VenaSeal Clinical Overview
 Highlights from Feasibility First in Man, eSCOPE and VeClose Clinical Studies

Thomas M. Proebstle

University Medical Center Mainz, Germany
Privatklinik Proebstle, Mannheim, Germany
Disclosure

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

X I do not have any potential conflict of interest
Objective

Introduction of a novel technique for occlusion of Refluxing GSVs based on Cyanoacrylate Adhesive

Requiring
- no tumescent anesthesia
- no routine postinterventional compression
- Causing no postprocedural paresthesia
Methods
Clinical Studies with VenaSeal™ System

Feasibility Study
- 38 Patients, enrollment completed Aug. 2011
- 1, 3, 6, 12, 24 and 36 month follow-ups
- Primary endpoint: Safety: rate of serious adverse events, Efficacy: vein closure during follow-up

eSCOPE (European multicenter study)
- 70 patients, enrollment completed Sept. 2012
- 2 day, 1, 3, 6, 12, 24 and 36 month follow-ups
- Primary endpoint: closure w/o use of sedation, tumescent anesthesia or compression stockings

VeClose (U.S. pivotal trial)
- 242 patients, enrollment completed Sept. 2013
- 3 day, 1, 3, 6, 12 months & 2, 3 year follow-ups
- Primary endpoint: non-inferior to RFA in GSV closure
- Secondary endpoint: superiority in reduction of post procedural pain and bruising
Three-Year Follow-Up of First Human Use of Cyanoacrylate Adhesive for Treatment of Saphenous Vein Incompetence

Jose Almeida, MD,
Miami Vein Center Miami, USA
Principal Investigator

Investigators
Ed Mackay, Julien Javier, Thomas Proebstle
CA First in Man Study

Mean length of ablated GSV segments was 33cm [range 15-52]

Average treatment duration was 20.3 minutes [range 11 – 33]

The mean volume of CA delivered was a total of 1.3 ml [range 0.63 - 2.25]
CA First in Man Study – Vein Occlusion
CA First in Man Study – VCSS

![Graph showing Total VCSS (mean ± SE) over time since treatment in months.](image-url)
VCSS Subscores – Freedom from Pain, Edema and Varicose Veins
Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence

Jose I Almeida¹, Julian J Javier², Edward G Mackay³, Claudia Bautista⁴, Daniel J Cher⁵ and Thomas M Proebstle⁶

Abstract
Objectives: To evaluate the safety and effectiveness of endovenous cyanoacrylate-based embolization of incompetent great saphenous veins.
Methods: Incompetent great saphenous veins in 38 patients were embolized by cyanoacrylate bolus injections under ultrasound guidance without the use of perivenous tumescent anesthesia or graduated compression stockings. Follow-up was performed over a period of 24 months.
Result: Of 38 enrolled patients, 36 were available at 12 months and 24 were available at 24 months follow-up. Complete occlusion of the treated great saphenous vein was confirmed by duplex ultrasound in all patients except for one complete and two partial recanalizations observed at 1, 3 and 6 months of follow-up, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92.0% (95% CI 0.836–1.0) at 24 months follow-up. Venous Clinical Severity Score improved in all patients from a mean of 6.1 ± 2.7 at baseline to 1.3 ± 1.1, 1.5 ± 1.4 and 2.7 ± 2.5 at 6, 12 and 24 months, respectively (p < .0001). Edema improved in 89% of legs (n = 34) at 48 hours follow-up. At baseline, only 13% were free from pain. At 6, 12 and 24 months, 84%, 78% and 64% were free from leg pain, respectively.
Conclusions: The first human use of endovenous cyanoacrylate for closure of insufficient great saphenous veins proved to be feasible, safe and effective. Clinical efficacy was maintained over a period of 24 months.
The 36 months update of the European Multicenter Study on Cyanoacrylate Embolization of Refluxing Great Saphenous Veins

Principal Investigators:
Thomas M. Proebstle and Alun Davies
Adjunctive Procedures Performed (Phlebectomy and Sclerotherapy)

<table>
<thead>
<tr>
<th>Procedure Performed</th>
<th>Number of Subjects</th>
<th>Number of Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-72 hours</td>
<td>0/70 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Day 30</td>
<td>0/70 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Month 3</td>
<td>2/70 (2.9%)</td>
<td>2</td>
</tr>
<tr>
<td>Month 6</td>
<td>23/70 (32.9%)</td>
<td>28</td>
</tr>
<tr>
<td>Month 12</td>
<td>13/68 (19.1%)</td>
<td>16</td>
</tr>
<tr>
<td>Month 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td></td>
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</tbody>
</table>

Notes: Includes procedures on either limb. Data Source: eSCOPE Table 20.1 (April 24, 2014)

Protocol did not allow adjunctive procedures until after Month 3 visit.
Figure 1 Kaplan Meier Curve for Freedom from Recanalization

36m: 88.5% (95%CI 78.3 - 94.1)
Figure 2 VCSS Score

[Box plot showing VCSS scores at different time points: Baseline, 30-Day, Month 3, Month 6, Month 12, Month 24, Month 36.]

Vertical axis: VCSS Total
Horizontal axis: Visit (Baseline, 30-Day, Month 3, Month 6, Month 12, Month 24, Month 36)
VenaSeal™ Closure System vs. Radiofrequency Ablation for incompetent Great Saphenous Veins

VeClose Study 24-Month Results

Principal Investigator:
Nick Morrison, Phoenix, AZ, USA
# Veclose Study Overview

<table>
<thead>
<tr>
<th>Title</th>
<th>VenaSeal™ Closure System vs. Radiofrequency Ablation for Incompetent Great Saphenous Veins</th>
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<tbody>
<tr>
<td>Purpose</td>
<td>Demonstrate the safety and effectiveness of the VenaSeal™ closure system for the treatment of lower extremity truncal reflux compared to RFA (ClosureFAST™ system).</td>
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<tr>
<td>Study Design</td>
<td><strong>US multi-center, randomized controlled IDE study.</strong> The study takes a non-inferiority approach to effectiveness for anatomical closure at 3 months. 24 months effectiveness assessed and compared across groups.</td>
</tr>
<tr>
<td>Enrollment / Sites</td>
<td>242 (20 roll-in and 222 randomized) subjects enrolled at 10 study sites (Sep 2013).</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Follow-up visits at 3 days post-procedure, 1, 3, 6, 12, 24 and 36 months.</td>
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</tbody>
</table>

### Primary endpoint

**COMPLETE CLOSURE**

94.3% closure rates, demonstrating continued non-inferiority to RFA (P=0.0075) thru 24 months

<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><strong>Month 24</strong></td>
<td><strong>94.3% (87)</strong></td>
<td><strong>94% (84)</strong></td>
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Proportion of Closure was based on complete case analysis.

Kolluri, R. VeClose 24 Month Results, Charing Cross, April 26, 2016
24-month: venous clinical severity score (vcss)

VCSS demonstrated statistically significant improvement out to Month 6 and sustained through 12M and 24M time points.

Kolluri, R. VeClose 24 Month Results, Charing Cross, April 26, 2016
AVVQ: a 13-question survey addressing physical symptoms, pain, ankle edema, ulcers, compression therapy use, and limitations on daily activities are examined, as well as the cosmetic effect of varicose veins and social issues.

Kolluri, R. VeClose 24 Month Results, Charing Cross, April 26, 2016
Conclusion

endovenous embolization of saphenous veins with cyanoacrylate glue is ready for routine use

- no anesthesia
- compression stockings optional
- without compression no risk of paresthesia
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