New Treatment Modalities for the Superficial Venous System:

*Data Non-Thermal, Non-tumescent Technologies*

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The Venous Institute of Buffalo
SUNY at Buffalo Department of Surgery
New Cardiovascular Horizons
June 4th, 2016
Disclosures

Principal Investigator:
- BTG international
- Medtronic

Honorarium/ Speaker’s Bureau:
- BTG international
- Medtronic

Consultant:
- BTG international
- Medtronic

Stockholder:
- None

Grant/Research Support:
- BTG international
- Medtronic

Medical/Scientific Boards:
- BTG international
Outcome Reporting
Clinical Outcome Reporting

- **Patient-perceived** Quality of Life Measures
  - Patient-Reported Outcomes (PRO)
  - VVSymQ, AVVQ, VEINES-QoL, CIVIQ

- **Clinician Reported** Outcomes (ClinRO)
  - CEAP Classification
  - Venous Clinical Severity Score (VCSS)

Duplex result is a *surrogate* outcome measure
## Revised VCSS Descriptor

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Absent (0)</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional</td>
<td>Daily</td>
<td>Daily limiting</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>None</td>
<td>Few</td>
<td>Calf or thigh</td>
<td>Calf and thigh</td>
</tr>
<tr>
<td>Venous edema</td>
<td>None</td>
<td>Foot and ankle</td>
<td>Above ankle, below knee</td>
<td>To knee or above</td>
</tr>
<tr>
<td>Skin Pigmentation</td>
<td>None</td>
<td>Perimalleolar</td>
<td>Diffuse, lower 1/3 calf</td>
<td>Wider, above lower 1/3 calf</td>
</tr>
<tr>
<td>Inflammation</td>
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</tr>
<tr>
<td>No. active ulcers</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Active ulcer size</td>
<td>None</td>
<td>&lt; 2 cm</td>
<td>2 – 6 cm</td>
<td>&gt; 6 cm</td>
</tr>
<tr>
<td>Ulcer duration</td>
<td>None</td>
<td>&lt; 3 mo</td>
<td>3 – 12 mo</td>
<td>&gt; 1 yr</td>
</tr>
<tr>
<td>Compression Therapy</td>
<td>None</td>
<td>Intermittent</td>
<td>Most days</td>
<td>Fully comply</td>
</tr>
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Image courtesy of Michael Vasquez, MD
### VCSS

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</table>

1 week post op

Image courtesy of Michael Vasquez, MD
VCSS

Pain=1, VV=2, Edema=2, Pigmentation=0, Inflammation=0, Induration=0, Active ulcers, size, duration=0, Compression therapy=2
Total VCSS Score = 7

Pain=0, VV=1, Edema=0, Pigmentation=0, Inflammation=0, Induration=0, Active ulcers, size, duration=0, Compression therapy=2
Total VCSS Score = 3
Non-Thermal, Non-Tumescent Saphenous Ablation (NTNT)
Non-Thermal, Non-Tumescent (NTNT)

- Mechanico-chemical ablation – MOCA (ClariVein)
- Polidocanol Injectable Microfoam - PEM (Varithena)
- Cyanoacrylate Glue – CAC (VenaSeal)
Mechanico-chemical ablation
Mechanico-chemical ablation

GSV and SSV
Mechanico-chemical ablation


TABLE 2: Anatomical success.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Occluded</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6th month</td>
<td>72</td>
<td>68</td>
<td>94</td>
</tr>
<tr>
<td>12th month</td>
<td>64</td>
<td>61</td>
<td>95</td>
</tr>
<tr>
<td>24th month</td>
<td>42</td>
<td>40</td>
<td>95</td>
</tr>
</tbody>
</table>
Mechanico-chemical ablation - VCSS

Median VCSS at baseline and during follow-up

Mechanico-chemical ablation - VCSS

VCSS scores at baseline, one month and six months follow-up – MOCA and RFA

Lane, T., Davies, A. et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. Phlebology May 24, 2016
Mechanico-chemical ablation - Pain

Maximum pain score during procedure for MOCA and RFA
(a) – visual analogue scale
19.3        34.5
(b) – number scale
2.6         4.4

Lane, T., Davies, A. et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. Phlebology May 24, 2016
Mechanico-chemical ablation

-Pain

**Average pain score** during procedure for MOCA and RFA
(a) – visual analogue scale  
   13.4          24.4
(b) – number scale  
   1.9            3.2

Lane, T., Davies, A. et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins - Final results of the Venefit versus Clarivein for varicose veins trial. *Phlebology May 24, 2016*
Mechanico-chemical ablation -PRO

AVVQ scores at baseline, one month and six months follow-up - MOCA and RFA

Cyanoacrylate Glue
Cyanoacrylate Glue

- Vascular closing agent
  - Cerebral AVM
  - Pelvic congestion syndrome
  - Varicocele
  - Gastric varices
  - Aortic aneurysms endoleak
VenaSeal™ Closure System

Position catheter 5 cm from SFJ

Compress cephalad to catheter
Inject 0.10 cc adhesive into the vein, pull back 1 cm, inject 0.10 cc pull back 3 cm

Inject 0.10 cc, pull back 3 cm, compress for 30 seconds
Cyanoacrylate Glue
VeClose Study (VenaSeal)

VeClose Study

Intraoperative Pain evaluation at Day 3:
Following procedure, self-rated pain experienced during 2 phases of the treatment procedure on a 0-10 NRS
- Phase 1: From initial local anesthesia injection at the access site to venous access with the micro-access catheter
- Phase 2: From introduction of the RFA or CAC catheter to completion of vein treatment and device removal

Ecchymosis at Day 3:
Investigator assessment of ecchymosis along the treated area using a 0-5 point grading scale:
0 - none
1 - involving <25% of the treatment area
2 - 25%-50%
3 - 50%-75%
4 - 75%-100%
5 - extension above or below the treatment segment

VeClose Additional endpoints

- Assessments related to venous disease severity:
  - Change in VCSS scores
  - Change in CEAP scores
- Assessments related to QoL:
  - Change in AVVQ scores
  - Change in EQ-5D TTO scores
- Comparison of adverse event rates related to target GSV

Primary Endpoint VeClose

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Closure Rate VenaSeal™ System N=108</th>
<th>Closure Rate RFA N=114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>100% (108)</td>
<td>99.1% (114)</td>
</tr>
<tr>
<td>Month 1</td>
<td>100% (105)</td>
<td>87.3% (110)</td>
</tr>
<tr>
<td>Month 3</td>
<td>99% (104)</td>
<td>95.4% (108)</td>
</tr>
<tr>
<td>Month 6</td>
<td>99% (101)</td>
<td>96.2% (105)</td>
</tr>
<tr>
<td>Month 12</td>
<td>96.8% (95)</td>
<td>95.9% (97)</td>
</tr>
<tr>
<td>Month 24</td>
<td><strong>94.3%</strong> (87)</td>
<td><strong>94%</strong> (84)</td>
</tr>
</tbody>
</table>

Secondary Endpoint VeClose

<table>
<thead>
<tr>
<th></th>
<th>CAC (N=108)</th>
<th>RFA (N=114)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumescent Anesthesia Volume (mL)</td>
<td>Not Applicable</td>
<td>272</td>
<td>-</td>
</tr>
<tr>
<td>Lidocaine Use During Procedure (mL)</td>
<td>1.6</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Cyanoacrylate delivered (mL)</td>
<td>1.2</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>Intraoperative pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During Vein Access</td>
<td>1.6</td>
<td>2.0</td>
<td>0.13</td>
</tr>
<tr>
<td>During Treatment</td>
<td>2.2</td>
<td>2.4</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Additional Endpoints - VCSS

Kolluri, R. VeClose 24 Month Results, Charing Cross, April 26, 2016.
Additional Endpoints - AVVQ

Kolluri, R. VeClose 24 Month Results, Charing Cross, April 26, 2016.
Veclose 24 month results

- **94.3%** occlusion rates at 24 months.
  - non-inferiority results to RFA (P=0.0075)
- VCSS and AVVQ significantly **improved**
  - no difference between groups at 24 months
- Adverse events comparable and low in both treatments
- Pain rating not significantly different
Polidocanol Endovenous Microfoam

- Varithena® microfoam  Physician-compounded foam

*All images compare foams within approximately 10 seconds of creation. Photos of physician-compounded foam feature examples of manually created foam made 1:4 with 1% polidocanol solution and room air, Tessari technique. Because of varying conditions and techniques, properties of physician-compounded foams may vary. Photos by RSSL (Reading Scientific Services Ltd, UK)
Polidocanol Microfoam

- Injectable liquid and gas uniform Microfoam with median bubble diameter $<100 \ \mu m$
  - Gas mixture of oxygen: carbon dioxide in a ratio of 65:35 makes highly absorbable
  - A low nitrogen ($<0.8\%$) concentration leaves minimal residual gas
- **Microfoam displaces blood**
  - surfactant chemically ablates vein
  - replaced by fibrous connective tissue
Polidocanol Endovenous Microfoam

- Indicated for incompetent *great saphenous* veins, accessory saphenous veins and visible varicosities above and below the knee

**VANISH-1 and VANISH-2: Endpoints**

**Endpoints**

- **Primary**
  - VVSymQ®
    - (Novel Patient-rated Symptom Scale)
  - Consistent with FDA PRO guidance and requirements for endpoints to demonstrate clinical benefit ("feel, function, survive")

- **Co-Secondary**
  - PA-V³
    - (Novel Patient-rated Appearance Scale)
  - IPR-V³
    - (Novel Physician-rated Appearance Scale)

- **Tertiary**
  - Duplex Response
    - (Physiological Measure of Vein Closure + Reflux)
  - VCSS
    - (Clinician-rated Measure of Disease Severity)
  - VEINES-QOL
    - (Patient-rated Quality of Life Score)

Vein closure is a "surrogate measure" commonly used as a primary endpoint by other products; by itself is not enough to fulfill FDA requirements.

**Specifications and Definitions**

- **VVSymQ®** = electronic daily diary of symptoms
- **PA-V³** = Patient Self-Assessment of Visible Varicose Veins
- **IPR-V³** = Independent Photography Review—Visible Varicose Veins
- **PRO** = patient-reported outcomes
- **VCSS** = Venous Clinical Severity Score
- **VEINES-QOL** = Venous Insufficiency Epidemiological and Economic Study—Quality of Life

VVSymQ® Symptoms

- Heaviness
- Achiness
- Swelling
- Throbbing
- Itching

- Duration scale 0–5
- Total score ranges from 0–25 averaged over 7 consecutive days
Polidocanol Microfoam

- 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 of Varithena™ (1.0%)

<table>
<thead>
<tr>
<th>Varithena™ (polidocanol injectable foam) 1%</th>
<th>Other sclerosants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patient experienced clinically important neurological or visual AEs, suggestive of cerebral gas embolism</td>
<td>Neurologic AEs (cerebrovascular accident, migraines) have been reported in patients following administration of physician compounded foam sclerosants</td>
</tr>
</tbody>
</table>
Polidocanol Microfoam

Duplex response is defined as:

- Elimination of reflux through the SFJ, and/or
- Complete occlusion of incompetent trunk veins (GSV, AASV, and/or PASV)

PEM and VVSymQ

VANISH-1 and VANISH-2 Integrated Analysis

<table>
<thead>
<tr>
<th>CEAP Class</th>
<th>Placebo</th>
<th>Varithena™ 1.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>C3</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>C4</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>C5 &amp; 6</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>GSV Diameter, mm</th>
<th>Placebo</th>
<th>Varithena™ 1.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>5 to &lt;8</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>8 to &lt;10</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>10 to &lt;12</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>≥12</td>
<td>15</td>
<td>14</td>
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Difference in Adjusted Mean Change From Baseline VVSymQ

In favor of Varithena™ 1.0%

In favor of Placebo

BTG Data on File.
Polidocanoli Endovenous Microfoam Studies - VVSymQ

Appearance, as measured by IPR-V³ (clinician assessment) and PA-V³ (patient self-assessment) scores
Microfoam significantly reduces the VCSS score\(^1\)

Clinician-based instrument\(^1,2\)
- 10 items, each rated 0–3
- Summed to produce scale of 0–30
- Higher scores indicate more severe venous disease

Mean Change From Baseline at Week 8\(^1\)

\[\text{Mean change in VCSS score from baseline at Week 8}\]

\(\text{Placebo} \quad \text{Varithena}^{\text{TM}} 1.0\%\)

\(\text{VANISH-1}\)
- Placebo: \(n=55\)
- Varithena\(^{TM} 1.0\%: \text{n}=49\)
- Mean change: \(-0.75\)
- \(P<0.0001^a\)

\(\text{VANISH-2}\)
- Placebo: \(n=56\)
- Varithena\(^{TM} 1.0\%: \text{n}=57\)
- Mean change: \(-1.52\)
- \(P<0.0001^a\)

\(^a\) Nominal \(P\) value.

Treatment-emergent adverse events (3% more than on placebo) through Week 8

<table>
<thead>
<tr>
<th>Adverse Reaction, n (%)</th>
<th>Placebo n=151 (%)</th>
<th>Varithena™ 1.0% n=149 (%)</th>
</tr>
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<tbody>
<tr>
<td>Pain in extremity</td>
<td>14 (9.3)</td>
<td>25 (16.8)</td>
</tr>
<tr>
<td>Infusion site thrombosis(^a)</td>
<td>0</td>
<td>24 (16.1)</td>
</tr>
<tr>
<td>Contusion/injection site hematoma</td>
<td>9 (6.0)</td>
<td>23 (15.4)</td>
</tr>
<tr>
<td>Limb discomfort</td>
<td>5 (3.3)</td>
<td>18 (12.1)</td>
</tr>
<tr>
<td>Tenderness/injection site pain</td>
<td>5 (3.3)</td>
<td>16 (10.7)</td>
</tr>
<tr>
<td>Venous thrombosis limb(^b)</td>
<td>0</td>
<td>12 (8.1)</td>
</tr>
<tr>
<td>Thrombophlebitis superficial</td>
<td>2 (1.3)</td>
<td>8 (5.4)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>7 (4.7)</td>
</tr>
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</table>

- 80% of pain events in the treated extremity resolved within 1 week.

\(^a\) Retained coagulum.

\(^b\) Common femoral vein thrombus extension (non-occlusive thrombi starting in the superficial vein and extending into the common femoral vein).

Microfoam Studies

- Correlation with change in VVSymQ™ (Pearson CC)
  - Duplex response $r = 0.26$
  - VCSS $r = 0.33$
  - VEINES-QOL $r = -0.72$

- Measure different aspects of the same disease
pre

VV SymQ - 12.9
VEINES-QoL – 47.4
CEAP - 3
VCSS - 11

8 weeks post op

VV SymQ – 0.1
VEINES-QoL – 87.4
CEAP - 2
VCSS - 3
8 weeks post op

- VV SymQ – 1.6 (week 4)
- VEINES-QoL – 90.5
- CEAP – 2
- VCSS – 2

pre

- VV SymQ – 2.7
- VEINES-QoL – 65.3
- CEAP – 3
- VCSS – 5
Pre:

- VV SymQ: 6.9
- VEINES-QoL: 63.2
- CEAP: 4
- VCSS: 7

8 weeks post op:

- VV SymQ: 0.1
- VEINES-QoL: 89.5
- CEAP: 4
- VCCS: 2
Conclusions NTNT

- Saphenous Vein Ablation in appropriate patients with saphenous reflux improves VCSS and PRO scores!
- Non-Thermal Not-Tumescent methods appear safe with similar adverse event profile
- NTNT occlusion rates comparable to ETA
Conclusions NTNT

- NTNT outcomes seem **durable pending** longer follow-up
- **Pain score** improved for MOCA, same for CAC, unknown yet for PEM
Personal Conclusions

- NTNT provide more tools for complexity
- NTNT perhaps best with average to small size saphenous veins
- Useful for below-knee GSV, tortuous SV, neovascularization, recurrence, ulcers
- More studies coming for perforators, ulcers!
Questions:

- True or False?
  1. NTNT ablation compared to ETA is performed with significantly less pain and complications.

  2. Combined, common clinical outcomes measures such as VCSS and PRO allow better comparison of new technology than Duplex result alone.
If you can’t explain it **simply**, you don’t understand it well enough.

– Albert Einstein
New Treatment Modalities for the Superficial Venous System: *Data Non-Thermal, Non-tumescent Technologies*

Michael A. Vasquez  MD, FACS, RVT
The Venous Institute of Buffalo
SUNY at Buffalo Department of Surgery
New Cardiovascular Horizons
June 4th, 2016