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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 205098
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Applicant: Provensis Ltd/BTG International Inc.
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1 EXECUTIVE SUMMARY

The overall efficacy conclusions are based on the efficacy results from the two pivotal studies, 015 and 016. These results demonstrate that treatment with pooled Polidocanol Endovenous Microfoam (PEM) leads to statistically significant improvements in the symptoms and appearance of chronic venous insufficiency, duplex ultrasound response, improvement in the clinical severity of venous disease, and improvement in patients' quality of life.

The efficacy of the pooled PEM was consistently demonstrated across efficacy endpoints and both studies, including:

- Improvement of symptoms as assessed by the patient (VVSymQ¹ score);
- Improvement of appearance as assessed by the patient (PA-V³ score) and by the blinded photography review panel (IPR-V³ score)
- Duplex response to treatment as assessed by an ultrasound technician blinded to PEM dose-concentration;
- Improvement in severity of patients' venous disease as assessed by the clinician (VCSS);
- Improvement in quality of life assessment as completed by the patient using the modified VEINES-QOL instrument.

2 INTRODUCTION

BTG International Ltd. has conducted three Phase 3 studies of PEM in the US: Study VAP.VV015, Study VAP.VV016 and Study VAP.VV017. PEM was studied as a treatment for incompetent veins of the great saphenous vein (GSV) system, including improvement of symptoms of superficial venous incompetence of the GSV system and improvement of appearance of visible varicosities of the GSV system.

2.1 Overview

Studies 015 and 016 are the pivotal trials for above indication. These two studies are both randomized, blinded, multi-center Phase 3 studies designed to evaluate the efficacy and safety of PEM 0.5%, 1.0% and 2.0% (Study 015) and PEM 0.5% and 1.0% (Study 016), compared with placebo, in the treatment of both symptoms and appearance in patients with saphenofemoral junction (SFJ) incompetence due to reflux of the GSV or major accessory veins.

In accordance with the principles of patient benefit set out in the FDA guidance document titled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims", the objectives of Study 015 and 016 were to measure changes in symptoms and appearance, the 2 most important concerns of patients suffering with this vein incompetence. Thus, the primary efficacy endpoint in these two studies is the improvement of symptoms as measure 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

¹ The detailed descriptions of these efficacy endpoints are listed in the section 3.2.1

PEM (pooled concentration groups), compared with Vehicle placebo. The co-secondary efficacy endpoints of both studies are the improvement of appearance as measured by both the absolute change from baseline in the central Independent Photography Review – Visible Varicose Veins (IPR-V³) score at Week 8 and the Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V³) score at Week 8 in patients treated with PEM (pooled concentration groups), compared with Vehicle placebo.

The third US Phase 3 study, Study 017, was a randomized, blinded, multi-center Phase 3 study in patients with SFJ incompetence, reflux of the GSV, and venous disease manifested by both symptoms and visible varicosities. Patients in Study 017 were required to be eligible for endogenous thermal ablation (ETA, either radio-frequency ablation (RFA) or endovenous laser ablation (EVLA)). Patients in this study received ETA treatment of the proximal GSV, followed immediately by a single, blinded treatment with PEM 0.5%, PEM 1.0% or Vehicle placebo for treatment of visible varicosities and incompetent areas of the GSV system not treated by ETA. The co-primary endpoints for this study were improvement in appearance as measured using the PA-V³ and IPR-V³ scores. The sponsor submitted that because ETA (not PEM) was the primary modality used to treat the proximal GSV in this study, with PEM being administered in a different manner than that in the pivotal studies 015 and 016, the data from Study 017 are not included in the integrated analyses of efficacy data. Clinical review found that although treatment with ETA + 0.5% and 1.0% pooled PEM produced statistically significant improvements over ETA + vehicle placebo for one of the co-primary endpoints of improvement in appearance (IPR-V³ score) but not statistically significant for the other co-primary endpoint (PA-V³ score). Also, the reduction in symptoms (using VCSS, VVSymQ and VEINES-QOL scores at week 8 post treatment) observed with ETA+PEM 0.5% and 1% were not statistically significant compared to ETA+vehicle placebo. (b) (4)

” Hence, the Study 017 would not be included in this review.

Table 1 listed the highlight information for all three phase 3 studies described above.

Table 1 Tabular Listing of All Phase 3 Studies

	Design	Test Products	Follow-up Period	# of Subjects per Arm	Study Population
VAP.VV015	<i>Multi-center, randomized, blinded Phase 3 efficacy and safety study</i>	<i>Patients were randomized 1:1:1:1:1 to PEM 0.125% (control), PEM 0.5%, PEM 1.0%, PEM 2.0% or placebo.</i>	<i>1 year</i>	<i>279 patients: PEM 0.125% (control):57 patients; PEM 0.5%:51 patients; PEM 1.0%:52 patients; PEM 2.0%:63 patients; Vehicleplacebo:56 patients;</i>	<i>Patients with SFJ incompetence and Symptomatic, Visible Varicose Veins</i>
VAP.VV016	<i>Multi-center, randomized, blinded Phase 3 efficacy and safety study</i>	<i>Patients were randomized 1:1:1:1 to PEM 0.125% (control), PEM 0.5%, PEM 1.0% or placebo.</i>	<i>1 year</i>	<i>232 patients: PEM 0.125% (control):57 patients; PEM 0.5%:60 patients; PEM 1.0%:58 patients; Vehicleplacebo:57 patients;</i>	<i>Patients with SFJ incompetence and Symptomatic, Visible Varicose Veins</i>
VAP.VV017	<i>Multi-center, randomized, blinded Phase 3 efficacy and safety study</i>	<i>Patients were randomized 1:1:1 to ETA + PEM 0.5%, ETA + PEM 1.0% or ETA + Vehicle placebo.</i>	<i>6 months</i>	<i>117 patients: ETA + PEM 0.5%: 39 patients; ETA + PEM 1.0%:40 patients; ETA + Vehicle Placebo:38 patients</i>	<i>Patients with GSV and SFJ Incompetence and Symptomatic, Visible Varicose Veins</i>

[Source: Sponsor's Tabular listing document]

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: <\\Cdsub1\evsprod\NDA205098\0000\m5\datasets>.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are not any statistical issues with the data and analysis quality.

- The reviewer reproduced the efficacy analysis datasets for the primary and co-secondary endpoints from the sdtm datasets.
- The randomized treatment assignments appeared to be adequate. Across treatment groups, the demographic characteristics of the patients randomized in each study were similar.
- BTG conducts clinical trials according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, BTG undertook a GCP audit program.
- The blinding and unblinding procedures were well documented throughout submission.
- The final statistical analysis plan (SAP) was submitted prior to unblinding.

3.2 Evaluation of Efficacy

The evaluation components of Studies 015 and 016, such as the description of the study designs, primary and secondary efficacy endpoints, demographic and baseline characteristics, patient disposition, statistical methodology used, results, and the reviewer's findings all have been summarized in the following sections.

3.2.1 Study Design and Endpoints

The Studies 015 and 016 were nearly identical with respect to their design and endpoints. All the study sites are the investigation centers in the United States.

3.2.1.1 VAP-VV015

The objective of this study is to evaluate the efficacy and safety of PEM 0.5%, 1.0% and 2.0%, compared with Vehicle, in patients with SFJ incompetence due to reflux of the GSV or major accessory veins, with venous disease manifested by both symptoms and visible varicosities.

This is a randomized, multicenter, parallel group study to evaluate the efficacy and safety of 4 double-blind dose concentrations of PEM (i.e., 0.125%, 0.5%, 1.0%, and 2.0%), compared with single-blind Vehicle placebo. Two hundred and fifty (250) treated patients who met the study entry criteria were randomized 1:1:1:1:1 to receive each PEM or placebo. Randomization occurred the day before or on the day of Visit 2 (baseline), and was stratified by site and by baseline Varicose Vein Symptoms Questionnaire (VVSymQ) score (≤ 14 or >14 on a scale of 0 to 25).

It was not possible to conduct double-blind study drug administration because placebo microfoam that is indistinguishable from PEM cannot be created using the PEM-generating canister system. Investigators were therefore blinded to the concentration of polidocanol received by patients randomized to receive PEM, but were not blinded to the study treatment of patients randomized to Vehicle. Patients were fully blinded to treatment assignment.

The primary efficacy endpoint (symptoms) is the absolute change from baseline in the 7- day average VVSymQ score at Week 8 using LOCF. The VVSymQ has been determined to be the symptoms most relevant to patients with varicose veins. The VVSymQ includes five symptom items: heaviness, achiness, swelling, throbbing, and itching. The individual scores of each of these 5 items are scored from 0 (“None of the time”) to 5 (All of the time) and will be summed to yield a daily VVSymQ score that ranges from 0 (no symptom burden) to 25 (worst symptom burden).

The co-secondary endpoints (appearances) are the absolute change from baseline at Week 8 in appearance assessed by: 1) the central Independent Photography Review panel IPR-V³ score and 2) the patient self-assessment of varicose vein appearance PA-V³ score. The photographs will be taken in a prescribed manner at each site in accordance with the photography manual and training. At baseline and each efficacy time point (4 weeks, 8 weeks and 1 year), standardized digital photographs will be taken of the medial view of the patient’s target leg from groin to ankle. These photos will be examined by an independent photography review panel consisting of 3 reviewers. The reviewer will score the appearance of the visible varicose veins, using IPR-V³ instrument, as none (0), mild (1), moderate (2), severe (3) or very severe (4).

As the co-secondary measure, the patients will evaluate the appearance of their visible varicose veins using the Patient Self-assessment of Visible Varicose Veins (PA-V³) instrument. On this single-item paper questionnaire, the instructions included a diagram of the medial view of a leg with the area between the ankle and the groin circled. The patient was instructed to choose 1 of 5 response options that best described the appearance of the visible varicose veins of the leg that was treated in the study. The patient was instructed not to consider the appearance of the leg outside the circled area or of any spider veins. Possible responses ranged from “Not at all noticeable” (a score of 0) to “Extremely noticeable” (a score of 4)

The tertiary endpoints are as follows:

- Response to treatment as determined by duplex ultrasound. The response was defined as: 1) 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 2) Complete occlusion of the GSV (or treated major accessory vein), as measured within 10 cm of the SFJ, where occlusion is defined as the demonstration of incompressibility of the treated vein with the absence of any flow by duplex ultrasound.
- The absolute change from baseline in the Venous Clinical Severity Score (VCSS). The instrument was used by a study investigator to rate 9 clinical characteristics of chronic

venous disease: pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, and number, duration, and size of ulcers. Each of these characteristics was graded on a 0 to 3 (i.e., “absent” to “severe”) scale.

- The absolute change from baseline for the modified Venous Insufficiency Epidemiologic and Economic Study – Quality of Life/Symptoms (VEINES-QOL) total score. On the instrument, patients answered questions about the duration of their varicose vein symptoms over the past week, pain over the past week, time of day when symptoms were most intense, limitations in activities of daily living, work, and family/social activities, the emotional/psychological burden of disease, and the current status of the leg problem, compared with 1 year ago. The score based on these responses is calculated on a 0-100 scale where 0 = worst possible quality of life and 100 = best possible quality of life.

3.2.1.2 VAP.VV016

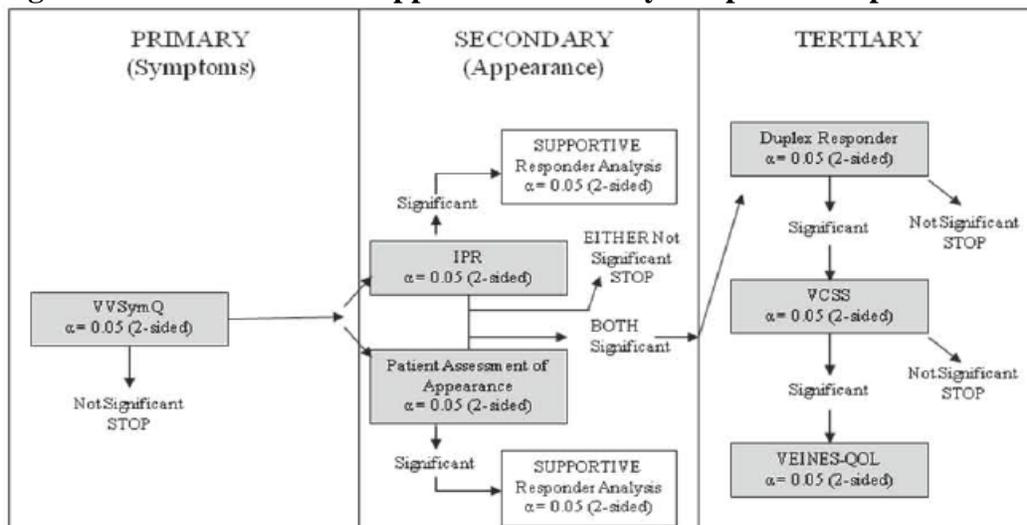
The Study 016 was nearly identical to Study 015 with respect to the design and endpoints, except that the PEM 2.0% was not studied in this trial.

3.2.2 Statistical Methodologies

The efficacy populations in both studies are defined as all patients who received at least one injection of PEM or Placebo and provided data for at least one post-baseline primary and/or secondary efficacy assessment. The analysis of efficacy endpoints used the last non-missing post baseline observation carried forward.

Since PEM concentrations of 0.5%, 1.0% and 2.0% are expected to be similar with respect to efficacy, a single primary comparison of a pooled PEM group (0.5% +1.0% +2.0% and 0.5% +1.0%) versus Placebo will be employed for all efficacy comparisons in Study 015 and 016, respectively.

Figure 1 Hierarchical Approach to Efficacy Endpoint Comparisons



[Source: Sponsor’s CSR Figure 1]

Within each study, across pre-specified endpoints (primary, secondary and tertiary), each comparison of pooled PEM versus Placebo will be conducted at $\alpha=0.05$ (two-sided) with study-wise Type I error controlled using a hierarchical approach (Figure 1).

More specifically, if the primary and both secondary endpoints are significant for the primary comparison, the tertiary endpoints will be analyzed using a sequential approach where testing of an endpoint is contingent upon demonstrating statistical significance in the preceding endpoint(s.) Statistical significance for determining testing of a subsequent endpoint will be set at the 0.05 level of significance for the primary comparison (pooled vs. 0.125% for duplex response and pooled vs. Placebo for VCSS and VEINES-QOL).

The continuous endpoints were to be evaluated using analysis of covariance with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate. The Response to treatment as assessed by duplex examination at Week 8 employing LOCF was to be compared between treatments using the CMH chi-square test stratified by site.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In study 015, two hundred and seventy-nine (279) patients received study drug. Over 98.6% of patients completed the study, one (1) placebo, one (1) PEM 0.125% and two (2) PEM 1.0% patients withdrawn due to lost to follow-up.

In study 016, two hundred and thirty-two (232) patients received study drug. Over 99.1% of patients completed the study, one (1) placebo and one (1) PEM 1.0% patient withdrawn due to lost to follow-up.

The demographic and baseline characteristics of the randomized patients are comparable in all major subgroups for both pivotal studies.

For Study 015, the mean age of patients randomized in this study was 49 years, and 75% of patients were women. The mean body mass index (BMI) for the randomized patients was 28 kg/m². Most patients (over 92%) were White. Table 2 displays the detailed demographic characteristics for this study.

Table 2 Patient Demographics and Baseline Characteristics, Study VAP-VV015

Subgroup	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%	Pooled PEM
	N=56	N=57	N=51	N=52	N=63	N=166
Age Mean (SD)	46.0 (11.31)	51.6 (9.60)	48.2 (11.78)	49.7 (10.49)	49.7 (10.49)	49.0 (10.38)
Sex, n(%)						
Male	12 (21.4)	15 (26.3)	14 (27.5)	14 (26.9)	16 (25.4)	44 (26.5)
Female	44 (78.6)	42 (78.6)	37 (72.5)	38 (73.1)	47 (74.6)	122 (73.5)
Race, n (%)						
White	52 (92.9)	51 (89.5)	46 (90.2)	50 (96.2)	61 (96.8)	157 (94.6)
Black	0 (0.0)	4 (7.0)	1 (2.0)	1 (1.9)	1 (1.6)	3 (1.8)
Other	4 (7.1)	2 (2.5)	4 (7.8)	1 (1.9)	1 (1.6)	6 (3.6)
Height Mean (SD)	170.3 (9.55)	169.4 (10.57)	169.2 (9.01)	170.0 (9.81)	171.0 (9.32)	170.2 (9.36)
Weight Mean (SD)	80.9 (20.4)	83.4 (22.4)	79.2 (21.5)	83.2 (19.9)	82.6 (17.0)	81.8 (19.4)
BMI Mean (SD)	27.7 (6.0)	28.8 (5.8)	27.4 (5.8)	28.6 (5.4)	28.3 (5.4)	28.1 (5.5)

[Source: Reviewer's results]

The baseline varicose vein symptom and appearance data are summarized in Table 3. There are no discernible differences among all treatment groups for these three key efficacy endpoints.

Table 3 Baseline Varicose Vein Characteristics (Symptom and Appearance Scores), All Randomized Patients, Study VAP-VV015

Endpoints	Safety Population				
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%
	N=56	N=57	N=51	N=52	N=63
VVSymQ Mean (SD)	8.7 (5.11)	9.0 (4.9)	9.3 (4.4)	8.9 (4.7)	9.5 (5.0)
IPR-V ³ Mean (SD)	1.8 (0.7)	1.9 (0.6)	2.1 (0.6)	2.0 (0.7)	2.1 (0.8)
PA-V ³ Mean (SD)	3.5 (0.8)	3.6 (0.6)	3.5 (0.8)	3.5 (0.7)	3.7 (0.6)

[Source: Sponsor's CSR Table 12]

Likewise, the demographic characteristics of the patients randomized in Study 016 were also similar across all treatment groups. The mean age of the patients was slightly older, 51 years, in this study. The female patients made up about 73% of all patients. Once again, most patients were White. The PEM 0.5% treatment group had a slightly higher percent of male patients (33.3%) and a higher mean weight, see Table 4.

Table 4 Patient Demographics and Baseline Characteristics, Study VAP-VV016

Subgroup	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	Pooled PEM
	N=57	N=57	N=60	N=58	N=118
Age Mean (SD)	50.8 (10.44)	52.8 (10.06)	50.4 (9.89)	50.0 (11.42)	50.2 (10.63)
Sex, n(%)					
Male	15 (26.3)	14 (24.6)	20 (33.3)	14 (24.1)	34 (28.8)
Female	42 (73.7)	43 (75.4)	40 (66.7)	44 (75.9)	84 (71.2)
Race, n (%)					
White	54 (94.7)	53 (93.0)	55 (91.7)	53 (91.4)	108 (91.5)
Black	2 (3.5)	1 (1.8)	3 (5.0)	0 (0.0)	3 (2.5)
Other	1 (1.8)	3 (5.2)	2 (3.3)	5 (8.6)	7 (6.0)
Height Mean (SD)	170.0 (9.45)	168.6 (9.38)	169.6 (10.5)	169.1 (9.27)	169.4 (9.86)
Weight Mean (SD)	83.7 (20.2)	85.3 (16.4)	88.8 (22.7)	81.4 (20.2)	85.2 (21.7)
BMI Mean (SD)	28.8 (5.8)	30.1 (5.4)	30.7 (6.3)	28.4 (6.4)	29.5 (6.4)

[Source: Review's results]

For patients randomized in this study, the mean baseline VVSymQ score was 9.0 points. The mean baseline VVSymQ score was slightly lower for patients in the PEM 1.0% treatment group (8.0 points) than for patients in the other treatment groups (range: 9.2-9.5 points). There are no discernible differences among all treatment groups for the two co-secondary efficacy endpoints, see Table 5.

Table 5 Baseline Varicose Vein Characteristics (Symptom and Appearance Scores), All Randomized Patients, Study VAP-VV016

Endpoints	Safety Population			
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%
	N=57	N=57	N=60	N=58
VVSymQ Mean (SD)	9.4 (5.0)	9.2 (4.5)	9.5 (4.4)	8.0 (4.6)
IPR-V ³ Mean (SD)	2.2 (0.5)	2.3 (0.5)	2.2 (0.7)	2.0 (0.7)
PA-V ³ Mean (SD)	3.3 (0.9)	3.5 (0.8)	3.6 (0.6)	3.5 (0.8)

[Source: Sponsor's CSR Table 12]

3.2.4 Results and Conclusions

The patients treated with PEM (pooled data) in Studies 015 and 016 had a statistically significantly greater improvement in symptoms at Week 8, as measured by the 7-day average daily e-diary VVSymQ score, compared to the patients treated with Placebo.

Furthermore, in both studies, the differences between PEM and Placebo treated patients were statistically significant for both the IPR-V³ and PA-V³ endpoints.

3.2.4.1 Efficacy results of VAP-VV015

Primary Efficacy Endpoint: Symptoms

The primary efficacy analysis compared the absolute change from baseline to Week 8 in the VVSymQ score for patients treated with the PEM 0.5%, 1.0%, and 2.0% dose concentrations versus Vehicle placebo. The VVSymQ score is a 26-point score ranging from 0 (no symptom burden) to 25 (greatest symptom burden). The pooled PEM was statistically significantly superior to Placebo at the p-value of 0.0001. The adjusted mean changes from baseline are -5.44 points and -2.13 points for the pooled PEM doses and Placebo, respectively (Table 6).

Table 6 Primary Efficacy Analysis: Absolute change from Baseline to Week 8 in VVSymQ Score (LOCF), Study VAP-VV015

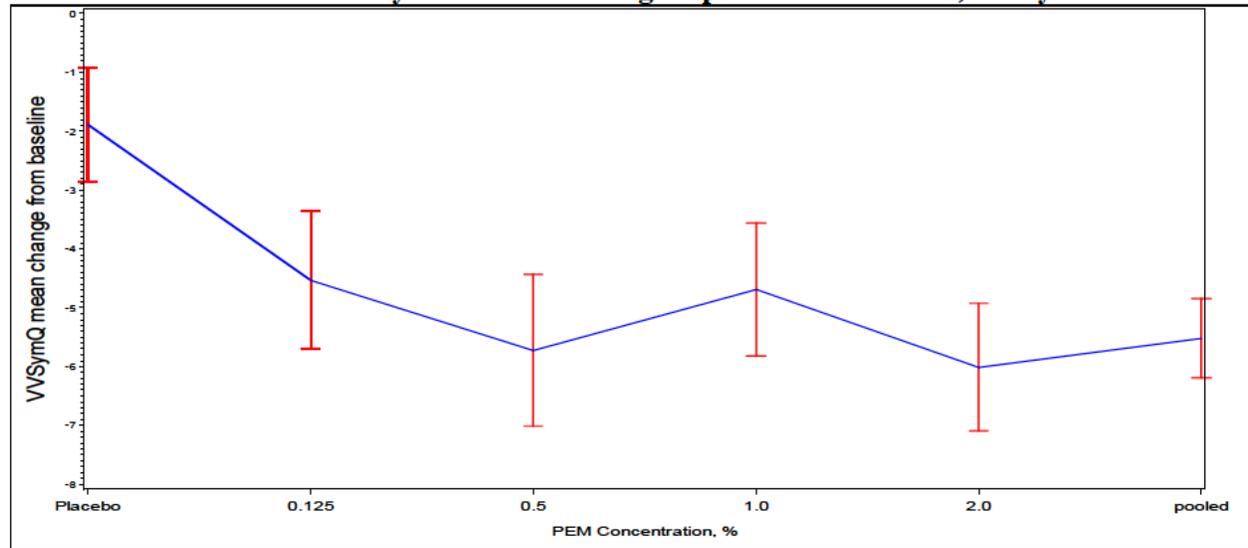
Treatment	N	Baseline		Adjusted Mean Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Mean	SE	$\Delta\Delta$ (95% CI)	P-value
Pooled PEM	164	9.23	0.366	-5.44	0.287	-3.31 (-4.31, -2.30)	0.0001
Placebo	55	8.60	0.687	-2.13	0.452	--	--
PEM 0.125%	56	9.01	0.650	-4.63	0.447	-2.49 (-3.72, -1.27)	--
PEM 0.5%	51	9.30	0.615	-5.68	0.483	-3.54 (-4.80, -2.29)	--
PEM 1.0%	50	8.82	0.663	-4.87	0.477	-2.73 (-3.98, -1.48)	--
PEM 2.0%	63	9.49	0.625	-5.78	0.425	-3.65 (-4.84, -2.46)	--

[Source: Reviewer’s results]

The above findings are very robust under the scrutiny of the missing data. The missing data had little impact on the primary endpoint. Recall, there were four patients unable to complete the study. The reviewer imputed those 4 Week 5 scores as either 0 or the maximum of all scores (18.25), which minimally altered the results of Table 6.

Furthermore, all PEM doses had numerical larger reductions of VVSymQ scores when compared to Placebo, see Figure 2. The 95% confidence interval of the Placebo group appears to be completely disjointed from and above each PEM treatment group and pooled PEM.

Figure 2 Dose-Response Curve: VVSymQ Mean Change from Baseline at week 8 with 95% Confidence Intervals by each Treatment group and Pooled PEM, Study VAP-VV015

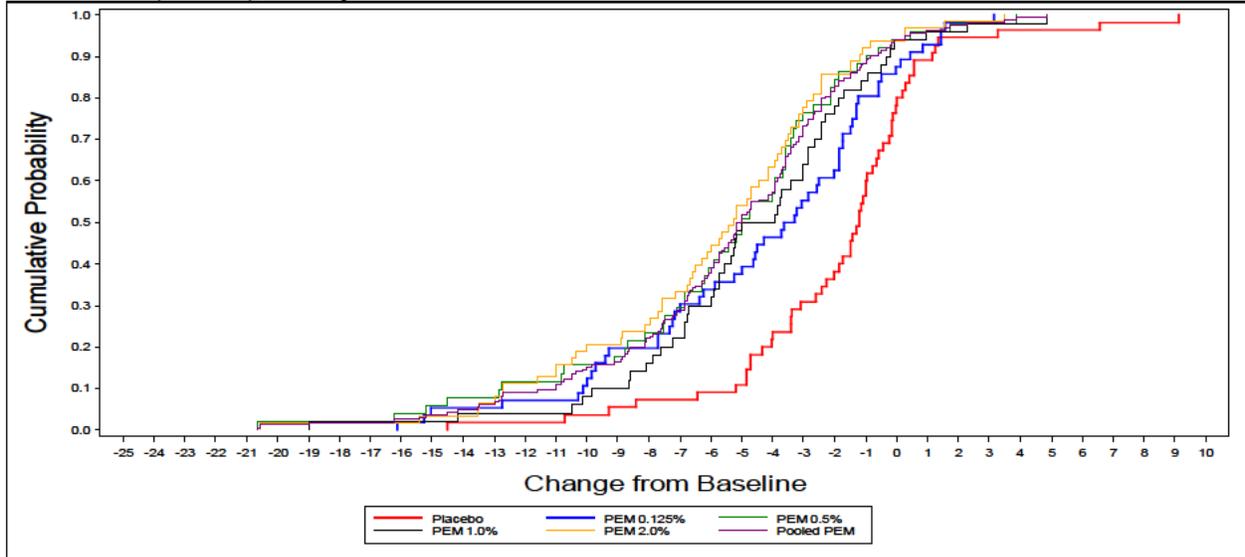


[Source: Reviewer’s Results]

Figure 3 shows the cumulative distribution of the change from baseline in VVSymQ score at Week 8 (LOCF) for each treatment group in the Efficacy Population. The cumulative percent of patients in each of the 4 PEM and Pooled PEM treatment groups to attain each reduction in VVSymQ score was markedly greater than the cumulative percent of patients in the Placebo

group to attain the same reduction. Throughout the distribution, the percent of patients who achieved a decrease (improvement) in VVSymQ scores was higher in each of the PEM treatment groups, compared with the Placebo treatment group.

Figure 3 Cumulative Distribution Function of the Change from Baseline for VVSymQ at Week 8 (LOCF), Study VAP-VV015



[Source: Reviewer’s Results]

Co-Secondary Efficacy Results (Appearance)

According to the primary endpoint must reach the statistical significance at $\alpha=0.05$ level for the primary comparison to permit testing of secondary endpoints. The study has two co-secondary efficacy endpoints: the absolute change from baseline in the central IPR Panel IPR-V³ score and the absolute change from baseline in appearance PA-V³. These two endpoints are 5-point scales in which higher scores indicate worse varicose vein appearance.

Table 7 Absolute Change from Baseline to Week 8 in IPR-V³, Study VAP-VV015

Treatment	N	Baseline		Adjusted Mean Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Mean	SE	$\Delta\Delta$ (95% CI)	P-value
Pooled PEM	161	2.07	0.055	-0.81	0.051	-0.80 (-0.98, -0.62)	0.0001
Placebo	55	1.82	0.097	-0.01	0.081	--	--
PEM 0.125%	56	1.95	0.086	-0.46	0.080	-0.45 (-0.66, -0.23)	--
PEM 0.5%	51	2.12	0.087	-0.77	0.086	-0.76 (-0.98, -0.53)	--
PEM 1.0%	49	1.98	0.103	-0.91	0.085	-0.75 (-0.97, -0.53)	--
PEM 2.0%	61	2.10	0.096	-0.81	0.077	-0.90 (-1.11, -0.68)	--

[Source: Reviewer’s results]

As shown in Table 7, the mean change from baseline to Week 8 in IPR-V³ scores were statistically significantly greater in the pooled PEM treatment group compared with Placebo (P-

value=0.001). The adjusted mean reduction scores were -0.81 points versus -0.01 points, respectively.

Similarly, as shown in Table 8, the mean change from baseline to Week 8 in PA-V³ scores were also statistically significantly greater in the pooled PEM treated groups compared with Placebo treated patients (P-value =0.0001). The adjusted mean reduction scores were -1.58 points versus -0.15 points, respectively.

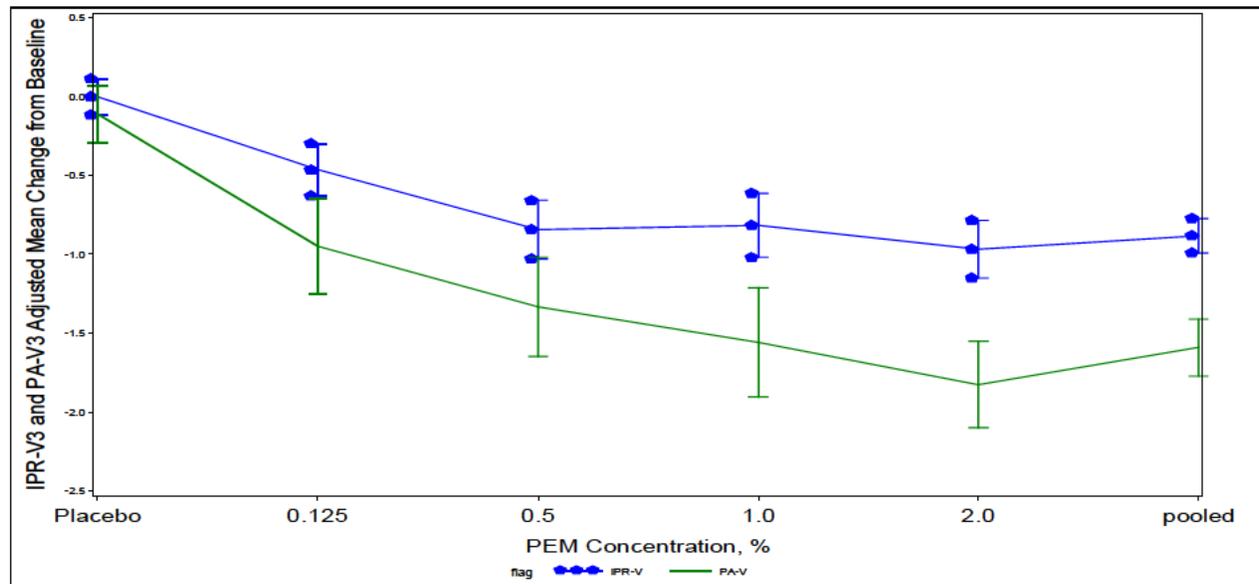
Table 8 Absolute Change from Baseline to Week 8 in PA-V³, Study VAP-VV015

Treatment	N	Baseline		Adjusted Mean Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Mean	SE	$\Delta\Delta$ (95% CI)	P-value
Pooled PEM	164	3.54	0.054	-1.58	0.091	-1.44 (-1.75, -1.12)	0.0001
Placebo	55	3.49	0.110	-0.15	0.143	--	--
PEM 0.125%	56	3.57	0.084	-0.93	0.142	-0.78 (-1.17, -0.40)	--
PEM 0.5%	51	3.45	0.110	-1.40	0.152	-1.26 (-1.65, -0.86)	--
PEM 1.0%	50	3.46	0.100	-1.60	0.151	-1.45 (-1.85, -1.06)	--
PEM 2.0%	63	3.68	0.071	-1.75	0.135	-1.60 (-1.98, -1.23)	--

[Source: Reviewer’s results]

Overall, all PEM treated patients had larger reduction both in IPR-V³ and PA-V³ scores at Week 8 when compared to Placebo. Similarly, the missing data had little impact on the co-secondary endpoints. The same imputation methods as the primary sensitivity analysis were applied to these two endpoints, which minimally altered the results of Table 7 and Table 8.

Figure 4 Dose-Response Curves: IPR-V³ and PA-V³ Mean Change from Baseline at Week 8 with 95% Confidence Intervals by each Treatment group and Pooled PEM, Study VAP-VV015



[Source: Reviewer’s Results]

The dose-response curves for the IPR-V³ and PA-V³ scores are displayed in Figure 4. Similar to the primary endpoint, VVSymQ score, there is a decreasing trend in both scores as the PEM dose increases. The 95% Confidence Intervals of the co-secondary endpoints for the Placebo are completely above each PEM dose and pooled PEM group, respectively.

Tertiary Efficacy Results

1. At Week 8, 74.5% of patients in the pooled PEM 0.5%, 1.0%, and 2.0% treatment group and 42.1% of patients in the PEM 0.125% group met the criteria for response to treatment, as assessed by duplex ultrasound examination. The difference between the percent of responders in the pooled PEM and PEM 0.125% treatment groups was statistically significant ($P<0.0001$).
2. Changes from baseline in VCSS were analyzed using ANCOVA. The VCSS is a 30-point scale that is used by clinicians to rate the severity of patients' venous disease. Higher scores indicate greater disease severity. At Week 8, the adjusted mean change from baseline in VCSS in the PEM 0.5%, 1.0%, and 2.0% (pooled) treatment group was -3.96 points, compared with -0.75 points in the Placebo group; the difference between these changes is statistically significant ($P<0.0001$).
3. Changes from baseline to Week 8 in VEINES-QOL scores were analyzed using ANCOVA. At Week 8, the mean increase from baseline (i.e., improvement) in VEINES-QOL score in the PEM 0.5%, 1.0%, and 2.0% groups (pooled) was statistically significantly greater than the change in the Placebo group ($P<0.0001$). The adjusted mean changes from baseline were -21.16 points and -7.67 points for the pooled PEM and Placebo, respectively.

3.2.4.2 Efficacy results of VAP-VV016

Primary Efficacy Endpoint: Symptoms

The primary efficacy analysis compared the absolute change from baseline to Week 8 in the VVSymQ score for patients treated with the PEM 0.5% and 1.0% dose concentrations versus Vehicle placebo. The pooled PEM was statistically significantly superior to Placebo at the p-value of 0.0001. The adjusted mean changes from baseline are -5.53 points and -2.0 points for the pooled PEM doses and Placebo, respectively (Table 9).

The Study 016 also had very few missing data, and various sensitivity analyses had minimal impact on the results of the primary endpoint.

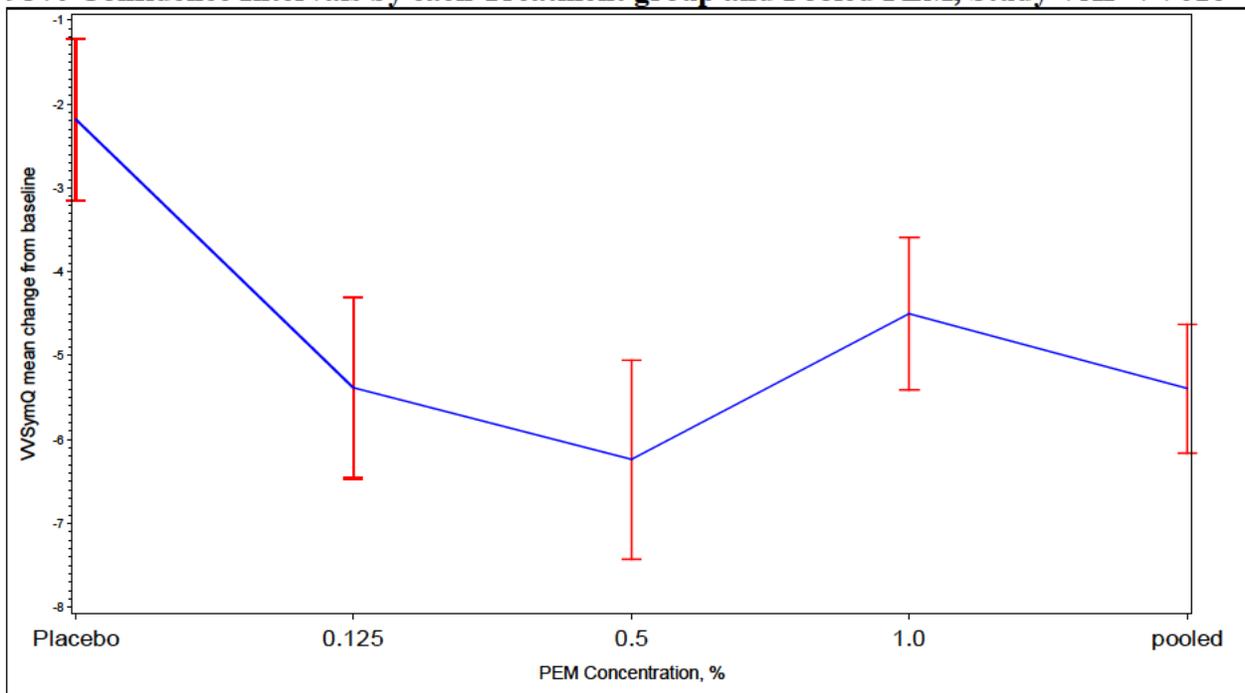
Table 9 Primary Efficacy Analysis: Absolute change from Baseline to Week 8 in VVSymQ Score (LOCF), Study VAP-VV016

Treatment	N	Baseline		Adjusted Mean Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Mean	SE	$\Delta\Delta$ (95% CI)	P-value
Pooled PEM	117	8.67	0.409	-5.53	0.330	-3.53 (-4.63, -2.42)	0.0001
Placebo	54	9.26	0.666	-2.00	0.474	--	--
PEM 0.125%	54	9.11	0.618	-5.34	0.476	-3.34 (-4.63, -2.04)	--
PEM 0.5%	60	9.48	0.573	-6.01	0.454	-4.00 (-5.26, -2.74)	--
PEM 1.0%	57	7.82	0.568	-5.06	0.463	-3.05 (-4.33, -1.77)	--

[Source: Reviewer’s results]

Furthermore, all PEM doses had numerical larger reductions of VVSymQ scores when compared to Placebo, see Figure 5. The 95% confidence interval of the Placebo group appears to be completely disjointed from each PEM treatment and pooled PEM.

Figure 5 Dose-Response Curve: VVSymQ Mean Change from Baseline at week 8 with 95% Confidence Intervals by each Treatment group and Pooled PEM, Study VAP-VV016

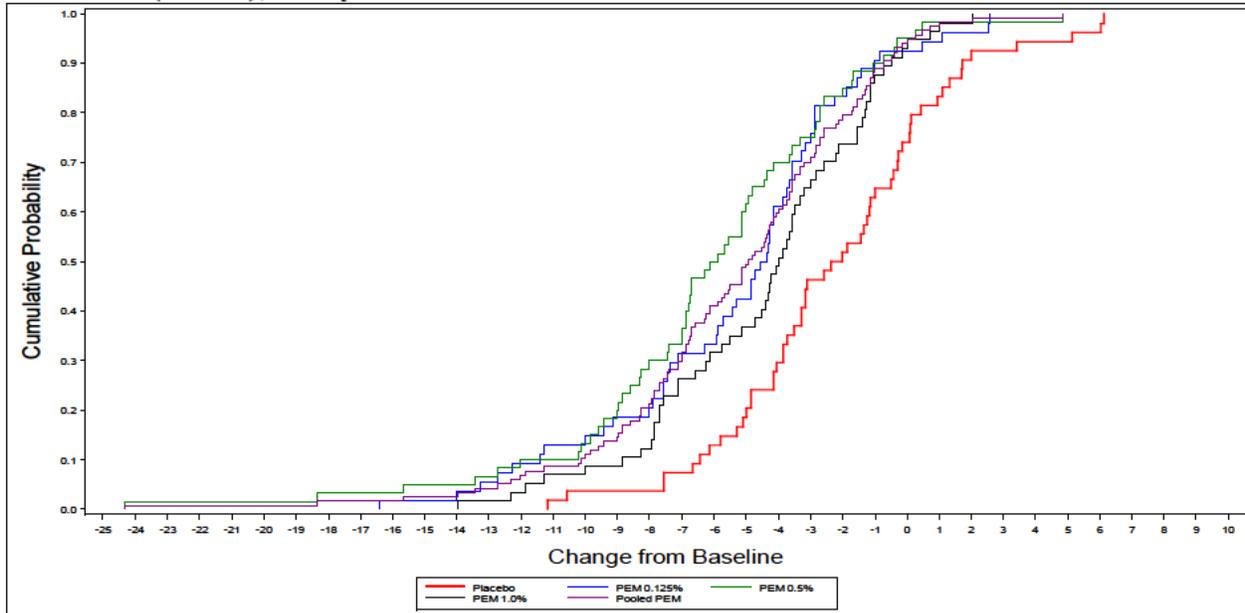


[Source: Reviewer’s Results]

Figure 6 shows the cumulative distribution of the change from baseline in VVSymQ score at Week 8 (LOCF) for each treatment group in the Efficacy Population. The cumulative percent of patients in each of the 3 PEM and Pooled PEM treatment groups to attain each reduction in VVSymQ score was markedly greater than the cumulative percent of patients in the Placebo group to attain the same reduction. Throughout the distribution, the percent of patients who

achieved a decrease (improvement) in VVSymQ scores was higher in each of the PEM treatment groups, compared with the Placebo treatment group.

Figure 6 Cumulative Distribution Function of the Change from Baseline for VVSymQ at Week 8 (LOCF), Study VAP-VV016



[Source: Reviewer’s Results]

Co-Secondary Efficacy Results (Appearance)

The primary endpoint was required to reach statistical significance at the 0.05 level for the primary comparison to permit testing of the secondary endpoints. As shown in **Table 10**, the mean change from baseline to Week 8 in IPR-V³ scores were statistically significantly greater in the pooled PEM treatment group compared with Placebo (P-value=0.001). The adjusted mean reduction scores were -0.89 points versus -0.07 points, respectively.

Table 10 Absolute Change from Baseline to Week 8 in IPR-V³, Study VAP-VV016

Treatment	N	Baseline		Adjusted Mean Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Mean	SE	$\Delta\Delta$ (95% CI)	P-value
Pooled PEM	117	2.11	0.066	-0.86	0.060	-0.79 (-0.98, -0.60)	0.0001
Placebo	56	2.18	0.073	-0.07	0.080	--	--
PEM 0.125%	56	2.27	0.070	-0.74	0.081	-0.66 (-0.88, -0.45)	--
PEM 0.5%	60	2.20	0.091	-0.89	0.078	-0.82 (-1.04, -0.61)	--
PEM 1.0%	57	2.02	0.095	-0.83	0.080	-0.75 (-0.97, -0.54)	--

[Source: Reviewer’s results]

Similarly, as shown in Table 11, the mean change from baseline to Week 8 in PA-V³ scores were also statistically significantly greater in the pooled PEM treated groups compared with Placebo

treated patients (P-value =0.0001). The adjusted mean reduction scores were -1.82 points versus -0.32 points, respectively.

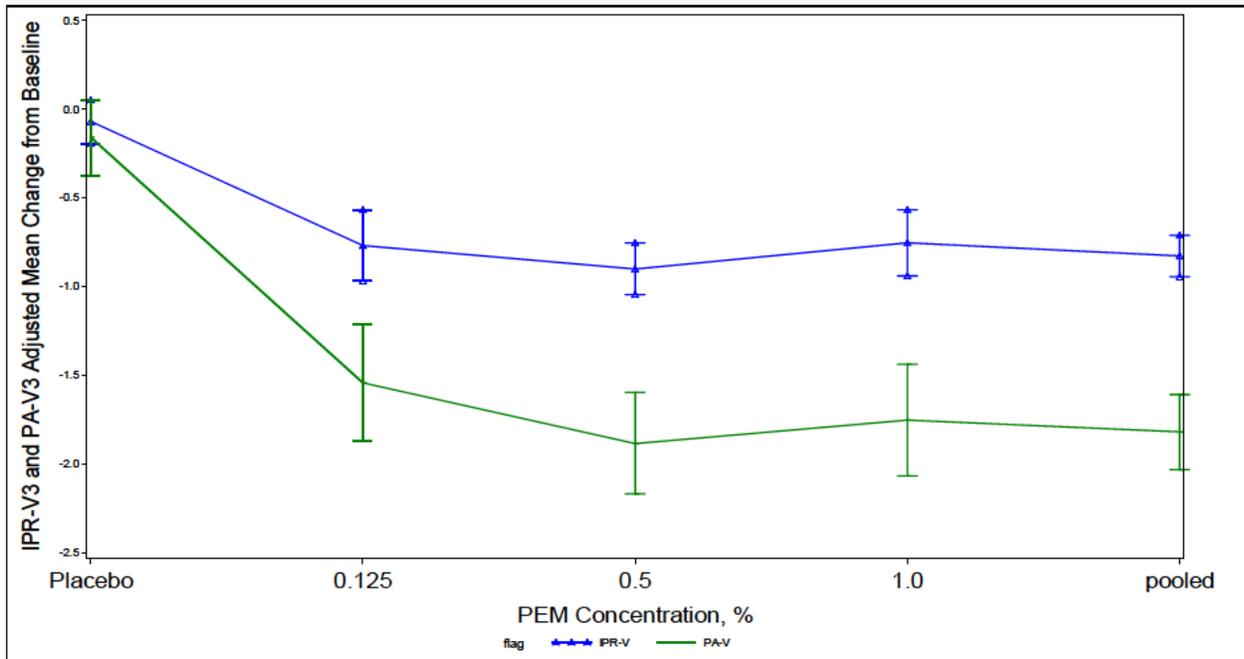
Table 11 Absolute Change from Baseline to Week 8 in PA-V³, Study VAP-VV016

Treatment	N	Baseline		Adjusted Mean Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Mean	SE	$\Delta\Delta$ (95% CI)	P-value
Pooled PEM	117	3.54	0.065	-1.82	0.094	-1.50 (-1.81, -1.19)	0.0001
Placebo	56	3.30	0.114	-0.32	0.133	--	--
PEM 0.125%	57	3.53	0.104	-1.55	0.131	-1.23 (-1.59, -0.87)	--
PEM 0.5%	60	3.58	0.080	-1.86	0.129	-1.54 (-1.90, -1.18)	--
PEM 1.0%	57	3.49	0.104	-1.79	0.130	-1.47 (-1.83, -1.11)	--

[Source: Reviewer’s results]

Overall, all PEM treated patients had larger reduction both in IPR-V³ and PA-V³ scores at Week 8 when compared to Placebo. The dose-response curves for the IPR-V³ and PA-V³ scores are displayed in Figure 7. Similarly, the missing data had little impact on the co-secondary endpoints. Similar to the Study 015, there is a decreasing trend in both scores as the PEM dose increases. The 95% Confidence Intervals of the co-secondary endpoints for the Placebo are completely above each PEM dose and pooled PEM group, respectively.

Figure 7 Dose-Response Curves: IPR-V³ and PA-V³ Mean Change from Baseline at Week 8 with 95% Confidence Intervals by each Treatment group and Pooled PEM, Study VAP-VV016



[Source: Reviewer’s Results]

Tertiary Efficacy Results

1. At Week 8, 84.7% of patients in the pooled PEM 0.5% and 1.0% treatment group and 59.6% of patients in the PEM 0.125% group met the criteria for response to treatment, as assessed by duplex ultrasound examination. The difference between the percent of responders in the pooled PEM and PEM 0.125% treatment groups was statistically significant ($P<0.0001$).
2. Changes from baseline in VCSS were analyzed using ANCOVA. The VCSS is a 30-point scale that is used by clinicians to rate the severity of patients' venous disease. Higher scores indicate greater disease severity. At Week 8, the adjusted mean change from baseline in VCSS in the PEM 0.5% and 1.0% (pooled) treatment group was -5.10 points, compared with -1.52 points in the Placebo group; the difference between these changes is statistically significant ($P<0.0001$).
3. Changes from baseline to Week 8 in VEINES-QOL scores were analyzed using ANCOVA. At Week 8, the mean increase from baseline (i.e., improvement) in VEINES-QOL score in the PEM 0.5% and 1.0% (pooled) treatment group was 21.6 points, compared with 7.42 points in the Placebo group; the difference between these changes is statistically significant ($P<0.0001$).

3.3 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The primary and secondary efficacy analyses by gender and age subgroup were explored. This review did not explore the subgroup analysis by race due to overwhelming majority of the patients were White in the two pivotal studies, recall Table 2 and Table 4. Furthermore, the entire program was conducted within the United States, so the subgroup analysis by geographic regions was also omitted.

The Fitzpatrick Skin Type is an instrument that was used by the clinician at the screening visit to classify a patient's skin type. This instrument consists of 10 questions concerning the patient's genetic predisposition (i.e., eye, skin, and hair color, and freckles in unexposed areas) and their reaction to sun exposure. A Fitzpatrick Skin Type is assigned based on the patient's total score. The Fitzpatrick Skin Types range from Skin Type I (very fair, always burns) to Skin Type VI (very dark, never burns). Therefore, the descriptive subgroup analyses of appearance outcomes (secondary endpoints) were also to be provided by baseline Fitzpatrick Skin Type classification in this section.

4.1 Gender and Age

Table 12 displayed the primary and secondary efficacy results by Sex and Age for Study 015. The adjusted mean change from baseline to Week 8 is listed for each treatment arm in the endpoints of VVSymQ, IPR-V³ and PA-V³. The comparisons of pooled PEM versus Placebo are also provided. There are not notable discrepancies between Male and Female for any endpoints.

However, the magnitude of treatment effects are mostly had been neutralized for the patients who are older than 60 years of age for the endpoints of VVSymQ and IPR-V³.

Table 12 Subgroup Analyses of Primary and Secondary Endpoints by Sex and Age, Study VAP-VV015

Parameters	Adjusted Mean Change from Baseline					Pooled PEM vs. Placebo
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%	ΔΔ (95% CI)
VVSymQ						
Sex						
Male (n=70)	-2.05	-3.59	-5.28	-5.10	-4.59	-2.94 (-5.53, -0.35)
Female (n=205)	-4.06	-2.65	-4.67	-3.68	-5.24	-3.18 (-4.34, -2.03)
Age						
<60 (n=238)	-2.03	-4.81	-5.58	-4.95	-5.90	-3.43 (-4.52, -2.35)
≥60 (n=37)	-4.49	-6.26	-1.95	-2.22	-4.32	-0.48(-4.14, 3.18)
IPR-V³						
Sex						
Male (n=70)	0.27	-0.45	-0.76	-0.80	-0.98	-1.12 (-1.56, -0.68)
Female (n=205)	-0.10	-0.47	-0.79	-0.73	-0.88	-0.70 (-0.91, -0.49)
Age						
<60 (n=238)	0.02	-0.44	-0.81	-0.72	-0.89	-0.82 (-1.02, -0.63)
≥60 (n=37)	-0.48	-0.62	-0.58	-1.20	-1.25	-0.53 (-1.29, 0.23)
PA-V³						
Sex						
Male (n=70)	-0.12	-1.37	-1.46	-2.14	-1.81	-1.68 (-2.43, -0.94)
Female (n=205)	-0.13	-0.80	-1.37	-1.40	-1.63	-1.35 (-1.71, -0.98)
Age						
<60 (n=238)	-0.16	-0.84	-1.37	-1.62	-1.66	-1.42 (-1.74, -1.04)
≥60 (n=37)	-0.07	-1.45	-1.21	-1.23	-2.10	-1.44 (-2.36, -0.52)

[Source: Reviewer's Results]

Table 13 displayed the primary and secondary efficacy results by Sex and Age for Study 016. The adjusted mean change from baseline to Week 8 is listed for each treatment arm in the endpoints of VVSymQ, IPR-V³ and PA-V³. The comparisons of pooled PEM versus Placebo are also provided. The results of these analyses are consistent within each subgroup.

Table 13 Subgroup Analyses of Primary and Secondary Endpoints by Sex and Age, Study VAP-VV016

Parameters	Adjusted Mean Change from Baseline				Pooled PEM vs. Placebo
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	$\Delta\Delta$ (95% CI)
VVSymQ					
Sex					
Male (n=61)	-1.21	-5.70	-5.49	-7.23	-5.15 (-7.78, -2.51)
Female (n=164)	-2.33	-5.46	-6.27	-4.59	-3.09 (-4.30, -1.89)
Age					
<60 (n=182)	-2.10	-5.43	-5.96	-5.28	-3.52 (-4.81, -2.23)
≥60 (n=43)	-1.39	-4.90	-6.46	-4.84	-4.26(-6.91, -1.62)
IPR-V³					
Sex					
Male (n=62)	-0.17	-0.48	-0.78	-0.98	-0.71 (-1.05, -0.36)
Female (n=167)	-0.03	-0.82	-0.91	-0.79	-0.83 (-1.05, -0.60)
Age					
<60 (n=185)	-0.07	-0.64	-0.96	-0.80	-0.81 (-1.02, -0.61)
≥60 (n=44)	-0.21	-0.90	-0.59	-0.81	-0.49 (-1.04, 0.07)
PA-V³					
Sex					
Male (n=62)	-0.07	-1.45	-2.14	-1.84	-1.92 (-2.64, -1.20)
Female (n=167)	-0.33	-1.50	-1.77	-1.71	-1.41 (-1.76, -1.06)
Age					
<60 (n=186)	-0.30	-1.50	-1.89	-1.86	-1.58 (-1.93, -1.23)
≥60 (n=44)	-0.26	-1.54	-1.94	-1.64	-1.53 (-2.53, -0.53)

[Source: Reviewer's Results]

4.2 Other Special/Subgroup Populations

4.2.1 Fitzpatrick Skin Type

The Fitzpatrick Skin Type is an instrument that was used by the clinician at the screening visit to classify a patient's skin type. The patients had been classified into 6 Fitzpatrick Skin Types, so this section pooled Types I to III and Types IV to VI together in order to have sufficient number of observations to make the inferences. The results of the appearance outcomes were consistent among the two different pooled Skin Types in both studies; see Table 14 and Table 15.

Table 14 Subgroup Analyses of Appearance Outcomes by Fitzpatrick Skin Types, Study VAP-VV015

Parameters	Adjusted Mean Change from Baseline					Pooled PEM vs. Placebo
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	PEM 2.0%	$\Delta\Delta$ (95% CI)
IPR-V³						
Type I-III (n=198)	-0.03	-0.35	-0.73	-0.80	-0.88	-0.77 (-0.98, -0.56)
Type IV-VI (n=74)	0.23	-0.60	-0.84	-0.54	-0.84	-0.97 (-1.35, -0.58)
PA-V³						
Type I-III (n=201)	-0.22	-1.00	-1.28	-1.53	-1.74	-1.30 (-1.67, -0.92)
Type IV-VI (n=74)	0.10	-0.66	-1.50	-1.60	-1.71	-1.71 (-2.39, -1.02)

[Source: Reviewer's Results]

Table 15 Subgroup Analyses of Appearance Outcomes by Fitzpatrick Skin Types, Study VAP-VV016

Parameters	Adjusted Mean Change from Baseline				Pooled PEM vs. Placebo
	Placebo	PEM 0.125%	PEM 0.5%	PEM 1.0%	$\Delta\Delta$ (95% CI)
IPR-V³					
Type I-III (n=181)	-0.07	-0.76	-0.75	-0.81	-0.71 (-0.94, -0.49)
Type IV-VI (n=48)	0.06	-0.43	-1.14	-0.89	-1.07 (-1.44, -0.71)
PA-V³					
Type I-III (n=182)	-0.33	-1.67	-1.73	-1.90	-1.49 (-1.86, -1.13)
Type IV-VI (n=48)	-0.24	-0.62	-2.05	-0.97	-1.27 (-1.90, -0.65)

[Source: Reviewer's Results]

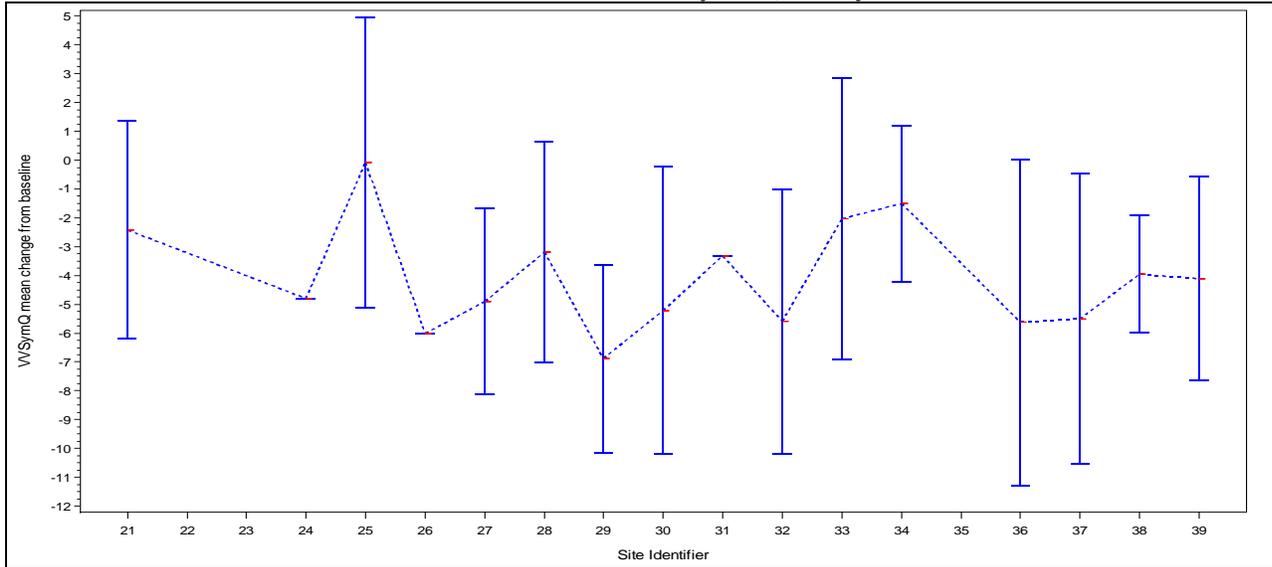
4.2.2 Site

The Study 015 and 016 each has 19 and 12 centers, respectively.

The number of subjects within each site ranged from 2 to 36 in Study 015. As we can see in Figure 8, the pooled PEM had larger VVSymQ score reductions than Placebo in all the evaluable sites. The sites 22, 23, and 35 did not have any Placebo subjects, so the mean differences between pooled PEM and Placebo cannot be displayed. Note the sizes of the bubbles are proportional to the site sample sizes.

Eleven (11) out of the remaining sixteen (16) sites had smaller mean differences than the population estimate of 3.31 (see Table 6). There are no extreme differences among each Site in terms of standard deviation, which ranged from 2.0 to 5.7. There are no site has more than 4 fold increases than any other site in sample size.

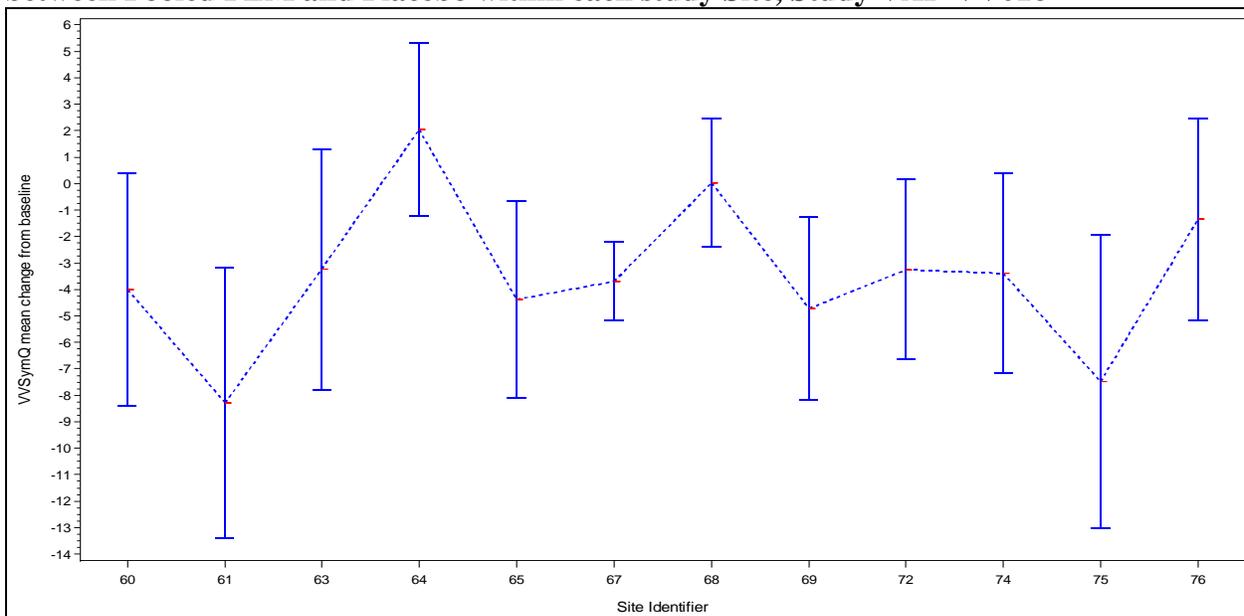
Figure 8 The Mean Differences and SD Bars in change from baseline VVSymQ scores between Pooled PEM and Placebo within each study Site, Study VAP-VV015



[Source: Reviewer’s Results]

The number of subjects within each site ranged from 5 to 24 in Study 016. As we can see in Figure 9, the pooled PEM again had larger VVSymQ score reductions than Placebo in all the sites, except for sites 64 and 68. There are no extreme differences among each Site in terms of standard deviation, which ranged from 1.5 to 5.6. There are no site has more than 5 fold increases than any other site in sample size.

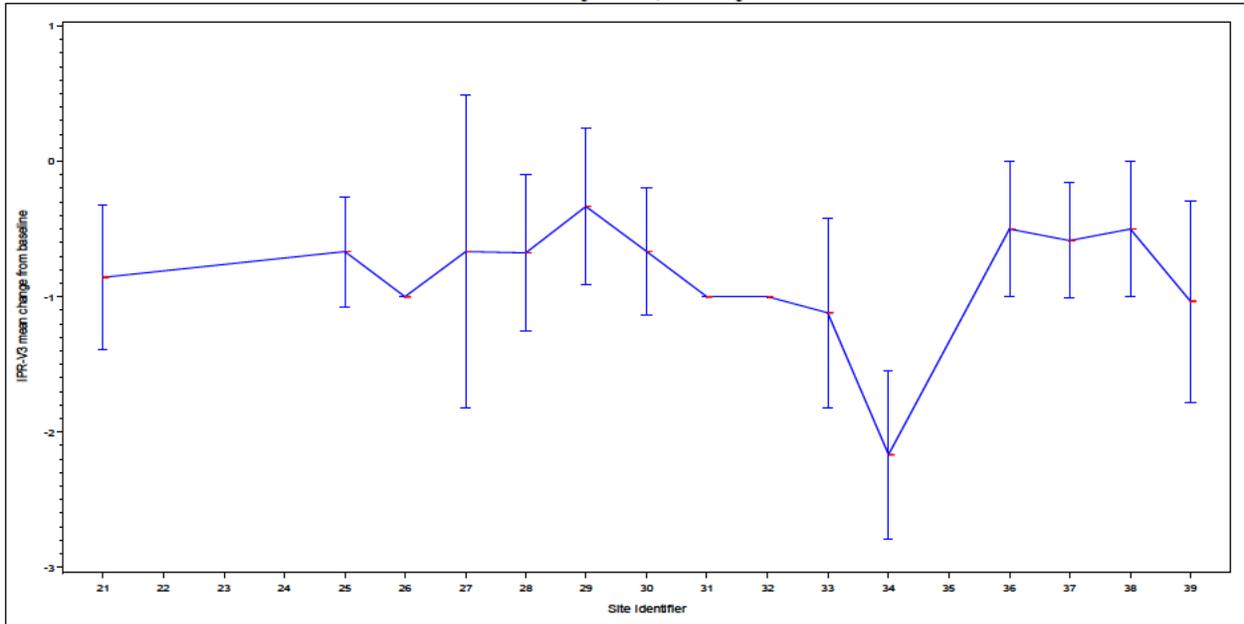
Figure 9 The Mean Differences and SD Bars in change from baseline VVSymQ scores between Pooled PEM and Placebo within each study Site, Study VAP-VV016



[Source: Reviewer’s Results]

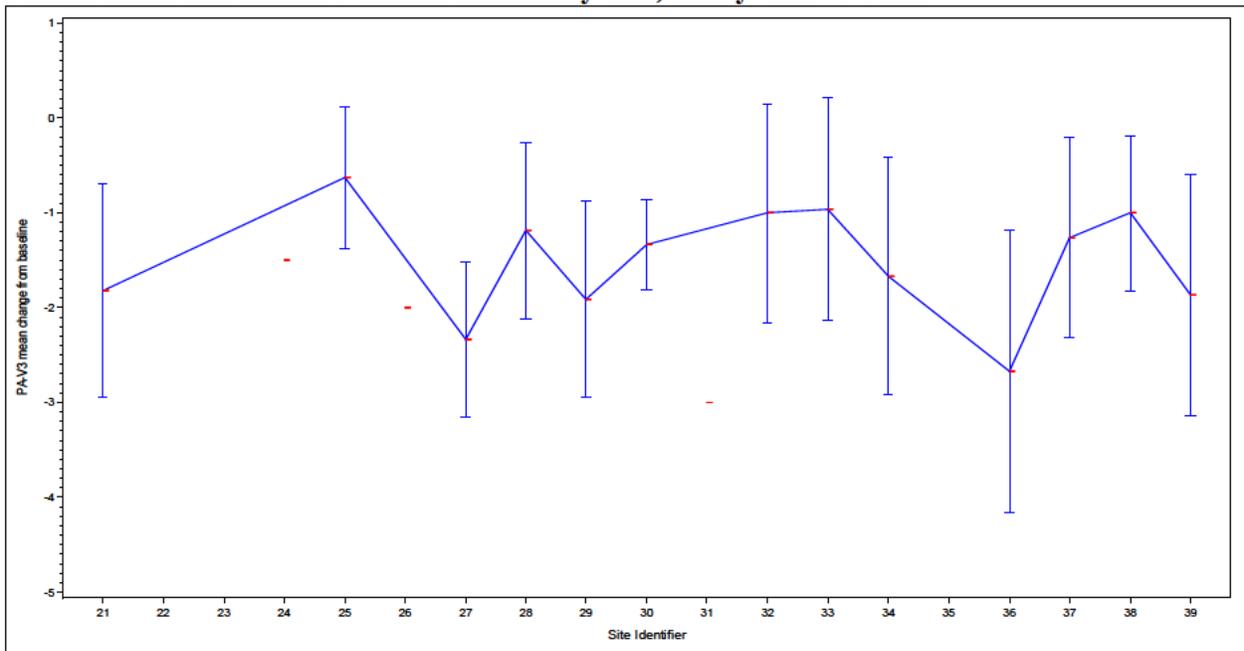
The co-secondary results are consistently in favor of the pooled PEM treatment group across all sites in both Study 015 and 016; see Figure 10 and Figure 13.

Figure 10 The Mean Differences and SD Bars in change from baseline IPR-V³ between Pooled PEM and Placebo within each study Site, Study VAP-VV015



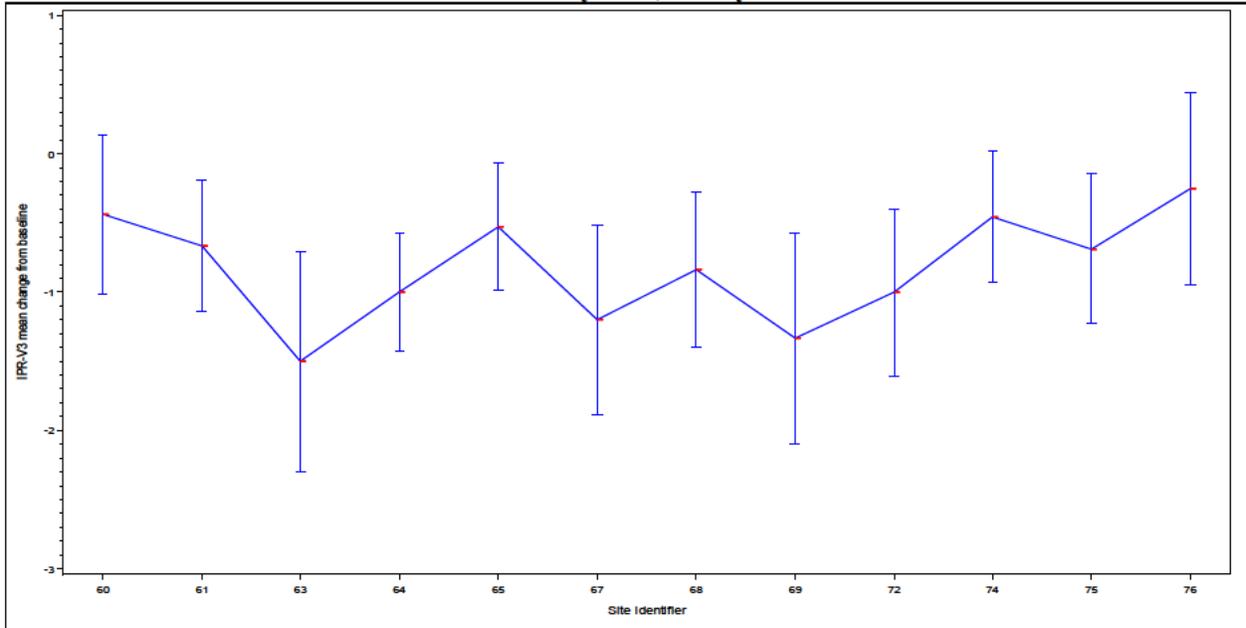
[Source: Reviewer's results]

Figure 11 The Mean Differences and SD Bars in change from baseline PA-V³ between Pooled PEM and Placebo within each study Site, Study VAP-VV015



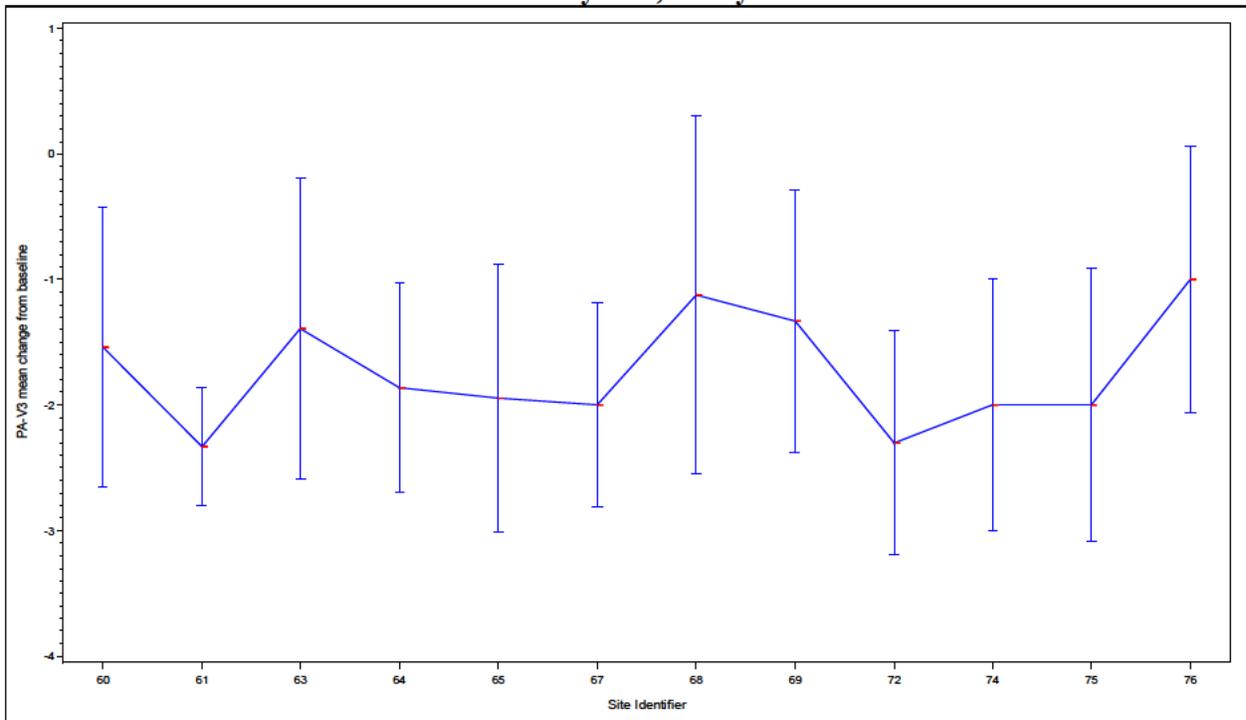
[Source: Reviewer's results]

Figure 12 The Mean Differences and SD Bars in change from baseline IPR-V³ between Pooled PEM and Placebo within each study Site, Study VAP-VV016



[Source: Reviewer's results]

Figure 13 The Mean Differences and SD Bars in change from baseline PA-V³ between Pooled PEM and Placebo within each study Site, Study VAP-VV016



[Source: Reviewer's results]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Study 015 demonstrated the blinded treatment with PEM 0.5%, 1.0% and 2.0% (pooled) was statistically significantly superior to 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) was also statistically significantly superior to placebo in the co-secondary efficacy analyses, improvement in the appearance of visible varicose veins, as measured on the IPR-V₃ and PA-V₃ instruments (both $P<0.0001$). 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). 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 placebo ($P<0.0001$ for all comparisons).

The Study 016 also demonstrated the blinded treatment with PEM 0.5% and 1.0% (pooled) was statistically significantly superior to placebo in the change in VVSymQ score from baseline to Week 8 ($P<0.0001$). The pooled PEM 0.5% and 1.0% was also statistically significantly superior to placebo in the co-secondary efficacy endpoints, as measured on the IPR-V₃ and PA-V₃ instruments (both $P<0.0001$). 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 with patients treated with Vehicle placebo ($P<0.0001$ for all comparisons).

5.2 Conclusions and Recommendations

The following conclusions are based on the efficacy results from the two pivotal studies, 015 and 016. These results demonstrate that treatment with pooled PEM (3 doses or 2 doses) leads to a robust improvement in the symptoms and appearance of chronic venous insufficiency, duplex ultrasound response, improvement in the clinical severity of venous disease, and improvement in patients' quality of life.

The efficacy of the pooled PEM was consistently demonstrated across efficacy endpoints and both studies, including:

- Improvement of symptoms as assessed by the patient (VVSymQ score);
- Improvement of appearance as assessed by the patient (PA-V₃ score) and by the blinded photography review panel (IPR-V₃ score)
- Duplex response to treatment as assessed by an ultrasound technician blinded to PEM dose-concentration;
- Improvement in severity of patients' venous disease as assessed by the clinician (VCSS);
- Improvement in quality of life assessment as completed by the patient using the modified VEINES-QOL instrument.

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/s/

STEVE G BAI
07/02/2013

HSIEN MING J HUNG
07/02/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205-098

Applicant: Provensis Ltd

Stamp Date: 2/04/2013

Drug Name: Varithena™

NDA/BLA Type: NDA

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		There are no subgroup analyses for gender, race, and country.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			(b) (4)
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.		X		
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Appropriate references for novel statistical methodology (if present) are included.	X		
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X		
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X		

Steve Bai 3/13/2013

 Reviewing Statistician Date

Hsien Ming Hung 3/13/2013

 Supervisor/Team Leader Date

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/s/

STEVE G BAI
03/13/2013

HSIEN MING J HUNG
03/14/2013