The VANISH-2 study: a randomized, blinded, multicenter study to evaluate the efficacy and safety of polidocanol endovenous microfoam 0.5% and 1.0% compared with placebo for the treatment of saphenofemoral junction incompetence

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Study design: VANISH-2 was a randomized, blinded, multicenter study designed to evaluate the efficacy and safety of 2 concentrations of polidocanol injectable foam, Varithena® 0.5% and 1.0%, compared with placebo. A sub-therapeutic dose, Varithena® 0.125%, was included as a control for double-blinding purposes. The study population (n=232) consisted of patients who had saphenofemoral junction (SFJ) incompetence due to reflux of the great saphenous vein (GSV) or major accessory veins as determined by duplex ultrasound, and superficial venous disease manifested by symptoms and visible varicosities. The primary efficacy endpoint was patient-reported improvement in symptoms as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ® Score. The co-secondary endpoints were the improvement in appearance of visible varicosities from baseline to Week 8, as measured by patients and by an independent physician review panel. One of 3 tertiary endpoints was response to treatment as determined by duplex ultrasound and defined as elimination of reflux through the SFJ and/or complete occlusion of the target vein(s).

Polidocanol endovenous microfoam 1.0% is FDA approved as Varithena® (polidocanol injectable foam).

This study was funded by BTG International Inc.

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

IMPORTANT SAFETY INFORMATION
Contraindications
The use of Varithena® is contraindicated in patients with known allergy to polidocanol and those with acute thromboembolic disease.

See the enclosed full-text article and Full Prescribing Information. See next page for additional Important Safety Information.
VANISH-2: Efficacy Results

Improvement in varicose vein symptoms

Symptom improvement as measured by VVSymQ® Score
• **VVSymQ® electronic daily diary**: Patient-reported outcomes instrument developed in accordance with FDA guidance document1
  - Patients rated daily duration of 5 symptoms: heaviness, achiness, swelling, throbbing, itching (HASTI™ Symptoms)
  - VVSymQ® Score averages 7 daily scores (range 0 to 25)

• **Results** with Varithena® (polidocanol injectable foam) 1.0%: Highly statistically significant improvement in symptoms as measured by VVSymQ® Score with Varithena® vs placebo at Week 4 and Week 8 (*P*<0.0001)*

![Clinically meaningful improvement in symptoms](chart)

**Clinically meaningful improvement in symptoms**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Varithena® 1.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 4</strong></td>
<td>19% (n=52)</td>
<td>77% (n=53)</td>
</tr>
<tr>
<td><strong>Week 8</strong></td>
<td>21% (n=52)</td>
<td>78% (n=54)</td>
</tr>
</tbody>
</table>

*Clinically meaningful improvement = “Moderately improved” or “much improved” as reported on patient global impression of change (PGIC) scale

*Primary endpoint: Symptom improvement in pooled Varithena® (0.5% and 1.0% concentrations) vs placebo, as measured by the change from baseline to Week 8 in VVSymQ® Score

Polidocanol endovenous microfoam 1.0% is FDA approved as Varithena® (polidocanol injectable foam).
See enclosed article for full study results.

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

Intra-arterial injection or extravasation of polidocanol can cause severe necrosis, ischemia or gangrene. Patients with underlying arterial disease may be at increased risk for tissue ischemia. If intra-arterial injection of polidocanol occurs, consult a vascular surgeon immediately.

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

See the enclosed full-text article and Full Prescribing Information. See next page for additional Important Safety Information.
Adverse events (AEs) in this study were mostly mild or moderate (95% for all dose groups). No unexpected or drug-related serious AEs at any dose were reported.
• No pulmonary emboli reported
• No clinically important neurologic or visual adverse events
• No cerebrovascular events or migraines
• No reported cases of anaphylactic shock

Physiologic response as measured by duplex ultrasound

The authors state that “a more rigorous duplex response definition than typically applied was used in this design.” Response was defined as elimination of reflux through the SFJ and/or complete occlusion of all incompetent target trunk vein(s): GSV, AASV, and/or PASV.* Response was achieved in 86% of patients treated with Varithena® 1.0% at Week 8, compared with 60% of the control group, who received a sub-therapeutic dose (Varithena® 0.125%) created for double-blinding purposes.

*IPR-V³: Independent photography review of visible varicose veins

Physiologic response as measured by duplex ultrasound

Patients also reported improvement in appearance

- Live self-assessments unaided by photographs
- Statistically significant and clinically meaningful improvement with Varithena® 1.0% vs placebo from baseline to Week 8 (P<0.0001)

Improvement in appearance of visible varicose veins

<table>
<thead>
<tr>
<th>Clinician-assessed improvement in appearance</th>
<th>Placebo (n=56)</th>
<th>Varithena® 1.0% (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean change in appearance scores from baseline to Week 8</td>
<td>0.0</td>
<td>(-0.07)</td>
</tr>
<tr>
<td></td>
<td>(-0.2)</td>
<td><strong>(-0.83)</strong></td>
</tr>
<tr>
<td></td>
<td>(-0.4)</td>
<td>(-0.8)</td>
</tr>
<tr>
<td></td>
<td>(-0.6)</td>
<td>(-1.0)</td>
</tr>
</tbody>
</table>

Decrease in scores indicates better outcome. Clinicians assessed severity of vein appearance (5-point IPR-V³ scale*) by reviewing photographs blinded for patient, time, and treatment.

*AASV: Anterior accessory saphenous vein; PASV: Posterior accessory saphenous vein

VANISH-2: Safety Results

Safety profile points of interest

Adverse events (AEs) in this study were mostly mild or moderate (95% for all dose groups). No unexpected or drug-related serious AEs at any dose were reported.
• No pulmonary emboli reported
• No clinically important neurologic or visual adverse events
• No cerebrovascular events or migraines
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IMPORTANT SAFETY INFORMATION

The most common adverse events observed were pain/discomfort in extremity, retained coagulum, injection site hematoma or pain, common femoral vein thrombus extension, superficial thrombophlebitis, and deep vein thrombosis.

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

See the enclosed full-text article and Full Prescribing Information. See next page for additional Important Safety Information.
VANISH-2: Conclusions

Varithena®:

- **Provided clinically meaningful improvement** in symptoms and appearance in patients with incompetent great saphenous veins (GSV), accessory saphenous veins, and visible varicosities of the GSV system. Improvement was measured by a patient global impression of change (PGIC) questionnaire at Week 8.

- **Was an effective and comprehensive minimally invasive treatment** for a wide range of varicose veins (CEAP clinical class C2 to C6 and GSV diameters from 3.1 to 19.4 mm).

  **Study design:** VANISH-2 was a randomized, blinded, multicenter study designed to evaluate the efficacy and safety of 2 concentrations of polidocanol injectable foam, Varithena® 0.5% and 1.0%, compared with placebo. The primary efficacy endpoint was patient-reported improvement in symptoms as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ® Score. The co-secondary endpoints were the improvement in appearance of visible varicosities from baseline to Week 8, as measured by patients and by an independent physician review panel.

- **Was associated with mild or moderate, manageable side effects**

  **Important Safety Information:** The most common adverse events observed were pain/discomfort in extremity, retained coagulum, injection site hematoma or pain, common femoral vein thrombus extension, superficial thrombophlebitis, and deep vein thrombosis.

* Percent of patients who reported their symptoms (or appearance of varicose veins) had “moderately improved” or “much improved” compared with baseline

For more information about Varithena®, call **1-855-971-VEIN (8346)** or visit VarithenaProfessional.com

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