spontaneously with signs or symptoms of a venous thrombus or worsening of an existing thrombus.

One patient presented with symptoms of pulmonary embolism (PE; i.e., chest pain and dyspnea); the symptoms resolved the same day, and PE was not diagnosed by laboratory investigations. No other patient presented with symptoms of PE, despite specific inquiry, and no pulmonary emboli were reported.

The thrombi that occurred in this study were small (median thrombus volume of 0.83 cm3), and all had resolved or stabilized as of the cutoff date for this report. The follow-up rate for patients with venous thrombus AEs was 100%. Most thrombi were asymptomatic (88%), and all resolved or stabilized within 100 days (median time to stabilization or resolution: 21 days), regardless of whether the patient was merely observed, or received a short course (< 2 weeks) of low molecular weight heparin (LMWH) or 3 months of anticoagulation.

9.4.3 Study 016

Title: - A randomized, blinded, multicenter study to evaluate the efficacy and safety of Varisolve® Polidocanol Endovenous Microfoam (PEM) 0.5% and 1% compared to Vehicle for the treatment of saphenofemoral junction (SFJ) incompetence

Objectives: The objectives of this study were similar to those of Study 015.

Study subjects: Study subjects were male and female patients of age of consent up to and including 75 years who had inclusionary and exclusionary criteria similar to those in Study 015. In order to have 204 evaluable patients for the primary efficacy analysis, 228 patients were planned to be randomized.

Treatments: Patients who met the study entry criteria were randomized 1:1:1:1 to receive PEM 0.125% (control), PEM 0.5%, PEM 1.0% or Vehicle placebo (maximum volume per treatment session: 15 mL). Randomization using IVRS occurred the day before or on the day of Visit 2 (baseline) and was stratified by site and by baseline VVSymQ score (≤14 or >14 on a scale of 0-25). Following treatment, all patients were to comply with a 14-day compression therapy protocol.

All patients had a treatment session with blinded study product on Study Day 1 (Visit 2); there was an optional, additional blinded treatment session 1 week later (Visit 3). Following Visit 5/Week 8, patients could have 1 or 2 optional, open-label (OL) treatment sessions with PEM 1.0%, 1 week apart (Visits 6 and 7). Patients who received an additional blinded and/or OL treatment with PEM were treated using the same canister that was used for the initial blinded or OL treatment, with the goal of supporting a multi-treatment configuration of the PEM canister.

All patients in this ongoing study were followed through Year 1; patients who consented to participate in long-term follow-up are being followed through Year 5. The total duration of the blinded and OL study periods was 15 months for patients participating through Year 1, or 62 months for patients participating through Year 5; these totals included a screening period of up to 60 days (2 months) before Visit 2.

Primary efficacy endpoint: The primary efficacy endpoint of this study was similar to that in Study 015.

Co-secondary and tertiary efficacy endpoints: The co-secondary and tertiary efficacy endpoints of this study were similar to those in Study 015.

Safety assessments: Safety assessments were similar to those in Study 015.

A sub-study was performed at 5 sites to determine post-treatment d-dimer concentrations. At these sites, a blood sample was to be obtained at Visit 3 from all (approximately 80) patients.

Exposure: 235 patients were randomized, and 232 patients received at least one study treatment.

Analysis sets: The Safety Population and the Efficacy Population were similar to those in Study 015.

Demographic and Baseline Characteristics: The study population was representative of the population that would be expected to receive treatment with PEM. Baseline characteristics were similar across treatment groups: the majority of patients were Caucasian women, the mean age of study patients was 50 years, the mean BMI was 30 kg/m^2. Over 90% of patients had venous disease that was CEAP Class C2, C3, or C4 at study baseline, and a few patients had CEAP Class C5 or C6.

Efficacy Results: *See Section 6 of this review for detailed review of efficacy results.*

Blinded treatment with PEM 0.5% and 1.0% (pooled) was statistically significantly superior to Vehicle placebo in the primary efficacy analysis, decrease in varicose vein symptoms as measured by the absolute change in VVSymQ score from baseline to Week 8 (P<0.0001). Treatment with PEM 0.5% and PEM 1.0% (pooled) led to a nearly 3-fold higher decrease (i.e., improvement) in VVSymQ score, compared with Vehicle placebo (-5.53 vs. -2.00 points).

Treatment with PEM 0.5% and 1.0% (pooled) was also statistically significantly superior to Vehicle placebo in the co-secondary efficacy analyses, improvement in the appearance of visible varicose veins,

as measured on the IPR-V^3 and PA-V^3 instruments (both $P<0.0001$). Treatment with pooled PEM led to a 12-fold greater decrease (i.e., improvement) in IPR-V^3 score, compared with Vehicle placebo (-0.87 vs. -0.07 points), and a 6-fold greater decrease in PA-V^3 score (-1.82 vs. -0.32 points).

In the tertiary endpoint analyses, patients treated with PEM 0.5% and 1.0% (pooled) had higher rates of response to treatment as determined by the duplex ultrasound at 8 weeks, compared with those treated with PEM 0.125% (control), and greater improvement from baseline to Week 8 in VCSS and modified VEINES-QOL scores, compared to patients treated with Vehicle placebo ($P<0.0001$ for all comparisons).

Safety Results: *See Section 7 of this review for detailed review of safety results.*

There were no PEM-related SAEs; no AEs leading to withdrawal; no detection of PE; no pregnancies; and no infections in patients who received an optional, additional blinded or OL treatment from the same canister of PEM, in any phase of this study.

No PEM-treated patient reported a visual disturbance or migraine, or was referred for evaluation of visual or neurological symptoms.

In the blinded phase of the study, patients treated with PEM 1.0% had a higher rate of AEs, severe AEs and related AEs than patients in the lower PEM dose-concentration groups. The TEAEs that occurred with the highest incidence in the 175 patients treated with PEM, compared with the Vehicle placebo group, were Infusion site thrombosis, Thrombophlebitis superficial and Venous thrombosis limb. The TEAEs that increased in incidence with higher PEM dose concentration were Infusion site thrombosis, Venous thrombosis limb, Deep vein thrombosis, Tenderness and Limb discomfort, all of which are expected events for the PEM procedure.

Venous thrombus AEs occurred in 24 patients treated with PEM; these were detected only by protocol-required duplex assessment at the protocol-specified visits; no patient presented outside of protocol-scheduled visits with symptoms of a venous thrombus. The venous thrombus AEs occurring in this study were generally mild and resolved, regardless of the treatment provided.

The rate of follow-up for venous thrombus AEs was 100%; no patient subsequently returned with recurrence or progression.

9.4.4 Study 017

Title: A multicenter, randomized, blinded study of endovenous thermal ablation (ETA) with or without Varisolve® Polidocanol Endovenous Microfoam treatment for patients with GSV incompetence and visible varicosities

Objective: To evaluate the efficacy and safety of PEM 0.5% and 1.0% compared with Vehicle placebo when used following ETA during the same treatment session in patients with SFJ incompetence and reflux in the GSV, and with venous disease manifested by both symptoms and visible varicosities. Specifically, the study objectives were as follows:

1. To evaluate the efficacy of ETA + PEM 0.5% and 1.0% at Week 8 compared with ETA + Vehicle placebo to improve the appearance of visible varicosities according to: 1) an Independent Photography Review (IPR) panel using the IPR-V^3 appearance assessment instrument, and 2) patient self-assessment of varicose vein appearance using the PA-V^3 instrument;

2. On an exploratory basis, to evaluate the efficacy at Week 8 of ETA + PEM 0.5% and 1.0% compared with ETA + Vehicle placebo in the improvement of symptoms as measured by a disease-specific symptom questionnaire (the paper VVSymQ).

Study subjects: Male and female patients from age of consent up to and including 75 years of age with SFJ incompetence associated with incompetence of the GSV, who were candidates for ETA (laser or radiofrequency ablation) of the proximal incompetent GSV and also required treatment of visible varicosities and other incompetent areas of the GSV system not treatable with ETA and had superficial

venous disease manifested by both symptoms and visible varicosities, where SFJ incompetence was the predominant source of reflux. Eligible patients had a screening paper VVSymQ instrument score of ≥7 points, a PA-V^3 score of moderately noticeable, very noticeable, or extremely noticeable in leg to be treated; and an IPR-V^3 score of moderate, severe, or very severe in leg to be treated.

Treatments: Patients were randomized 1:1:1 by a central automated IVRS to receive single treatment session with ETA (laser or radiofrequency ablation according to the usual practice at the study site) followed immediately by treatment of visible varicosities and incompetent areas of the GSV system not treated with ETA using PEM 0.5%, PEM 1.0%, or Vehicle placebo (maximum volume of injection: 15 mL).

Co-primary efficacy endpoints: Absolute change from baseline in appearance as assessed by 1) the Independent Photography Review panel (IPR-V^3 at Week 8), and 2) the patient (PA-V^3 at Week 8).

Other efficacy endpoints: (i) Percent of patients who received additional treatment for residual varicose veins ≥3 mm in diameter between Week 8 and the end of study; (ii) absolute change from baseline at Week 8 in the VCSS, paper VVSymQ and VEINES-QOL scores; (iii) duplex response to treatment, as assessed in a subset of patients treated for reflux of the distal GSV, as determined by duplex ultrasound (elimination of reflux through the distal GSV and/or complete occlusion of distal GSV).

Safety assessments: Safety assessments were similar to those in Study 015.

Exposure: 118 patients were randomized and 117 patients were treated in this study.

Analysis sets: The Safety Population and the Efficacy Population were similar to those in Study 015.

Demographic and Baseline Characteristics: The mean age of patients randomized in this study was 52 years (range: 25-72 years): approximately 70% of patients were women and most patients were Caucasian. The mean BMI for the randomized patients was 28.4 kg/m^2. Across treatment groups, the demographic characteristics of the patients were similar. Over 95% of study patients at study baseline had venous disease that was CEAP Class C2, C3 or C4, and a few patients had CEAP Class 5 or 6.

Table 42 Co-Primary Analyses in Study 017

Instrument Treatment Group		Baseline[a] Score		Raw Mean Change from Baseline		Adjusted Mean[b] Change from Baseline		Comparison vs. ETA+Vehicle	
	N[c]	Mean	SE	Mean	SE	Adjusted[b] Mean	SE	Estimate (95% CI)[d]	*P*- value[e]
IPR-V^3									
ETA + Vehicle	38	2.37	0.133	-0.82	0.135	-0.80	0.102		
ETA + PEM 0.5%	39	2.08	0.118	-1.18	0.132	-1.30	0.100	-0.51 (-0.78, -0.23)	0.0005
ETA + PEM 1.0%	40	2.15	0.111	-1.05	0.087	-1.11	0.097	-0.31 (-0.59, -0.04)	0.0252
ETA + PEM Pooled[f] (0.5%+1.0%)	79	2.11	0.081	-1.11	0.079	-1.21	0.070	-0.41 (-0.65, -0.17)	0.0010
PA-V^3									
ETA + Vehicle	38	3.55	0.105	-1.58	0.209	-1.59	0.142		
ETA + PEM 0.5%	39	3.67	0.085	-1.92	0.139	-1.81	0.140	-0.22 (-0.61, 0.17)	0.2649
ETA + PEM 1.0%	40	3.48	0.113	-1.75	0.163	-1.85	0.136	-0.25 (-0.64, 0.13)	0.1939
ETA + PEM Pooled[f] (0.5%+1.0%)	79	3.57	0.071	-1.84	0.107	-1.83	0.098	-0.24 (-0.57, 0.10)	0.1645

[a] Visit 2 (baseline); [b] 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; [c] Number of patients with both a baseline value and a value at the corresponding visit
[d] 95% Confidence Interval for comparison of ETA + PEM vs. ETA + Vehicle placebo based on adjusted means, unadjusted for multiple comparisons
[e] Two-sided significance level for paired comparisons; [f] Co-primary efficacy endpoints; Source: Table 14.2.1.1 and Table 14.2.2.1 in CSR for Study 017.

Efficacy Results: For one of the co-primary appearance endpoints, as measured by the absolute change in IPR-V^3 score from baseline to Week 8, blinded treatment with ETA+ PEM 0.5% and 1.0% (pooled) was statistically significantly superior to ETA+ Vehicle placebo (Table 42).

However, for other the co-primary appearance endpoint, as measured by the absolute change in PA-V[3] score from baseline to Week 8, patients treated with ETA+ PEM 0.5% and 1.0% (pooled) showed greater improvement compared to those treated with ETA+ Vehicle placebo, but the difference was not statistically significant (Table 42).

Thus, the co-primary endpoint for this study was not achieved.

Between Week 8 and Month 6, statistically fewer treatments of residual varicose veins were required, and there was better elimination of SFJ reflux, for patients treated with ETA + PEM 0.5% and 1.0% (pooled) versus ETA + Vehicle placebo.

The absolute change in mean values of the following measures favored the ETA + PEM treatment groups (pooled) over ETA+ Vehicle placebo at both 8 weeks and 6 months post-treatment, but the differences were not statistically significant:

- Improvements in clinical severity (VCSS score) as assessed by the study investigator
- Disease-related quality of life (VEINES-QOL score) as assessed by the patient
- Improvement of symptoms as assessed by the patient (paper VVSymQ score)

Safety results: No deaths or AEs leading to withdrawal occurred. One patient experienced a non-fatal SAE of breast cancer (ETA + Vehicle placebo), and one patient had a pregnancy (ETA + PEM 0.5%) which began about 3 months following treatment, and the outcome was followed to a normal birth.

The percent of patients with one or more AEs increased in a dose-dependent manner, from 74% in the ETA + PEM 0.5% group to 88% in the ETA + PEM 1.0% group. The most common AEs in PEM-treated patients were Thrombophlebitis superficial, Pain in extremity and Contusion.

Venous thrombus events occurred in 6 patients treated with ETA + PEM and 1 patient treated with ETA + Vehicle placebo, and three patients had venous thrombi in gastrocnemius veins; all resolved. Infusion site thromboses were treated by thrombectomy in 8% of ETA + PEM-treated patients.

Small decreases in hemoglobin and hematocrit were observed 1 week after study treatment; there were no other notable changes in laboratory parameters.

9.4.5 Study 008

Title: An open-label single-center study in patients with great saphenous vein incompetence to investigate the pharmacokinetic properties of polidocanol endovenous microfoam (PEM)

The main objective of this study was to assess pharmacokinetic (PK) properties of two different concentrations of PEM. In addition, serial ECGs were evaluated prior to and following treatment to assess the impact of PEM, if any, on cardiac function by direct comparison of ECG intervals and morphology on treatment compared to a pre-treatment baseline and by a PK-PD model

This study was a five week, single center, open-label, randomly assigned by gender, parallel group study. Patients were assigned in a 1:1 ratio to receive either 1.0% (6 males and 6 females) or 2.0% (6 males and 6 females) PEM. The total volume of PEM administered was 10 mL, given in two injections (5 mL per injection) 10 minutes apart. Study enrollment was stopped after 21 patients were treated (instead of the planned 24 patients) because the PK data from the 21 patients was consistent enough to achieve the objectives of the study.

The study primary endpoints were pharmacokinetic. Using plasma samples, the C_{max}, T_{max}, AUC, K_{el}, $T_{½}$ clearance and volume of distribution were calculated and mean concentration-time profiles was plotted. For the purpose of this clinical review, the following results of the PK-PD relationship between the plasma concentrations of PEM 1% and PEM 2% and the ECG parameters are noted.

The mean change from base line for the 1% and 2% dose groups of PEM, respectively, for:

- heart rate showed a change of +1.1 bpm and +1.3 bpm.

- PR interval duration showed a change of +3.9 ms and +0.6 ms.
- QRS interval duration showed a change of -3.1 ms and -1.1 ms.
- QTcF duration using the time-averaged data showed a change of -4.8 ms and -5.0 ms (The time point data also show no signal of any significant effect of PEM on cardiac repolarization).

In outlier analyses, no subjects had an abnormal U wave or a new >500 ms change in QTcF or a >60 ms change from baseline, or a 30-60 ms change from baseline.

No subjects developed new morphologic changes in this trial.

The study concluded that there was no significant effect of PEM on cardiac repolarization.

The findings are summarized in Table 43.

Table 43 Time-averaged mean change from baseline and new outliers by dose group for ECGs

Dose Group	PEM 1%	PEM 2%
Total N	9	12
Heart Rate in bpm (mean change from baseline)	1.1	1.3
Heart Rate Bradycardic Outliers N (%)	0	0
Heart Rate Tachycardic Outliers N (%)	0	0
PR in ms (mean change from baseline)	3.9	0.6
PR Outliers N (%)	0	0
QRS in ms (mean change from baseline)	-3.1	-1.1
QRS Outliers N (%)	0	0
QT in ms (mean change from baseline)	-6.7	-7.7
QT new >500 ms N (%)	0	0
QTcF in ms (mean change from baseline)	-4.8	-5.0
QTcF new >500 ms N (%)	0	0
QTcF new >480 ms N (%)	0	0
QTcF 30-60 ms N (%)	0	0
QTcF >60 ms N (%)	0	0
QTcB in ms (mean change from baseline)	-3.7	-3.6
QTcB new >500 ms N (%)	0	0
QTcB new >480 ms N (%)	0	0
QTcB 30-60 ms N (%)	0	1 (8%)
QTcB >60 ms N (%)	0	0
New abnormal U waves N (%)	0	0
New ST segment depression changes N (%)	0	0
New ST segment elevation changes N (%)	0	0
New T wave inverted N (%)	0	0
New 2nd and 3rd Degree Heart Block, N (%)	0	0
New AF N (%)	0	0
New Complete RBBB & LBBB N (%)	0	0
New MI N (%)	0	0

9.4.6 Study 012

Title: An open-label multicenter safety study of the Varisolve™ procedure for the treatment of varicose veins in patients with right to left cardiac shunt.

The main objective was to determine whether subjects with bubbles detected in the middle cerebral artery (MCA) during the Varisolve™ procedure experienced any subclinical, safety-related events, such as abnormalities on brain magnetic resonance imaging (MRI), neurologic examination, visual field testing, markers of cardiac ischemia, or other symptoms or signs.

The study was a Phase 2, open label, multicenter study. All subjects treated with Varisolve™ were monitored for signs of DVT by duplex scans at 7 and 28 days. Efficacy was assessed by duplex ultrasound at 7 and 28 days post-treatment. AEs were recorded throughout the study period. The protocol design requires a 1-year post treatment follow-up visit; however, the clinical study report pertains to subject evaluations up to and including the Day 28 visit only.

Recruitment of subjects (estimated 100) was to continue until 50 subjects were identified with bubbles in the MCA during or following the Varisolve™ procedure. All subjects were tested for the presence of cardiac right-to-left shunt using agitated saline contrast and subsequent detection of bubbles in the MCA by Transcranial Doppler (TCD). To increase the percentage of study subjects with detection of MCA bubbles during the Varisolve™ procedure, subjects were required to be positive for right-to-left shunt in order to enroll, with the exception of five familiarization subjects at each study center who were to be shunt-negative. Subjects also must have had a normal MRI of the brain within 5 days prior to treatment with Varisolve™.

The primary efficacy endpoints were the frequency and proportion of elimination of reflux in the GSV 2 – 5 cm distal to its point of termination at the SFJ or complete occlusion of the GSV immediately distal to significant tributaries and within 10 cm of the SFJ.

The safety endpoints were evaluated among subjects with detectable MCA bubbles during the Varisolve™ procedure for:

- The frequency and proportion of subjects with lesions suggestive of embolism or infarction on the diffusion-weighted MRI scan at 24 hours and 28 days according to the core lab
- The frequency and proportion of subjects with any MRI lesions not present on the baseline MRI scan according to the core lab
- Changes from baseline in neurological examinations, fundoscopy or visual field testing at 24 hours, 7 days, or 28 days.

Efficacy results: Eighty-one (81) subjects treated with polidocanol endovenous microfoam had at least one post-treatment duplex assessment of efficacy. Elimination of reflux or complete occlusion was reported for 80 of 81 (98%) subjects at Day 7, and for 74 of 81 (91%) subjects at Day 28:

- At Day 28, 71/81 subjects (87.7%) had complete occlusion of the GSV.
- At Day 28, 73/78 subjects (93.5%) had elimination of reflux. (The remaining 3 subjects did not have reflux times recorded at this time point).

Safety results: Detailed review of the neurological safety results are presented earlier in Section 7 (page 69 – 74) of this review.

Pain in the treated extremity and hematoma evacuation was the most common AE. The only serious adverse event was DVT which was reported in six subjects. None were life-threatening or required in-patient hospitalization, and all resolved without clinical sequelae. Post-ablation superficial thrombus extensions (PASTE) into the common femoral vein occurred in four subjects.

One subject complained of “twinkly lights” in her peripheral vision, which occurred approximately one hour after treatment and lasted for 20 seconds. An ophthalmology examination and visual fields immediately after this incident were normal.

There were no new abnormalities on MRI, neurological examination, fundoscopy, or visual fields. No new abnormalities were observed in any subject with respect to cardiac markers or ECG following treatment.

9.4.7 Study 013

Title: A Randomized, single-blind, placebo controlled, multicenter study to evaluate efficacy and safety of Varisolve™ (Polidocanol Endovenous Microfoam) for the treatment of symptomatic, visible varicose veins with saphenofemoral junction (SFJ) incompetence

The main objectives of the study were:

1. To evaluate the efficacy of PEM 1% and placebo (agitated saline) treatment in the relief of symptoms as measured by 2 disease-specific questionnaires (VEINES-Sym/VEINES-Quality of Life [QOL], Chronic Venous Disease Symptoms [CIVIQ-2] Questionnaires)
2. To establish a minimal important difference (MID) for VEINES-Sym and VEINES-QOL
3. To evaluate the efficacy of PEM 1% and agitated saline treatment to improve the appearance of visible varicosities:
   - According to patient and medical global assessments aided by pre-and post-treatment photographs
   - According to a central independent assessor evaluating pre- and post-treatment photographs
4. Using duplex ultrasonography, to evaluate the efficacy of PEM 1% and agitated saline treatment on the elimination of saphenofemoral junction [SFJ] reflux or occlusion of the treated vein
5. To determine whether the agitated saline procedure blinds the patient to treatment assignment.

An additional objective identified during the study was the need to establish an entry criterion for enrolment into the study based on a minimum symptoms score (implemented in Protocol Amendment 3).

The study was a 12-week, randomized, single-blind, placebo-controlled, parallel group, multicenter trial in which patients were randomized 1:1 to receive one of the following treatments:

- Ultrasound-guided endovenous administration of PEM 1%
- Agitated saline injection

The study population consisted of male and female patients aged 18 - 65 years; baseline VEINES-Sym score of < 75 points (at Amendment 3: 29 patients were enrolled after Amendment 3, and 48 patients prior to that); varicose veins with a baseline CEAP Class of C2, C3, C4 or C5; and SFJ incompetence associated with reflux in the great saphenous vein (GSV) or major accessory vein.

Each patient received a single treatment (one leg) during the single-blind period of study. All patients wore compression bandages and a compression stocking (30 to 40 mmHg) on the treated leg for the first 48 hours after treatment. Following that, the compression stocking alone was worn 24 hours a day for a further 12 days. Patients were required to walk 5 consecutive minutes during each waking hour during the first week following treatment, beginning immediately following completion of the compression.

The Investigator was unblinded to treatment assignment, while the patients and an independent observer at each study site remained blinded throughout the study. Patients returned to the site for follow up efficacy and safety assessments at 1, 4, 8, and 12 weeks after administration of PEM 1% or agitated saline treatment. After completion of the 12-week assessments, each patient was unblinded to treatment received. Those who had received agitated saline had the option to receive open-label treatment with PEM 1% in the same leg that had been treated with agitated saline.

The primary efficacy endpoint was the absolute change from baseline in VVSymQ (total score) at Week 8.

Secondary endpoints were:

(a) Symptom Assessment

- The absolute changes from baseline in the VVSymQ score at Weeks 4 and 12; the VEINES-Sym and VEINES-QOL summary scores at Weeks 4, 8, and 12; and the CIVIQ-2 score at Weeks 4, 8 and 12.
- Change from baseline in VCSS at Weeks 4, 8, and 12.
- Patient Global Assessment of symptoms at Weeks 4, 8, and 12.

(b) Improvement in Appearance

- Patient Global Assessment of improvement in appearance compared to baseline at Weeks 4, 8, and 12 using a 7-point scale (baseline and post-treatment photographs were made available to assist with assessment).

- Independent Photography Review (IPR) of improvement in appearance at Weeks 4, 8, and 12 compared to baseline using a 7-point scale. This assessment was based on central blinded review of baseline and post treatment photographs of the treated leg and was scored for overall improvement in varicose vein appearance.

(c) Duplex Ultrasound

Response to treatment as determined by duplex ultrasound at Weeks 4 and 12 was defined as follows:

- Elimination of reflux through the SFJ. Reflux was measured in the GSV 1 to 3 cm distal to the SFJ and was defined as the demonstration of retrograde flow of >0.5 sec by duplex ultrasound and spectral display following augmentation of flow by calf compression and subsequent release.
- Complete occlusion of the GSV (or treated major accessory vein as designated by the Investigator prior to treatment). Complete occlusion was measured within 10 cm of the SFJ and was defined as the demonstration of incompressibility of the treated vein with absence of any flow by duplex ultrasound.

The fulfillment of either or both of the duplex criteria constituted a response to treatment, i.e., 'duplex responder'. Response rates were compared for the two treatment groups.

Safety: Safety assessments included venous duplex scanning for presence of DVT, monitoring of AEs, and pre- and post-treatment vital signs.

Efficacy results: Compared to agitated saline, the following specific results for PEM 1% were observed:

Symptom Assessment: Treatment with PEM 1% resulted in (Table 44) statistically significantly greater

- improvement in symptoms as assessed by various patient reported outcomes measures including the VVSymQ (adjusted mean change from baseline at Week 8 [LOCF] of 30.7 vs. 16.7 for agitated saline; p=0.0009) and other venous insufficiency disease-specific questionnaires (VEINES-QOL/Sym, CIVIQ-2; all p<0.05 at Week 8).
- percentage of patients who achieved the identified VVSymQ responder threshold (Minimum Important Difference) of 24 points (i.e., change from baseline in VVSymQ of 24 points or more) (53.8% vs. 21.6% for agitated saline at Week 8 [LOCF]; p=0.0015).

Table 44 Statistical analyses of changes from baseline in symptom questionnaire scores at Wk 8

	Adjusted Mean[a] Change from Baseline (SE)		Comparison vs. Agitated Saline		
Questionnaire	Agitated Saline (n=37)[b]	Varisolve™ PEM 1% (n=39)[b]	Estimate	(95% CI)[c]	P-value[d]
VVSymQ	16.7 (3.18)	30.7 (3.04)	14.05	(6.0 – 22.1)	0.0009
VEINES-Sym	14.2 (2.83)	27.1 (2.70)	12.88	(5.7 – 20.0)	0.0006
VEINES-QOL	13.7 (2.59)	26.6 (2.48)	12.89	(6.3 – 19.5)	0.0002
CIVIC-2	-11.3 (2.30)	-18.9 (2.20)	-7.66	(-13.5 - -1.8)	0.0110

SE = standard error; CI = confidence interval; LOCF = last observation carried forward; [a] 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. [b] Number of patients having both a baseline value and a value at Week 8. [c] 95% confidence interval for comparison PEM 1% vs. agitated saline based on adjusted means. Unadjusted for multiple comparisons. [d] Two-sided significance level for paired comparisons.

Improvement in appearance: Treatment with PEM 1% resulted in statistically significantly greater improvement in the appearance of visible varicosities according to

- patient global assessment aided by pre-treatment photographs (mean score at Week 8 [LOCF] of 1.9 vs. 0.1 for agitated saline; p<0.0001); and
- independent, blinded photography review (IPR) of pre- and post-treatment photographs (mean score at Week 8 [LOCF] of 1.8 vs. 0.1 for agitated saline; p<0.0001).

Duplex Ultrasound: Treatment with PEM 1% was associated with a significantly larger percentage of patients with elimination of SFJ reflux and/or occlusion of the treated vein as documented by venous duplex ultrasonography (69.2% [Week 12] vs. 5.3% for agitated saline; p<0.0001).

Safety results: Treatment with PEM 1% was generally well-tolerated; the most frequently reported AEs were associated with the treatment procedure, including contusion (25.6%), incision site hematoma (10.3%), and incision site complication (7.7%).

Overall, nine of 73 (12.3%) patients experienced DVT in this study, which appeared to be related to the volume administered, and was notably reduced after enhancements to the treatment procedure and reduction of the maximum volume administered from 30 mL to 15 mL per treatment session. The majority of these thrombotic events were asymptomatic and resolved completely without sequelae. There were no clinical signs of pulmonary embolism in any patient. All DVTs were reported as SAEs.

Two other SAEs reported included one patient on agitated saline group who had a transient ischemic attack, and one in PEM 1% group who had sick sinus syndrome resulting in placement of a pacemaker.

9.4.8 Study 014

Title: An open-label, single-dose pilot study to evaluate the efficacy and safety of Varisolve™ (polidocanol endovenous microfoam; PEM) 0.125% [0.2%] for the treatment of symptomatic, visible varicose veins with saphenofemoral junction (SFJ) incompetence

The study was an 8-week, single-dose, open-label, pilot study to evaluate the efficacy and safety of 0.125% PEM in the treatment of symptomatic, visible varicose veins. The objective of this pilot study was to determine the lowest concentration of PEM suitable for use in a blinded planned Phase 3 dose-ranging study. Eligible patients received a single treatment of ultrasound guided endovenous microfoam ablation (EMA) using 0.125% PEM plus compression therapy. During the pretreatment (screening) period and at 8 weeks following treatment, patients provided subjective assessments of venous symptoms and improvement of appearance. After the completion of Week 8 follow-up assessments, patients who required additional treatment (as determined by the Investigator) had the option to receive a single treatment with PEM 1% in the same leg, using the standard EMA protocol. These patients were assessed one week and 4 weeks following treatment.

16 patients were planned to receive PEM 0.125% [0.2%]. Following treatment of 5 patients with PEM 0.125%, it was determined that the characteristics of 0.125% were sufficiently indistinguishable from previously tested 1% PEM and, therefore, PEM 0.2% was not studied in the protocol. In this study:

- 46 patients were screened; of which, 30 failed screening.
- 16 patients were treated with PEM 0.125%, and all 16 completed study and were included in the analyses of safety and efficacy.
- 11 patients (68.8%) received optional additional treatment with PEM 1%.

The study population consisted of male and female patients, age of consent to 75 years; with a baseline VEINES-Sym score < 75 points as measured by the 10 Symptom questions on the VEINES-QOL/Sym questionnaire; superficial venous disease manifested by visible varicosities; varicose veins with a CEAP Class of C_2 through C_5; SFJ incompetence (reflux > 0.5 seconds on duplex ultrasonography) associated with incompetence of the GSV or other major accessory vein; and who signed informed consent.

Each patient underwent ultrasound guided EMA with PEM 0.125% that was injected into the incompetent GSV (or incompetent accessory saphenous vein) via an intravenous cannula. If appropriate, visible distal varicosities were treated with further injections of PEM 0.125% using a butterfly needle. The maximum volume of PEM 0.125% administered was 15 mL. After completion of Week 8 assessments, patients who required additional treatment could receive treatment with open label PEM 1% in the same leg.

For each patient, the study duration was approximately 10 weeks, including the screening period and 8 weeks following treatment. If patients were additionally treated with PEM 1%, they were followed for an additional 4 weeks (total of 14 weeks).

The efficacy parameters are:

- Response to treatment as determined by the duplex ultrasound at 1, 4 and 8 weeks according to the

following criteria (fulfillment of either or both of the duplex criteria constituted a response):

- − Elimination of reflux through the SFJ.
- − Complete occlusion of the GSV (or treated major accessory vein as designated by the Investigator prior to treatment)

- The absolute changes from baseline in VVSymQ, VEINES-Sym, and VEINES-QOL summary scores at 8 weeks
- Patient Global Assessment of symptoms at 8 weeks using a 7-point scale ranging from -3 (much worse) to 3 (much improved)
- Patient Global Assessment of improvement of appearance at 8 weeks using a 7-point scale ranging from -3 (much worse) to 3 (much improved). Photographs were used to assist the patient in their assessment.
- Independent Photography Review (IPR): Assessment of appearance based solely on review of baseline and post-treatment photographs. Each of six individual venous segments were scored using a 4-point scale ranging from 0 (no visible varicosities) to 3 (severe) and summed to generate a total score ranging from 0 to 18.

The safety parameters included Clinical laboratory tests (obtained at Screening only), vital signs (blood pressure, heart rate) obtained before and after treatment, duplex ultrasound assessment of the deep venous system at 1, 4 and 8 weeks post-treatment, and adverse event monitoring throughout study.

Efficacy results: The study demonstrated that PEM 0.125% would not be suitable as a 'no effect' control treatment in the Phase 3 studies based upon its efficacy as demonstrated by duplex ultrasound, patient self-assessment of symptoms, independent photography review, and patient self-assessment of appearance. The following results were obtained:

- Treatment with PEM 0.125% resulted in a Week 8 response rate (elimination of reflux through the SFJ and/or complete occlusion of the GSV as assessed by duplex ultrasonography) that was comparable to that observed with PEM 1% at Week 12 in Study 013.
- Treatment with PEM 0.125% resulted in an improvement in VVSymQ, VEINES-Sym, VEINES-QOL summary scores, and Patient Global Assessment of symptoms scores.
- Improvement in VVSymQ summary score obtained with PEM 0.125% was numerically, but not statistically, less than that observed with PEM 1% in a previous study.
- Improvements in VEINES-Sym and VEINES-QOL summary scores obtained with PEM 0.125% were comparable to those observed with PEM 1% in a Study 013.
- Treatment with PEM 0.125% resulted in modest improvement in appearance of varicose veins based on Independent Photography Review and Patient Global Assessment of appearance scores.

Safety results: There were no unexpected adverse events with PEM 0.125% treatment and the safety profile of PEM 0.125% was generally similar to that observed in previous studies with PEM 1%.

Conclusion: The findings of this study indicate that PEM 0.125%, the lowest dose-concentration that can be created using the PEM canister system, is a suitable concentration for evaluation in a Phase 3 double-blind, dose-ranging study of PEM as the PEM and EMA characteristics of PEM 0.125% were indistinguishable from that of PEM 1%.

9.4.9 Comparison of Efficacy Results of Pivotal Studies

The efficacy results of the pivotal studies 015 and 016 are found to be comparable (See Section 6 of this clinical review).

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/s/

KHIN M U

07/12/2013

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is approvable pending the sponsor's response to comply with postmarketing requirements and changes in labeling.

CLINICAL FILING CHECKLIST FOR NDA 205-098 – Varithena™

NDA Number: 205-098 **Applicant: Provensis Ltd** **Stamp Date: 04-Feb-2013**

Drug Name: Varithena™ **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	√			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: **VAP.VV015** Study Title: (see item 14, below) Sample Size: 279 patients Arms: 5 Location in submission: Module 5, under section 5.3.5.1 Study Number:**VAP.VV016** Study Title: (see item 14, below) Sample Size: 232 patients Arms: 4 Location in submission: Module 5, under section 5.3.5.1	√			Both pivotal studies evaluated >1 dose. The study designs specified a sample size adequate to provide point estimates and 95% CIs for each treatment group effect on the primary efficacy endpoint.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	√			Two pivotal studies (VAP.VV015 and VAP.VV016) are

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: **VAP.VV015:** A Randomized, Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Varisolve® Polidocanol Endovenous Microfoam (PEM) 0.5%, 1.0%, and 2.0% Compared to Vehicle for the Treatment of Saphenofemoral Junction (SFJ) Incompetence Pivotal Study #2: **VAP.VV016:** A Randomized, Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Varisolve®® Polidocanol Endovenous Microfoam (PEM) 0.5% and 1% Compared to Vehicle for the Treatment of Saphenofemoral Junction (SFJ) Incompetence Indication (***the same for both pivotal studies***): Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV above and below the knee to improve the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system				submitted. Efficacy results from the two pivotal studies are integrated and the results presented in the ISE.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	No foreign data in pivotal trials.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			√	The Division agreed at End-of-Phase 2 meeting (7/22/09) that in lieu of a TQT study, QT safety could be ascertained by well-standardized ECGs in triplicate at peak plasma concentration in study VAP.VV008
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be			√	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	Administered i.v. by physician only.
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	There are no foreign data in the pivotal trials.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			√	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 205-098 – Varithena™

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

A request was sent to the sponsor to provide the following:

(1) sets photographs (pre- and post-treatment) and scores made by independent assessors for the sample of 32 patients in the pivotal studies shown in the following list:
Study VV015:

21-1017; 22-1078; 23-1005; 27-2001; 29-1034; 32-1007; 33-1004; 33-1023; 33-1035; 33-1057; 34-1002; 34-1005; 36-1024; 37-1006; 39-1033; 39-1091

Study VV016:
60-1011; 60-1015; 60-1022; 60-1041; 63-1003; 63-1008; 64-1036; 64-1052; 67-1006; 68-1003; 68-1051; 69-1018; 72-1018; 75-1005; 75-1025; 76-1026

(2) Reasons for the difference in responder rates in the control groups in Studies 015 and 016 for each of the efficacy variables: VVSymQ, IPR-V^3 and PAV^3 scores

(3) Results of statistical test(s) of correlation/association between (i) the VVSymQ score and the IPR-V^3 score, (e.g., using Kendall's tau and/or Spearman rank correlation), and (ii) the IPR-V^3 score and EACH of the five symptoms that make up the VVSymQ score.

(4) Results of statistical test(s) of correlation/association, (Kendall's tau and/or Spearman rank correlation) between the following pairs of efficacy variables:
a. the PAV^3 score and the IPR-V^3 score
b. the IPR-V^3 score and the Duplex ultrasound response
c. VVSymQ score and the Duplex ultrasound response

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/s/

KHIN M U
03/12/2013

THOMAS A MARCINIAK
03/12/2013