The European Sapheon™ Closure System
Observational ProspectivE (eSCOPE) Study –
clinical results and side effects of Venaseal

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Disclosure

Speaker name:
Thomas Proebstle

I have the following potential conflicts of interest to report:

☐ X Consulting, Speaker Bureau
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☐ 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
- no postprocedural paresthesia
Compression is applied with the practitioner’s free hand simultaneously with the compression being held with the transducer for a full 3 minutes.
Methods
clinical picture 1 day after treatment of right GSV
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
CA First in Man Study

Mean length of ablated GSV segments was 33 cm [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

2 complete / 4 partial recanalizations
CA First in Man Study – VCSS
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 anestheisa 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.
CLINICAL RESEARCH STUDIES

From the American Venous Forum

The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins

Thomas Michael Proebstle, MD, Jens Alm, MD, Sameh Dimitri, MD, Lars Rasmussen, MD, Mark Whiteley, MS, FRCS (Gen), James Lawson, MD, Daniel Cher, MD, and Alun Davies, MA, DM, FRCS, FEBVS, Mainz and Hamburg, Germany; Chertsey, Guildford, and London, United Kingdom; Naestved, Denmark; Alkmaar, The Netherlands; and Palo Alto, Calif

Objective: Cyanoacrylate (CA) embolization of refluxing great saphenous veins (GSVs) has been previously described. The outcomes from a multicenter study are still lacking.

Methods: A prospective multicenter study was conducted at seven centers in four European countries to abolish the reflux by endovenous CA embolization. No local anesthetic or post-treatment compression stockings were used. Varicose tributaries remained untreated until at least 3 months after the index treatment. Clinical examination, quality of life assessment, duplex ultrasound evaluation, and venous clinical severity score were performed at 2, 4, 6, and after 1, 3, 6, and 12 months.

Results: In 70 patients (79.7%) were available for 12-month follow-up, 70 GSVs were treated. Two-day follow-up showed one proximal and one distal partial recanalization. Three additional proximal recanalizations were observed at 3-month (n = 2) and 6-month (n = 1) follow-up. Cumulative 12-month survival free from recanalization was 92.9% (95% confidence interval, 87.0%-99.1%). Mean (standard deviation) venous clinical severity score improved from 4.3 ± 2.3 at baseline to 1.1 ± 1.3 at 12 months. Aberdeen Varicose Vein Questionnaire score showed an improvement from 16.3 at baseline to 6.7 at 12 months (P < .0001). Side effects were generally mild; a phlebitic reaction occurred in eight cases (11.4%) with a median duration of 6.5 days (range, 2-12 days). Pain without a phlebitic reaction was observed in five patients (8.6%) for a median duration of 1 day (range, 0-12 days). No serious adverse event occurred. Paresthesia was not observed.

Conclusions: Endovenous CA embolization of refluxing GSVs is safe and effective without the use of tumescent anesthesia or compression stockings. (J Vasc Surg: Venous and Lym Dis 2015;3:2-7.)
Doctors like glue reference the glue studies.

San Diego, June 3rd 2017:

Most Highly Cited Paper Award of the Soc Vasc Surg / JVS for One Year

Results of the European Multicenter Cohort Study on Cyanoacrylate Embolization of Refluxing Great Saphenous Veins.


June 3, 2017
Doctors like Glue reference the glue studies in San Diego, June 3rd 2017.

Most Highly Cited Paper Award of the Society for Vascular Surgery (SVS)/Journal of Vascular Surgery (JVS) for One Year.

Results of the European Multicenter Cohort Study.
eSCOPE Freedom from Recanalization

36m: 88.5% (95%CI 78.3 - 94.1)
eSCOPE Time Course of VCSS
_VenaSeal™ Closure_ System vs. Radiofrequency Ablation for incompetent Great Saphenous Veins

VeClose Study 36-Month Results

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

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

## Primary endpoint
**COMPLETE CLOSURE**

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>VenaSeal (N=108)</th>
<th>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>95.3% (86)</td>
<td>94% (84)</td>
</tr>
<tr>
<td>Month 36</td>
<td>94.4% (72)</td>
<td>91.9% (74)</td>
</tr>
</tbody>
</table>

94.4% closure rate, demonstrating long term durability at 36 months; and continued non-inferiority results to RFA (P=0.005) through 36 months.

Morrison, N. *VenaSeal Closure System vs. Radiofrequency Ablation for Incompetent Great Saphenous Veins (VeClose).* 36 Month Results presented at: IVC; April 20, 2017; Miami, Fl.
36 Month - Venous Clinical Severity Score (VCSS)

VCSS: an evaluative instrument that is responsive to changes in disease severity over time and in response to treatment.

Follow-up Months

VCSS, Mean (SE)

36 Month Results

VS 1.25 ± 1.60
RFA 1.69 ± 2.42
p-value = 0.5643*

Treatment
VenaSeal
RFA

Morrison, N. VenaSeal Closure System vs. Radiofrequency Ablation for Incompetent Great Saphenous Veins (VeClose). 36 Month Results presented at: IVC; April 20, 2017; Miami, FL

VeClose 36 Month Results | IVC.April 2017 | DC00066465
endovenous embolization of saphenous veins with cyanoacrylate glue is ready to provide excellent routine results

- no anesthesia
- compression stockings optional
- without compression no risk of paresthesia
Adverse Events with Glue after 3 months

VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins

Nick Morrison, MD, Kathleen Gibson, MD, Michael Vasquez, MD, Robert Weiss, MD, Daniel Cher, MD, Monte Madsen, RVT, RPhS, and Andrew Jones, MD. Scottsdale, Ariz. Bellevue, Wash. Buffalo, NY. Hunt Valley, Md. Palo Alto and Santa Rosa, Calif. and Bend, Ore

ABSTRACT

Objective: Endovenous cyanoacrylate closure (CAC) is a new U.S. Food and Drug Administration-approved therapy for treatment of clinically symptomatic venous reflux in saphenous veins. The device is indicated for the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV). Early results from a randomized trial of CAC have been reported previously. Herein we report 1-year outcomes.

Methods: There were 222 subjects with symptomatic GSV incompetence randomly assigned to receive either CAC (n = 108) or radiofrequency ablation (RFA; n = 114). After the month 3 visit, subjects could receive adjunctive therapies aimed at treating visible varicosities and incompetent tributaries. Vein closure was assessed at day 3 and months 1, 3, 6, and 12 using duplex ultrasound. Additional study visit assessments included the Venous Clinical Severity Score; Clinical, Etiology, Anatomy, and Pathophysiology classification; EuroQol-5 Dimension; and Aberdeen Varicose Vein Questionnaire. Both time to closure and time to first reopening of the target vein were evaluated using survival curve analysis. Adverse events were evaluated at each visit.

Results: Of 222 enrolled and randomized subjects, a 12-month follow-up was obtained for 192 (95 CAC and 97 RFA; total follow-up rate, 192/222 [86.5%]). By month 1, 100% of CAC subjects and 87% of RFA subjects demonstrated complete occlusion of the target vein. By month 12, the complete occlusion rate was nearly identical in both groups (97.2% in the CAC group and 97.0% in the RFA group). Twelve-month freedom from recanalization was similar in the CAC and RFA groups, although there was a trend toward greater freedom from recanalization in the CAC group (P = .08). Symptoms and quality of life improved equally in both groups. Most adverse events were mild to moderate and not related to the device or procedure.

Conclusions: In patients with incompetent CSVs, treatment with both CAC and RFA results in high occlusion rates. Time to complete occlusion was faster with CAC, and freedom from reopening was higher after CAC. Quality of life scores improved equally with both therapies. (J Vasc Surg: Venous and Lym Dis 2017;5:321-30.)
## Adverse Events with Glue up to 6 months

<table>
<thead>
<tr>
<th></th>
<th>VSCS (N=108)</th>
<th>RFA (N=114)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Subjects with events (%)</strong></td>
<td>34 (31%)</td>
<td>29 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Reported AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis, any zone</td>
<td>22 (20.4%)</td>
<td>16 (14.0%)</td>
<td>0.3571</td>
</tr>
<tr>
<td>Phlebitis in treatment zone</td>
<td>11 (10.2%)</td>
<td>10 (8.8%)</td>
<td>0.8199</td>
</tr>
<tr>
<td>Phlebitis not in treatment zone</td>
<td>8 (7.4%)</td>
<td>4 (3.5%)</td>
<td>0.2430</td>
</tr>
<tr>
<td>Phlebitis in both</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia in treatment zone</td>
<td>3 (2.8%)</td>
<td>3 (2.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stocking irritation</td>
<td>2 (1.9%)</td>
<td>3 (2.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Access site infection</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>4 (3.7%)</td>
<td>3 (2.6%)</td>
<td>0.7157</td>
</tr>
<tr>
<td>Access site burn</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia not in treatment zone</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia in treatment zone</td>
<td>3 (2.8%)</td>
<td>3 (2.6%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Table II. Adverse events between 3 and 12 months in the VeClose trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse event description</th>
<th>Related to device</th>
<th>Related to procedure</th>
<th>Severity</th>
<th>Days to adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC</td>
<td>Stomach pains</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>113</td>
</tr>
<tr>
<td>CAC</td>
<td>Pain after sclerotherapy</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>105</td>
</tr>
<tr>
<td>CAC</td>
<td>Seroma</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>182</td>
</tr>
<tr>
<td>CAC</td>
<td>Low back pain</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>288</td>
</tr>
<tr>
<td>CAC</td>
<td>Foot pain</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>184</td>
</tr>
<tr>
<td>CAC</td>
<td>Sinus pressure</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>288</td>
</tr>
<tr>
<td>CAC</td>
<td>Pregnancy</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>169</td>
</tr>
<tr>
<td>CAC</td>
<td>Patient pregnant</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>209</td>
</tr>
<tr>
<td>CAC</td>
<td>Rash above upper lip</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>163</td>
</tr>
<tr>
<td>CAC</td>
<td>Erythema</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>132</td>
</tr>
<tr>
<td>CAC</td>
<td>Phlebitis</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>105</td>
</tr>
<tr>
<td>CAC</td>
<td>Phlebitis</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>175</td>
</tr>
<tr>
<td>CAC</td>
<td>Symptomatic venous stasis</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>173</td>
</tr>
<tr>
<td>CAC</td>
<td>Thrombosed veins after sclerotherapy</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>176</td>
</tr>
<tr>
<td>CAC</td>
<td>Tenderness over phlebectomy site</td>
<td>Not related</td>
<td>Not related</td>
<td>Moderate</td>
<td>116</td>
</tr>
<tr>
<td>CAC</td>
<td>Pneumonia</td>
<td>Not related</td>
<td>Not related</td>
<td>Moderate</td>
<td>107</td>
</tr>
<tr>
<td>CAC</td>
<td>Tenderness left leg</td>
<td>Not related</td>
<td>Not related</td>
<td>Moderate</td>
<td>168</td>
</tr>
<tr>
<td>CAC</td>
<td>Asthma</td>
<td>Not related</td>
<td>Not related</td>
<td>Moderate</td>
<td>258</td>
</tr>
<tr>
<td>CAC</td>
<td>Small bowel obstruction</td>
<td>Not related</td>
<td>Not related</td>
<td>Severe</td>
<td>286</td>
</tr>
<tr>
<td>CAC</td>
<td>Thyroid cancer</td>
<td>Not related</td>
<td>Not related</td>
<td>Severe</td>
<td>232</td>
</tr>
<tr>
<td>CAC</td>
<td>Pain in right medial thigh</td>
<td>Not related</td>
<td>Not related</td>
<td>Moderate</td>
<td>221</td>
</tr>
<tr>
<td>CAC</td>
<td>Chronic phlebitis</td>
<td>Possibly related</td>
<td>Possibly related</td>
<td>Mild</td>
<td>92</td>
</tr>
<tr>
<td>RFA</td>
<td>DVT nonindex leg</td>
<td>Definitely related</td>
<td>Definitely related</td>
<td>Moderate</td>
<td>172</td>
</tr>
<tr>
<td>RFA</td>
<td>EHT</td>
<td>Definitely related</td>
<td>Definitely related</td>
<td>Moderate</td>
<td>172</td>
</tr>
<tr>
<td>RFA</td>
<td>Abdomen pain</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>175</td>
</tr>
<tr>
<td>RFA</td>
<td>Lower abdomen pain</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>174</td>
</tr>
<tr>
<td>RFA</td>
<td>Lower right-sided back pain</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>269</td>
</tr>
<tr>
<td>RFA</td>
<td>Cervical radicular pain</td>
<td>Not related</td>
<td>Not related</td>
<td>Mild</td>
<td>277</td>
</tr>
</tbody>
</table>
Peripholesitic Reaction after Cyanoacrylate embolization of the GSV
1 – 5% of cases, typically 1–2 wks after Tx
NSAIDs and antihistamines
Challenging Case Inhouse

Generalized Urticaria after Cyanoacrylate embolization of the GSV

male dentist, 55y
occupational use of cyanoacrylate, no allergy known

Day 7: periphlebitic reaction
Day 14: phone consultation:
    generalized itching and erythematous flares
Day 16: clinical and duplex exam
Challenging Case Inhouse
Generalized Urticaria after
Cyanoacrylate embolization of the GSV
Challenging Case Inhouse
Generalized Urticaria after Cyanoacrylate embolization of the GSV
male dentist, 55y
occupational use of cyanoacrylate, no allergy

Day 16: start of prednisolone 80 mg/d once daily
Day 18: ongoing itching over night -> cetirizine
Day 23-30: prednisolone tapered, cetirizine continued
Challenging Case Inhouse
Generalized Urticaria after Cyanoacrylate embolization of the GSV

male dentist, 55y
occupational use of cyanoacrylate, no allergy

23 months after Tx (today):
• urticaria diminished in frequency and extent
• relapses in stress situations
• always responds on cetirizine
Challenging Case – Tx alio loco

Cyanoacrylate protrusion into CFV after embolization of the GSV

female 25y, C2 disease

Referral 2 weeks after procedure alio loco. Partial obliteration of CFV proximal to SFJ

Patient reports:
surgeon claimed himself that he could not display saphenofemoral junction well while positioning catheter and deploying the glue

Surgeon had less than 3 months glue-experience
Challenging Case – Tx alio loco

Cyanoacrylate protrusion into CFV after embolization of the GSV
Challenging Case – Tx alio loco

Cyanoacrylate protrusion into CFV after embolization of the GSV
Challenging Case – Tx alio loco

Cyanoacrylate protrusion into CFV after embolization of the GSV
Conclusion final

endovenous embolization of saphenous veins with cyanoacrylate glue is the current high-end-procedure

however, its safe administration requires expert ultrasound skills