VARITHENA SUMMARY: PHASE 3 TRIALS

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Disclosures
• Consultant for AngioDynamics
• Consultant for Amsel
• Consultant for Vascular Insights
• Consultant for Veneti

Proprietary Polidocanol Foam Indication
Treatment
incompetent (GSV)
visible varicocities of the GSV system

Varithena® Efficacy: VANISH 1 & 2 Pivotal Trials
Randomized, placebo-controlled, blinded, multicenter pivotal trials; n=511

Primary
VVSymQ® Electronic Daily Diary Score
Patient Reported Outcome (PRO)

Co-Secondary

Tertiary

Venous Clinical Severity Score (VCSS)
VEINES-QOL

Tool Development and Phase 3
• FDA required to establish clinical benefit through use of PRO
  - With the FDA patient reported outcome primary endpoint, VVSymQ to satisfy the requirement of an endpoint that demonstrates clinical benefit (“feel, function, survive”)
• 3 new instruments in the Varithena® clinical trials
  - VVSymQ® for patient symptoms
  - PA-V® for appearance from patient view
  - IPR-V® for appearance from clinician view
• Two studies (RS-002 and RS-003) conducted in parallel with Phase III trials demonstrated that VVSymQ®, PA-V® and IPR-V® instruments are “Fit for Purpose”
• VVSymQ® was the primary endpoint in VANISH-1 and VANISH-2 to determine the safety and efficacy of Varithena®
VVSymQ®: Screening Eligibility

- Paper Questionnaire
- Entry Criterion: Score of >7 at Screening
- Eligibility
  - M/F Ages 18-75 years
  - SFJ reflux >0.5 sec
  - Incompetent GSV or major accessory (ultrasound)
  - Symptomatic
  - Visible Varicose Veins

Primary Endpoint: VVSymQ® Validated PRO Electronic Daily Diary Score

- Measures five most relevant symptoms to patients:
  - Heaviness
  - Aching
  - Swelling
  - Throbbing
  - Itching
- Each symptom rated 0–6 and summed
- Duration scale 0–5 "How much of the time?"
- Averaged over 7 consecutive days
- Patient compliance > 95% with all data points

Change From Baseline to Week 8 in VVSymQ® Individual Symptom Scores in VANISH-1

Analysis: VVSymQ® Score Improved Regardless of CEAP Class or GSV Diameter

Are the Results Clinically Meaningful?

Patient Global Impression of Change (PGIC) from Baseline

Clinically Meaningful Improvement in Symptoms at Week 8 (PGIC)

Todd et al., Phlebology 2013;1-1
**Varithena® Efficacy: VVSymQ® Primary Endpoint**

**VANISH -1**

- Placebo vs Varithena® 1%
  - Mean baseline score: 8.60 vs 8.82
  - Mean change from baseline at Week 8:
    - Placebo: -2.00
    - Varithena® 1%: -2.13
  - p < 0.0001

**VANISH -2**

- Placebo vs Varithena® 1%
  - Mean baseline score: 8.60 vs 8.82
  - Mean change from baseline at Week 8:
    - Placebo: -2.00
    - Varithena® 1%: -2.13
  - p = 0.0005

**Varithena® Efficacy Across Subgroups**

**CEAP Class and GSV Diameter**

<table>
<thead>
<tr>
<th>CEAP Class</th>
<th>Placebo Mean Change</th>
<th>Varithena® 1% Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>-2.00</td>
<td>-4.00</td>
</tr>
<tr>
<td>C3</td>
<td>-2.39</td>
<td>-4.87</td>
</tr>
<tr>
<td>C4</td>
<td>-3.12</td>
<td>-5.64</td>
</tr>
<tr>
<td>C5/C6</td>
<td>-3.88</td>
<td>-5.86</td>
</tr>
</tbody>
</table>

**Varithena® Durability**

- Symptom improvement sustained at one year post treatment with Varithena®

**Varithena® Safety Profile**

- Clinical significance of embolization gas bubble during polidocanol endovenous ultra-low nitrogen microbubbles ablation and correlation with magnetic resonance imaging in patients with right to left shunt

- No evidence of lesion on diffusion weighted MRI sequence
- No neurological symptoms
- No elevation in cardiac troponin levels

**Patient Demographics and Baseline Disease Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VANISH -1</th>
<th>VANISH -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (SD)</td>
<td>48.9 (10.5)</td>
<td>48.8 (10.5)</td>
</tr>
<tr>
<td>Range</td>
<td>19 - 74</td>
<td>21 - 73</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>208 (74.6)</td>
<td>169 (72.8)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>260 (93.2)</td>
<td>215 (92.7)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>28.2 (5.6)</td>
<td>29.5 (6.0)</td>
</tr>
<tr>
<td>Range</td>
<td>16 - 44</td>
<td>17 - 48</td>
</tr>
</tbody>
</table>

**Tertiary Endpoint:**

**Duplex Ultrasound Response Elimination of SFJ Reflux and/or Complete Occlusion of Incompetent GSV and Major Accessory Veins**

- VANISH-1
  - Varithena® 1%: 61.1%
  - Placebo: 42.1%
  - p = 0.0001

- VANISH-2
  - Varithena® 1%: 60.6%
  - Placebo: 59.6%
  - p = 0.0005
**Tertiary Endpoint:**
**VCSS Venous Clinical Severity Score**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mean Baseline Score</th>
<th>Varithena 1% Mean Baseline Score</th>
<th>Vanish-1 Mean Baseline Score</th>
<th>Vanish-2 Mean Baseline Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.11</td>
<td>7.39</td>
<td>7.11</td>
<td>7.39</td>
</tr>
<tr>
<td>Varithena™ 1%</td>
<td>7.28</td>
<td>1.22</td>
<td>7.28</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**Mean Change from Baseline at Week 8**

- Placebo: -0.75
- Varithena™ 1%: -1.52

**Tertiary Endpoint:**
**VEINES-QOL Modified Venous Insufficiency Epidemiologic and Economic Study – Quality of Life**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mean Baseline Score</th>
<th>Varithena™ 1% Mean Baseline Score</th>
<th>Vanish-1 Mean Baseline Score</th>
<th>Vanish-2 Mean Baseline Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>53.72</td>
<td>57.64</td>
<td>53.72</td>
<td>57.64</td>
</tr>
<tr>
<td>Varithena™ 1%</td>
<td>54.86</td>
<td>54.22</td>
<td>54.86</td>
<td>54.22</td>
</tr>
</tbody>
</table>

**Mean Change in Baseline at Week 8**

- Placebo: -1.0
- Varithena™ 1%: -1.0

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**Treatment-Emergent Adverse Reactions (3% more on Varithena® 1% than on Placebo through Week 8 [n=588])**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo/ Vehicle Mean (n=532)</th>
<th>Varithena® 1.0% Mean (n=532)</th>
<th>Varithena® Pooled Mean (n=437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in extremity</td>
<td>14 (8.3)</td>
<td>25 (15.0)</td>
<td>45 (10.3)</td>
</tr>
<tr>
<td>Infusion site thrombosis</td>
<td>0</td>
<td>24 (16.1)</td>
<td>46 (10.5)</td>
</tr>
<tr>
<td>Contusion/injection site hematoma</td>
<td>9 (6.0)</td>
<td>23 (15.4)</td>
<td>38 (8.7)</td>
</tr>
<tr>
<td>Limb discomfort</td>
<td>5 (3.3)</td>
<td>18 (12.1)</td>
<td>32 (7.3)</td>
</tr>
<tr>
<td>Tenderness/injection site pain</td>
<td>5 (3.3)</td>
<td>16 (10.7)</td>
<td>30 (6.9)</td>
</tr>
<tr>
<td>Venous thrombosis limb</td>
<td>0</td>
<td>12 (8.1)</td>
<td>24 (5.5)</td>
</tr>
<tr>
<td>Thrombophlebitis superficial</td>
<td>2 (1.3)</td>
<td>8 (5.4)</td>
<td>40 (9.2)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>7 (4.5)</td>
<td>10 (2.3)</td>
</tr>
</tbody>
</table>

**Incidence of Neurologic and Visual AEs Within 1 Day of Varithena® Treatment**

- None of the 1333 patients in Varithena® trials experienced clinically important neurological or visual adverse events suggestive of cerebral gas embolism

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