

MEDCAC

**Lower Extremity Chronic Venous Disease:
Varicose Veins**

July 20, 2016

Disclosure



Speaker:

Jim Harmon

Vice President of Global Market Access, BTG International Inc.

- Salaried employee of BTG International Inc.
- Major financial association (> \$10,000)

Chronic venous disease is progressive and can lead to significant morbidity

CEAP Classification¹

Varithena®



C₁
Telangiectasia



C₂
Varicose veins



C₃
Edema



C₄
Lipodermatosclerosis
or hyperpigmentation



C₅
Healed ulcer



C₆
Active ulcer

CEAP = Clinical, Etiologic, Anatomy, Pathophysiologic classification of venous disorders.

Up to 1.9% adults progress to ulceration related to chronic venous disease²

- ~ 33% of patients will experience clinical worsening within 6 months³
- 66% of patients progressing to C₆ have episodes of ulceration lasting more than five years⁴
- Severe chronic venous disease (C₃-C₆) can lead to loss of limb or death²

References: 1. Eklöf B, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg.* 2011;53(suppl 5):2S-48S. 2. Gloviczki P, et al. *J Vasc Surg.* 2011;53(suppl 5):2S-48S. 3. Labropoulos N, Leon L, Kwon S, et al. Study of the (C3 – C6) venous reflux progression. *J Vasc Surg.* 2005;41(2):291-295. 2004;40(6):1248-1252. 4. Callam MJ, et al. Chronic ulcer of the leg: clinical history. *Brit Med J.* 1987;294:1389-1391.

Patients seek treatment because of symptoms more often than appearance¹

Vein closure is a surrogate outcome, not a clinical endpoint

- Only measures technical success; fails to capture and may not correlate with patient benefit⁴
- Vein closure ≠ symptom relief
- Resolution of symptoms, independent of vein closure, can be considered to be a successful clinical outcome

Treatment Option	GSV Closure Success Rate ^{2 4}
Stripping/ligation, Laser/RF ablation	75–90%
Physician Compounded Foam Sclerotherapy	67–88%
Liquid, direct-injection sclerotherapy	17.5%

FDA recommend patient-reported outcomes as a Primary Endpoint

- BTG developed the patient-reported VVSymQ[®] symptoms scoring instrument for the primary endpoint in studies, in collaboration with the FDA
- Satisfies FDA requirement of an endpoint that demonstrates clinical benefit (“feel, function, survive”)⁵

References: 1. Eberhardt RT, et al. *Circulation*. 2005;111:2398-2409 2. Vasquez MA, et al. *J Vasc Surg*. 2007;45:1008-1014. 3. Gloviczki P, et al. *J Vasc Surg*. 2011;539(suppl 5):2S-48S. 3. Murad MH, et al. *J Vasc Surg*. 2011;53(suppl 5):49S-65S. 4. Rasmussen LH, et al. *Br J Surg*. 2011;98:1079-1087. 5. Food and Drug Administration. December 2009. Available online at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. Accessed June 17, 2015.

Evidence In Support of Treatment Chronic Venous Insufficiency



Varithena® Review by FDA

- New Drug Application (NDA)
 - Much more rigorous data requirements than 510(k)
 - 1,333 patients enrolled in clinical research program
- Closure as a measure of outcome was deemed insufficient by FDA
 - Drove BTG to measure patient reported symptom relief as a primary endpoint
 - Closure rate deemed to be tertiary endpoint
 - At request of FDA, BTG developed a tool to measure Patient Reported Outcomes (PRO)
 - The tool, called VVSymQ®, was accepted by FDA and is now a standard for measuring symptoms
 - VVSymQ® assesses the 5 HASTI symptoms, e.g., heaviness, achiness, swelling, throbbing, itching pre & post treatment
 - VANISH 1 & VANISH 2 trials
 - VVSymQ®-like measures being captured as part of multiple registries
 - Coverage for symptomatic CVD versus cosmetic

VANISH-1 and VANISH-2 Trials



Randomized, blinded, parallel-group, multicenter studies¹

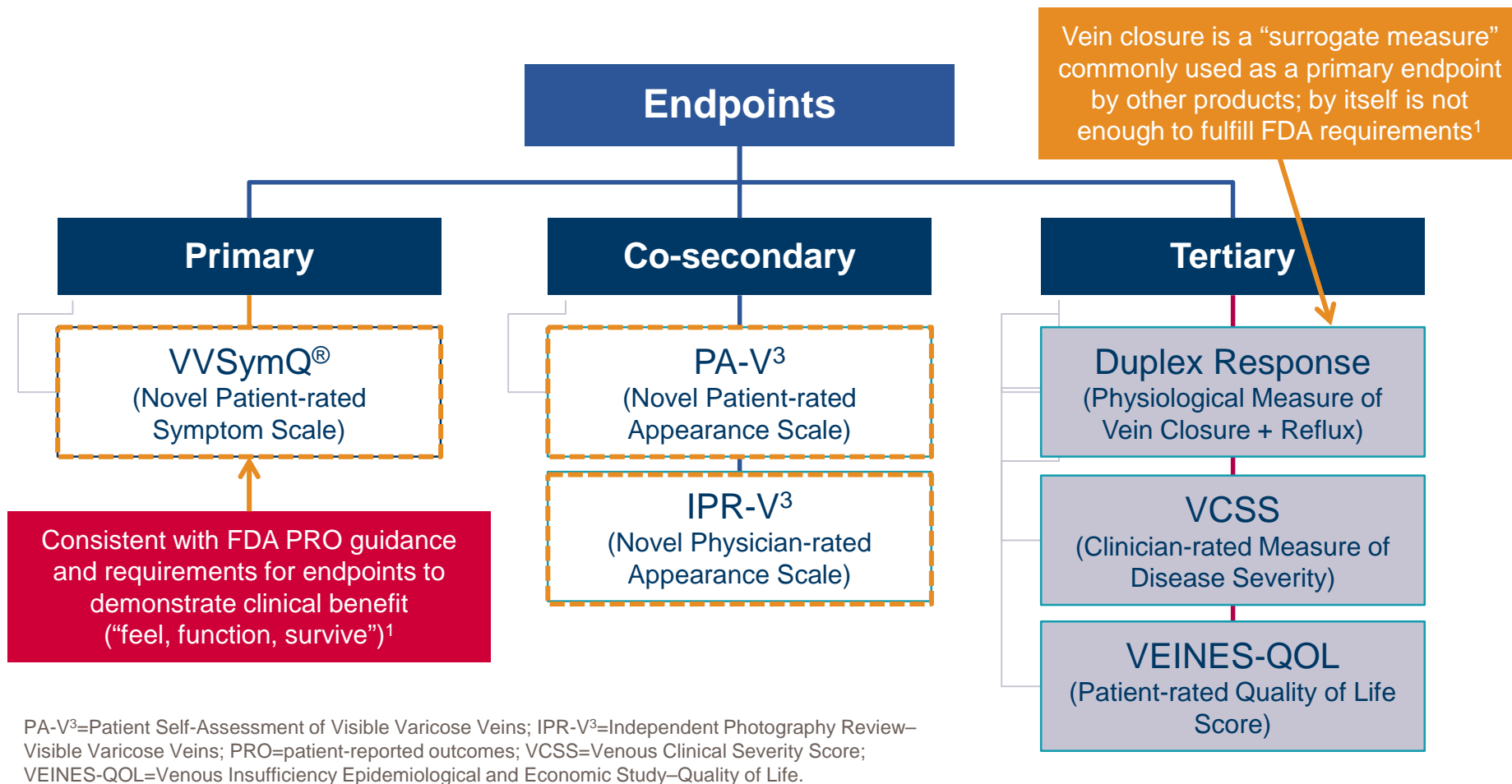
- **VANISH-1** evaluated the safety and efficacy of a single-blinded treatment (up to 15 mL) with Varithena® vs placebo
 - Mean vein diameter 7.6mm (range 1.5 – 25.9mm)
- **VANISH-2** allowed for a second blinded treatment, 1 week after the first
 - Mean vein diameter 8.7mm (range 3.1mm to 19.4mm)
 - In total, 519 patients were studied, including 52 patients in VANISH-1 and 58 patients in VANISH-2 who were treated with the approved dose concentration – Varithena® 1%

Primary endpoint¹

- **Improvement in symptoms** as measured by change in VVSymQ® score at Week 8
 - Aligned with FDA position on importance of patient-reported symptoms measures as endpoints
 - VVSymQ® was developed in collaboration with the FDA to meet the requirement of an endpoint that demonstrates clinical benefit (“feel, function, survive”)²

References: 1. Varithena® prescribing information. Provensis Ltd, a BTG International group company. March 2015. 2. Food and Drug Administration. December 2009. Available online at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. Accessed June 17, 2015.

VANISH-1 and VANISH-2 Endpoints



Reference: 1. Food and Drug Administration. December 2009. Available online at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. Accessed June 17, 2015.

Significant improvement in symptoms at week 8 as measured by VVSymQ^{®1}



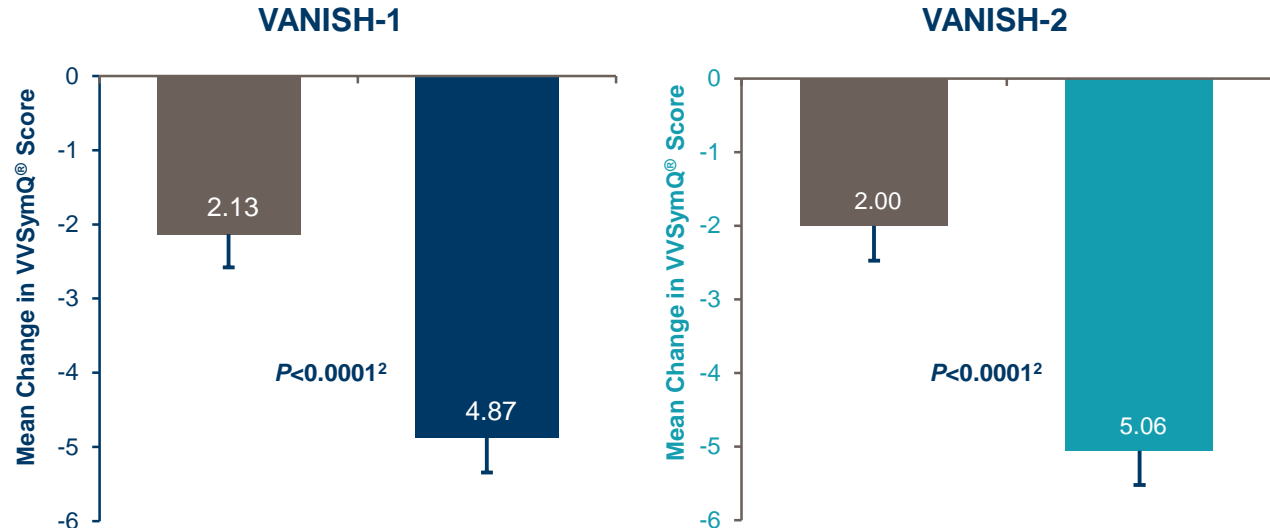
The VVSymQ[®] measures 5 most relevant symptoms via electronic daily diary:¹

- Heaviness
- Achiness
- Swelling
- Throbbing
- Itching

Each symptom rated 0–5; cumulative score averaged over 7 days.²

Reduction in VVSymQ[®] score indicates symptom improvement.

Mean improvement from baseline at week 8¹



Significant improvement with Varithena[®] regardless of CEAP class or GSV diameter

CEAP=clinical, etiologic, anatomy, pathophysiologic classification of venous disorders.

References: 1. Varithena[®] prescribing information. Provensis Ltd, a BTG International group company. March 2015. 2. Wright DD, Paty J, Turner-Bowker DM, Bradbury A. The VVSymQ[®] instrument: Use of a new patient-reported outcome measure for assessment of varicose vein symptoms. Patient. 2016 Mar 25. [Epub ahead of print]

VANISH-1 and VANISH-2 VVSymQ[®] Score

Consistent outcomes across subgroups

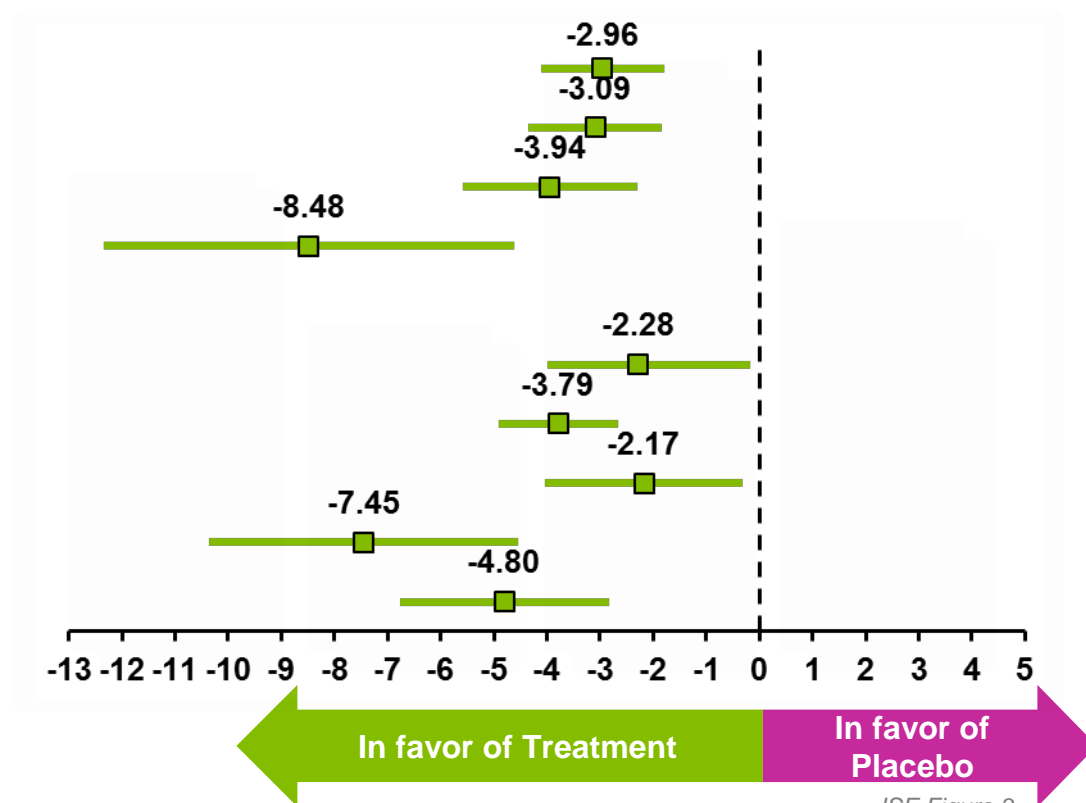


CEAP Class and GSV Diameter

CEAP Class	Placebo n	Treatment n
C2	41	122
C3	43	81
C4	20	68
C5&6	5	10
GSV diameter, mm		
<5	20	50
5 to <8	49	106
8 to <10	17	54
10 to <12	6	27
≥12	15	37

^a Difference in least squares mean change from baseline and 95% CI; ANCOVA model with baseline covariate, study, treatment group, subgroup and treatment group by subgroup interaction effects.

**Difference^a in LS mean change from baseline
(Treatment vs Placebo)**



ISE Figure 3.

VANISH-1 and VANISH-2 VVSymQ[®] Score

Consistent outcomes across subgroups



Subgroup		Placebo n	Pooled Treatments n	Difference in LS mean change from Baseline (Pooled Treatment vs. Placebo)	Difference ^a (95% CI)	
Age	18 - 40	29	58		-3.52	(-5.02, -2.03)
	41 - 64	72	203		-3.43	(-4.33, -2.53)
	≥ 65	8	20		-4.05	(-6.80, -1.30)
Sex	Male	26	78		-4.49	(-5.96, -3.02)
	Female	83	203		-3.19	(-4.03, -2.35)
Race	White	102	262		-3.44	(-4.20, -2.67)
	Non-White	7	19		-4.59	(-7.66, -1.52)
BMI	< 25	35	85		-3.61	(-4.92, -2.30)
	25 - < 30	37	87		-3.85	(-5.13, -2.57)
	≥ 30	37	109		-3.12	(-4.38, -1.86)



In favor of pooled treatment

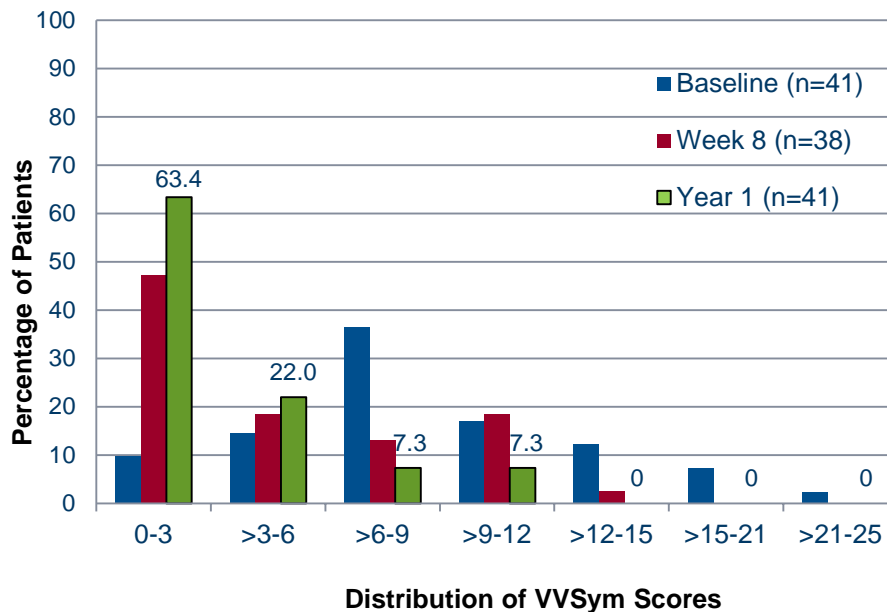
^a Difference in least squares mean change from baseline ; ANCOVA model with baseline covariate, study, treatment group, subgroup and treatment group by subgroup interaction effects.

Durability of Varithena® Treatment Effect

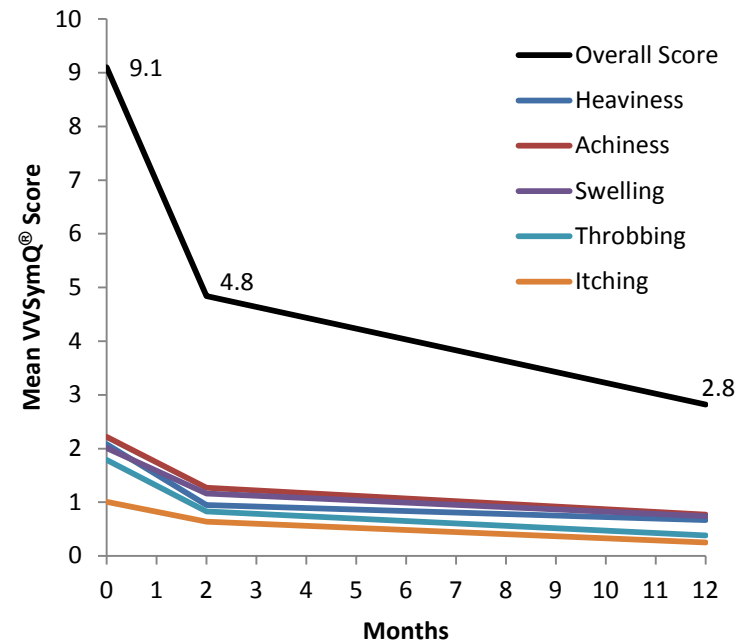
VANISH-1 One-Year Data



Durability of treatment effect observed in VANISH-1 patient population



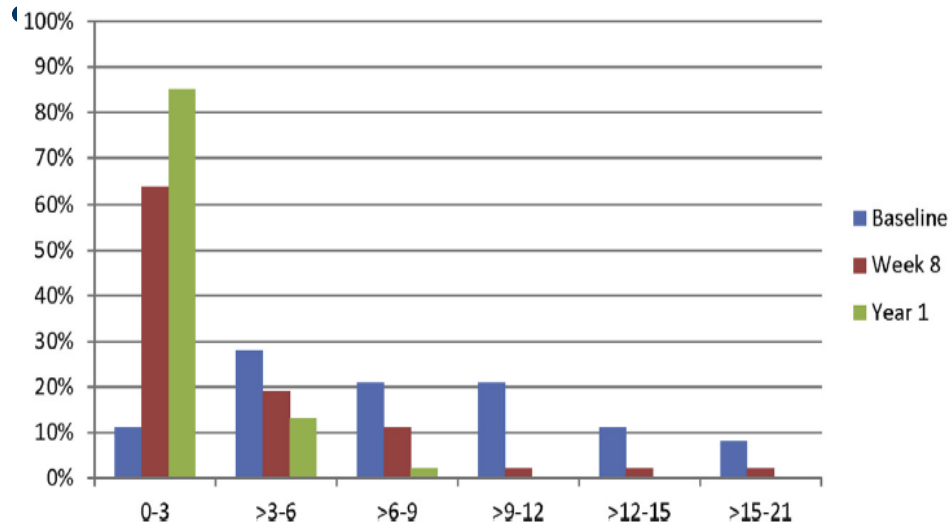
Distribution of VVSymQ® scores at Baseline, Week 8 and Year 1



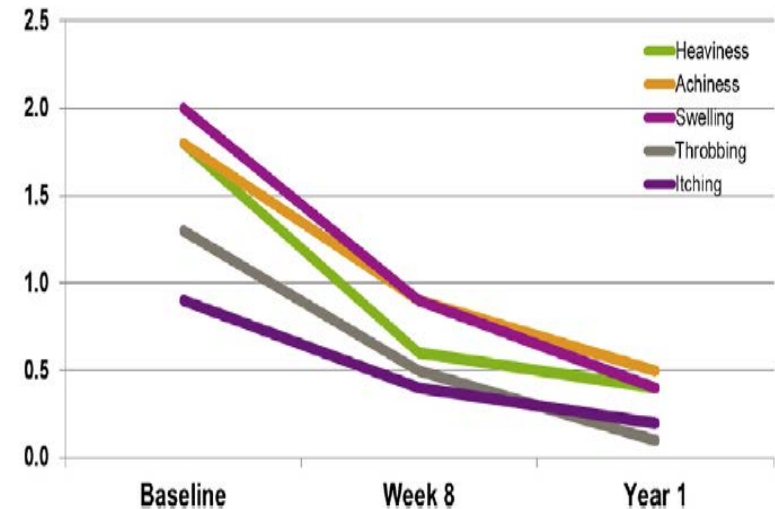
Changes from Baseline to Week 8 and Year 1 in individual symptom scores

Durability of Varithena® Treatment Effect

VANISH-2 One-Year Data



Distribution of VVSymQ® scores at Baseline, Week 8 and Year 1



Changes from Baseline to Week 8 and Year 1 in individual symptom scores

Reference: King JT, O'Byrne M, Vasquez M, Wright D, for the VANISH-1 Investigator Group. Treatment of truncal incompetence and varicose veins with a single administration of a new polidocanol endovenous microfoam preparation improves symptoms and appearance. *Eur J Vasc Endovasc Surg*. 2015 Dec;50(6):784-93

Summary of Publications (1)



VANISH-1	As part of the wider Phase III program, this pivotal, randomized, controlled study in 279 patients demonstrated the clinically significant benefits of Varithena® as measured by patient reported outcomes (VVSymQ® scores for pooled Varithena® patients were significantly superior to placebo at Week 8 (p < .0001); visible appearance (mean changes from baseline to Week 8 in IPR-V ₃ and PA-V ₃ scores were significantly greater in the pooled Varithena® group compared with placebo (p < .0001); and GSV closure (duplex ultrasound response rates for pooled and individual Varithena® patients ranged from 59% to 83%). Similarly to the VANISH-2 study patients treated with Varithena® achieved a successful outcome in that their veins looked better, felt better and their quality of life improved in addition to the good levels of GSV closure that were shown in the study.
VANISH-2	This pivotal, randomized, controlled trial in 232 patients established the efficacy and safety of Varithena®. Efficacy was demonstrated in a number of ways. Patient-reported improvement in symptoms (VVSymQ®) was highly statistically significant following Varithena® at Weeks 4 and 8 vs placebo (P<0.0001); improvement in visible appearance as assessed by the patient (PA-V ₃) and independent clinicians (IPR-V ₃) was statistically significant following Varithena® at Week 8 vs placebo (P<0.0001), and duplex response was achieved by 83% and 86% of patients receiving 0.5% Varithena® and 1.0% Varithena®, respectively. A highly tolerable adverse event profile was seen, with 60% of Varithena®-treated patients reporting an adverse event compared with 39% of placebo patients. Importantly, these results were seen across a broad spectrum of vein disease which supports the relevance of these results in a real-world setting.
MRI Safety Study	In foam sclerotherapy utilizing air-base physician compounded foams, adverse events have been reported that are believed to be a result of embolic events either from the bubbles or the nitrogen gas within the bubble. In this study, a cohort of 60 high-risk patients with R-L cardiac shunt, and therefore at higher risk of cerebral embolic events, had their coexisting GSV disease treated with Varithena®. Doppler was utilized to demonstrate the flow of Varithena® bubbles across the shunt and into the cerebral circulation. Although MCA bubble emboli were detected in 60 patients during or after treatment with Varithena®, there was no evidence of cerebral or cardiac microinfarction. This study demonstrates that as presence of bubbles in the cerebral circulation is essentially inevitable in patients with a R-L shunt it is imperative that the treatment is proven to be safe in this regard. Duplex ultrasound was used to measure efficacy, which confirmed complete occlusion of the GSV in 71 of 81 patients (88%) and elimination of saphenous reflux in 73 of 81 patients (90%).
Safety and Efficacy Study of 1% Varithena®	This randomized, controlled trial, in addition to showing that Varithena® improves symptoms and appearance of varicose veins, established the acceptably safe volume of Varithena® 1% and contributed to the validation of the patient-reported VVSymQ® instrument that has been developed and the VVSymQuick® instrument that is under development. Varithena® provided greater mean changes from Baseline in patient-reported assessments of symptoms [[primary endpoint (30.7 points vs 16.7 points, P=0.0009); and modified-VEINES-QOL/Sym (p<0.001)], physician-assessed VCSS, and physician- and patient-assessed appearance compared with placebo.
VANISH-2 One-Year Data	This one-year data in 232 patients from the pivotal, randomized, controlled VANISH-2 trial demonstrates the durability of treatment effect with Varithena®. A group of patients from the original VANISH-2 study were followed up for 12 months following treatment with Varithena® and efficacy measures (56 patients total assessed for efficacy) were repeated at this point in time. Patients reported continued clinically meaningful improvements in the primary endpoint of VVSymQ® (results at visit 10/year 1 were as good as or better than (64% with total VVSymQ® scores of 3 or less at week 8 vs 85% at year 1) those seen at visit 5/week 8.) and also the secondary endpoints relating to visible appearance as determined by both the patient and an independent investigator (improvements from baseline in appearance as assessed by both patients (PAV ₃ score) and blinded experts reading standardized photographs (IPR-V ₃ score) were maintained, with a small trend toward further improvement between visit 5/week 8 and visit 10/year 1). These key results demonstrate the longevity of treatment effect with Varithena® which is important when considering the modality of treatment to be used.

Summary of Publications (2)



Varithena® with Endothermal Ablation	This randomized, controlled trial in 117 patients assessed the effect of combination therapy on varicose vein appearance, which had not previously been studied. Physician-rated vein appearance at Week 8 was significantly better with Varithena® (p=0.001 vs placebo); patient-assessed appearance trended similarly. Additionally, Varithena® reduced the proportion of patients who received additional treatment for residual varicosities between Week 8 and Month 6 (p<0.05), and increased the proportion of patients with successful elimination of saphenofemoral junction reflux at Week 8 (ETA+ Varithena® 87.3% vs ETA alone 79.9%).
Varisolve (Varithena®) European Study	This trial demonstrated the non-inferiority of Varithena® to surgery and sclerotherapy in 710 patients. Varisolve® (Varithena®) was shown to be superior to alternative sclerotherapy at 12 months, with an overall response rate of 78.9% vs 80.4%, respectively. When patients received Varithena® compared to surgery, they suffered less pain (day 6: surgery median VAS score 9, Varithena® VAS score 2, full scale 0-100; P < 0.001).and were able to return to work sooner (median time to resumption of normal activities following treatment was considerably shorter in the Varithena® group (2 days) than in the surgery group (13 days; P < 0.001).
Expected Costs of Interventional Therapies for Treatment of Chronic Venous Disease	This analysis—evaluating expected patient-level total costs and health plan–level budgetary impact of Varithena® from a third-party payer perspective, based on published CMS professional payment and Hospital Outpatient Prospective Payment System schedules, published wholesale drug costs, and retreatment rates compared with traditional therapeutic interventions—showed that Varithena offers a cost-neutral alternative to other interventional options for the treatment of varicose veins. From a health plan perspective, this drug is likely to have a relatively low budget impact even as it becomes more widely used.
Interventional Treatment Timing and Outcomes for Varicose Veins	This retrospective analysis of a large US commercial and Medicare claims database showed that only about 30% of patients received interventional treatment for varicose veins. Among patients who did receive interventional treatment, early vs. later initiation of interventional treatment was significantly associated with a decreased risk of disease progression and costs.
Relationship between patient-reported outcomes and disease pathophysiology in varicose veins	This secondary analysis of pooled data from two clinical studies in patients with varicose veins evaluated patient-reported symptoms, functional limitations, and psychological impact of varicose vein disease in relation to pathophysiology, demographic and behavioral factors. Substantial patient-reported functional limitation and psychological impact of varicose veins was observed; limitations on work, standing for prolonged periods and clothing choice were most impacted. Patient-reported VVSymQ® symptom score, rather than CEAP-based clinical severity or GSV diameter, was the key predictor of patient-reported VEINES-QOL functional limitations and psychological impact. Above-average symptom and functional limitation levels led to much greater psychological impact. Physicians should routinely ascertain symptom levels and functional limitations levels in order to enhance quality of care and as part of documenting medical necessity.
Cost effectiveness of interventional therapies used in the treatment of chronic venous disease	This analysis—evaluating 8-week expected patient-level total costs and health plan–level budgetary impact of Varithena® from a third-party payer perspective, based on published CMS professional payment and Hospital Outpatient Prospective Payment System schedules, published wholesale drug costs, and one-year retreatment rates compared with traditional therapeutic interventions—showed that Varithena® offers a cost-neutral alternative to other interventional options for the acute treatment of varicose veins. From a health plan perspective, this drug is likely to have a relatively low budget impact even as it becomes more widely used.

Summary of Publications (3)



Treatment patterns, outcomes and costs in patients diagnosed with varicose veins	This large retrospective claims data study of over 140,000 patients with diagnosed varicose veins found that about 70% of patients did not receive interventional therapy for varicose veins. Those receiving interventional treatment were likely to be younger, female and associated with fewer comorbid conditions. Among the patients that did receive interventional treatment, surgery was associated with lowest 8-week and 1-year retreatment rates; on the other hand, laser and radiofrequency ablation when performed alone, were associated with highest retreatment rates.
Costs of treatment of varicose veins with polidocanol endovenous microfoam 1%	This analysis—evaluating 1-year expected patient-level total costs and health plan-level budgetary impact of Varithena® from a third-party payer perspective, based on published CMS professional payment and Hospital Outpatient Prospective Payment System schedules, published wholesale drug costs, and one-year retreatment rates in Varithena® clinical data compared with corresponding one-year retreatment rates for traditional therapeutic interventions in retrospective claims data —showed that Varithena® offers a cost-neutral alternative to other interventional options for the treatment of varicose veins. From a health plan perspective, this drug is likely to have a relatively low annual budget impact even as it becomes more widely used.
Functional impairments in patients with varicose veins and improvement with treatment	In pooled clinical studies comparing treatment with PEM 1% vs. placebo in patients with varicose veins (VV), there was substantial patient-reported functional limitation at baseline. About 76% of patients were limited at baseline on activities requiring standing and 62% were limited on activities requiring sitting for prolonged periods. About 45% of patients had difficulty at work and 28% actually cut down on work. At end of 8-week treatment, only 36% of patients in the PEM 1% group vs. 59% in the placebo group continued to be limited on activities requiring standing for prolonged periods and 29% vs. 56% respectively continued to be limited on activities requiring sitting for prolonged periods. There were similar patterns across the treatment groups in improvement on work function. US health plans' emphasis on persistent symptoms and functioning is well placed but treatment choices should also be evaluated in terms of improvement on symptoms and functioning.
Clinical and economic impact of delayed interventional therapy in the treatment of varicose veins	This retrospective analysis of a large US commercial and Medicare claims database showed that only about 30% of patients with varicose veins received interventional treatment. Among patients who did receive interventional treatment, early, compared to later, initiation of interventional treatment was significantly associated with a decreased risk of disease progression and costs.
Cost effectiveness of interventional therapies used in the treatment of chronic venous disease	This analysis—evaluating cost-effectiveness of Varithena® from a third-party payer perspective, based on published CMS professional payment and Hospital Outpatient Prospective Payment System schedules, published wholesale drug costs, retreatment rates, prevention of new ulcers and symptom-free time compared with corresponding claims data evidence on traditional therapeutic interventions—showed that Varithena® was a cost-effective alternative to laser and radiofrequency ablation modalities. Compared to surgical modalities, Varithena® was less costly and less effective in terms of retreatment rates but more cost-effective in terms of ulcer prevention and overall quality-adjusted life years.

Lack of Consistency Unfair to Patients and Physicians

- Variability between MACs
- Inconsistencies in language
- Not necessarily consistent with evidence
- Difficult for physicians to decipher requirements
- Difficult for processors – delays in reimbursement
- Subjectivity

Consistent & Data Driven Policies are Needed