VenaSeal™ Closure System
Product Code: VS-402

Instructions for Use

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Caution: Federal law restricts this device to sale, distribution, and use by or on the order of a physician

1. DESCRIPTION

The VenaSeal™ closure system is a medical device provided as a sterile, single patient kit comprised of the VenaSeal™ adhesive and VenaSeal™ delivery system components. The kit is designed to be used as a system, and its contents are not intended for use as individual components. The VenaSeal™ system is intended to be used by a licensed physician while using high resolution ultrasound imaging. The VenaSeal system is indicated for the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV), through endovascular embolization with coaptation. The VenaSeal system is intended for use in adults with clinically symptomatic venous reflux as diagnosed by duplex ultrasound (DUS).

The VenaSeal™ adhesive, an n-butyl-2-cyanoacrylate (n-BCA) based formulation, is a clear, free-flowing liquid that is provided sterilize following exposure to dry heat. The VenaSeal adhesive polymerizes in the vessel via an anionic mechanism (i.e., VenaSeal adhesive begins to polymerize into a solid material upon contact with body fluids or tissue). This acute coaptation halts blood flow through the insufficient vein until the implanted adhesive becomes fibrotically encapsulated to establish a durable, chronic occlusion of the treated vein. The VenaSeal™ delivery system components facilitate the placement and delivery of VenaSeal adhesive within the target vessel. The VenaSeal delivery system components include a catheter, introducer, dilator, dispenser gun, dispenser tips, 3-cc syringes, and 0.035" J-wire guidewire. The VenaSeal™ system kit is provided sterile by exposure to ethylene oxide (EtO).

Figure 1:
VenaSeal™ Closure System

2. INTENDED USE/INDICATIONS

The VenaSeal™ closure system (VenaSeal™ system) is indicated for use in the permanent closure of lower extremity superficial truncal veins, such as the great saphenous vein (GSV), through endovascular embolization with coaptation. The VenaSeal system is intended for use in adults with clinically symptomatic venous reflux as diagnosed by duplex ultrasound (DUS).

3. CONTRAINDICATIONS

SEPARATE USE OF THE INDIVIDUAL COMPONENTS OF THE VenaSeal™ CLOSURE SYSTEM IS CONTRAINDICATED. THESE COMPONENTS MUST BE USED AS A SYSTEM.

The use of the VenaSeal™ system is contraindicated when any of the following conditions exist:

- previous hypersensitivity reactions to the VenaSeal™ adhesive or cyanoacrylates;
- acute superficial thrombophlebitis;
- thrombophlebitis migrans;
- acute sepsis exists.

Prior to use, read all package insert warnings, precautions and instructions. Failure to do so may result in severe patient injury and/or death.

4. WARNINGS

- The VenaSeal™ system should only be used by a trained physician with experience in diagnosis and treatment of venous reflux disease through endovenous techniques. Physicians require training using the VenaSeal system by the manufacturer prior to performing this procedures independently.
- Due to the risk of exposure to HIV or other blood borne pathogens, health care workers should always use standard blood and body fluid precautions in the care of all patients. Sterile techniques should be strictly adhered to during any handling of the device.
- The VenaSeal system is not designed for use in the coronary and cerebral vasculature, pulmonary vasculature, diseased and atherosclerotic arteries.
- Do not flush the catheter with saline or fluid as this will make it unusable with the VenaSeal™ adhesive.
- Manipulate the catheter ONLY under ultrasound imaging guidance.
- Confirm position of the catheter tip in the desired location by ultrasound imaging before activation of the device.
- Injection of the VenaSeal adhesive should be done by hand injection only and using the VenaSeal™ delivery system provided. Do not use a power injector.
- Do not kink the catheter. Do not use the catheter if kinked.
- Use the introducer in the VenaSeal delivery system for access to the peripheral vasculature. Failure to use the introducer for access may result in damage to the vessel, or failure of the VenaSeal system to perform as intended.

5. PRECAUTIONS

- The safety and effectiveness of the VenaSeal™ system in pregnant women and in pediatric patients have not been established.
- The VenaSeal system is sterile unless the package is opened or damaged. The package should be examined prior to use. If the package is damaged DO NOT USE.
- The VenaSeal system is intended for single patient use only. DO NOT REUSE or RE-STERILIZE.
- Prior to use, carefully examine the VenaSeal system components and verify they, and their packaging, have not been damaged during shipment. If the components show any sign of damage DO NOT USE.
- Do not use after the expiration date.
- Verify that the VenaSeal™ adhesive is a clear and free-flowing liquid prior to use. Material that is discolored should be discarded.
- The VenaSeal adhesive will adhere to most surfaces. Avoid contact with non-disposable surfaces.
- Gloves and eye/face protection are recommended when handling the VenaSeal adhesive.
- The VenaSeal adhesive is intended to be delivered via the VenaSeal™ delivery system components only.

6. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the VenaSeal™ system. The adverse events associated with the device are similar to those with traditional endovenous thermal ablation procedures. In addition, there are several risks unique to the VenaSeal system due to its material and product design as an implant. These potential adverse events include, but are not limited to, the following:

- Allergic reactions to cyanoacrylates, such as hives, asthma, hay fever and anaphylactic shock
- Arteriovenous fistula
- Bleeding from the site of access
- Deep vein thrombosis (DVT)
- Edema in the treated leg
- Embolization, including pulmonary embolism (PE)
- Hematoma
- Hyperpigmentation
- Infection at the access site
- Non-specific mild inflammation of the cutaneous and subcutaneous tissue
- Pain
- Paresthesia
- Phlebitis
- Superficial thrombophlebitis
- Urticaria or ulceration may occur at the site of injection
- Vascular rupture and perforation
- Visible scarring

7. SUMMARY OF CLINICAL STUDIES

The clinical evidence supporting the safety and effectiveness of the VenaSeal™ closure system is derived from a combination of three clinical studies, as outlined in **Table 1**. The pivotal clinical study, VeClose Study, was used to establish a reasonable assurance of safety and effectiveness of treating symptomatic superficial truncal veins with the VenaSeal™ system for permanent closure by embolization with coaptation of the vein walls in the United States under IDE G120204. Data from this clinical study were the basis for the PMA approval decision.

Table 1: Summary of VenaSeal™ Closure System Clinical Studies

Study	Title	Objective
VeClose Pivotal	VenaSeal™ Sapheon Closure System vs. Radiofrequency Ablation for Incompetent Greater Saphenous Veins (VeClose)	To demonstrate safety and effectiveness of the VenaSeal™ system for the treatment of lower extremity truncal reflux compared to radiofrequency ablation (RFA) performed using the Covidien ClosureFast™ system.
eSCOPE	European Sapheon Closure System Observational Prospective (eSCOPE) Study	To assess the role of the Sapheon Closure System in closure of incompetent great saphenous veins in a routine clinical setting
Feasibility	Sapheon™ Closure System First-In-Man Study	Assess safety and effectiveness in a first in man setting

8. PRIMARY CLINICAL STUDY (VECLOSE)

Study Design:

Patients were treated between March 11, 2013 and September 11, 2013. The database for this PMA P140018 reflected data collected through October 8, 2014 and included 242 patients. There were 10 investigational sites.

The VeClose pivotal study was a controlled, randomized, prospective, multicenter, pivotal study in which patients with venous reflux in the great saphenous vein (GSV) were treated with either VenaSeal™ or radiofrequency ablation (RFA) therapy. Prior to initiation of the randomized cohort at each site, a non-randomized training cohort of 2 subjects per clinical site (roll-in phase) was enrolled and treated with the VenaSeal system. Subjects were then randomized at each site, 1:1, as stratified by random blocks sizes of 4 and 6. Following treatment, subjects were followed at 3 days, and 1, 3, 6, 12, 24 and 36 months. No adjunctive treatments were permitted until after the 3 month follow up visit

Safety was assessed by monitoring procedure-specific and systemic adverse events. A combined Data Safety Monitoring Board (DSMB)/Clinical Events Committee (CEC) was

established to oversee the study, increase the reliability of the data, and adjudicate the study's safety reported events.

The primary effectiveness endpoint was the proportion of subjects at 3 months with complete closure of the target GSV as determined by duplex ultrasound and assessed by the independent vascular ultrasound core laboratory (Vascular Ultrasound Core Lab (VasCore), Massachusetts General Physicians Organization, Inc. (Boston, MA)).

Up to 244 subjects (including 2 roll-in subjects per clinical site (up to 12 clinical sites) and 220 randomized) with symptomatic venous reflux in the GSV were planned to be enrolled. The sample size of 110 subjects per group in the randomized arm was calculated assuming underlying success rates of 95% in each group, a 10% non-inferiority delta, a one-sided alpha of 0.025 and 10% loss to follow-up in each group. The 95% success rate was based on the complete occlusion rate in the feasibility study as well as individual randomized controlled trials reporting RFA efficacy rates of 97% at 3 months,[1] and 100% and 95.2% at 1 month and one year respectively[2]. Adding 2 roll-in subjects per each site (12 sites) the final sample size was 244 subjects. All subjects were followed for a minimum of 12 months following treatment with extended follow up at 24 and 36 months.

The primary objective of this study was to demonstrate safety and effectiveness of the VenaSeal™ system for the treatment of lower extremity truncal reflux compared to RFA therapy using a legally marketed device with similar indications for use.[3] The two secondary endpoints, intraoperative pain and ecchymosis at Day 3, were analyzed to demonstrate standard statistical superiority of the VenaSeal™ system over RFA. The Holm stepdown method was used adjust for multiplicity in secondary endpoint analysis.

- Intraoperative pain experienced during the procedure (from after vein access through the end of the procedure) was rated on a 0-10 numerical rating scale (NRS) and compared across groups using a two-tailed student's t test.
- Ecchymosis, rated by the physician on a 0-5 scale at the Day 3 visit, was compared across groups using a two-tailed Wilcoxon test.

Preoperatively, the patient's medical history was collected, as well as demographic data and current medications. A physical examination, including assessment of ecchymosis on the target limb, Clinical Etiology Anatomy Pathophysiology (CEAP; Classification of Venous Disorders) status and Venous Clinical Severity Score (VCSS) were performed. A pregnancy test was performed on women of child-bearing potential prior to treatment. The subject was asked to complete the Aberdeen Varicose Vein Questionnaire (AVVQ)

[1] Nordon IM, Hinchiffe RJ, Brar R, et al. A prospective double-blind randomized controlled trial of radiofrequency versus laser treatment of the great saphenous vein in patients with varicose veins. Ann Surg. 2011;254(6):876-81.
[2] Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg*. 2011;98(8):1079-87.
[3] The ClosureFAST™ Radiofrequency Catheter (Covidien) is intended for endovascular coagulation of blood vessels in patients with superficial vein reflux (K111887).

and EuroQol Quality of Life Questionnaire (EQ-5D) quality of life instruments. Duplex ultrasound of the target limb was conducted by the qualified vascular or ultrasound technologist. Intraoperatively, the secondary endpoint of intraoperative pain experienced during the procedure (from after vein access through the end of the procedure) was rated on a 0-10 NRS by the subject. Postoperatively, the objective parameters measured during the study included:

- Target GSV closure assessed by duplex ultrasound at all postoperative follow-up visits
- Procedure related pain at Day 3
- Extent of ecchymosis of the skin over the treated segment at Day 3
- CEAP at all postoperative follow-up visits starting at Month 3
- VCSS at all postoperative follow-up visits starting at Day 3
- AVVQ and EQ-5D at all postoperative follow-up visits starting at Month 1
- Subject satisfaction questionnaire at Day 0 and Months 3, 6, 12, 24 and 36
- Adverse events and complications were recorded at all visits

a. Clinical Inclusion and Exclusion Criteria

Enrollment in the VeClose study was limited to patients who met the following inclusion criteria:

1. Age ≥21 years and ≤ 70 years of age at the time of screening
2. Reflux in the great saphenous vein (GSV) greater than 0.5 sec reflux
3. One or more of the following symptoms related to the target vein: aching, throbbing, heaviness, fatigue, pruritus, night cramps, restlessness, generalized pain or discomfort, swelling
4. GSV diameter while standing of 3-12 mm throughout the target vein as measured by Duplex ultrasound
5. Clinical Etiology Anatomy Pathophysiology (CEAP; Classification of Venous Disorders) classification C2 (if symptomatic) – C4b
6. Ability to walk unassisted
7. Ability to attend follow-up visits
8. Ability to understand the requirements of the study and to provide informed consent

Patients were not permitted to enroll in the VeClose study if they met any of the following exclusion criteria:

1. Life expectancy < 1 year
2. Active treatment for malignancy other than non-melanoma skin cancer
3. Symptomatic peripheral arterial disease with ankle brachial index (ABI) <0.89
4. Daily use of narcotic or non-steroidal anti-inflammatory pain medications to control pain associated with GSV reflux
5. Current, regular use of systemic anticoagulation (e.g., warfarin, heparin)

6. Previous or suspected deep vein thrombosis (DVT) or pulmonary embolus (PE)
7. Previous superficial thrombophlebitis in GSV
8. Previous treatment of venous disease in target limb, other than spider vein treatment
9. Known hypercoagulable disorder
10. Conditions which prevent vein treatment with either RFA or VenaSeal
11. Immobilization or inability to ambulate
12. Pregnant prior to enrollment
13. Tortuous GSV, which, in the opinion of the investigator, will limit catheter placement or require more than one primary access site
14. Aneurysm of the target vein with local vein diameter >12 mm
15. Significant, incompetent, ipsilateral small saphenous, intersaphenous or anterior accessory great saphenous vein(s)
16. Known sensitivity to cyanoacrylate (CA) adhesives
17. Current participation in another clinical study involving an investigational agent or treatment, or within the 30 days prior to enrollment
18. Patients who require bilateral treatment during the next 3 months
19. Patients who require additional ipsilateral treatments on the same leg within 3 months following treatment

Study Population Demographics and Baseline Parameters

A total of 242 subjects were enrolled into the study from 10 U.S. based centers, including 20 roll-in VenaSeal™-treated subjects, 108 randomized VenaSeal-treated subjects, and 114 randomized RFA-treated subjects. The demographics and baseline parameters of the study population are typical for a varicose vein study performed in the US (see **Tables 2-5**). Overall mean age was 50 years (range 25 – 70) and consistent with the known female predominance of venous disease, with primarily female subjects (80%). The majority of subjects (56.6%) entered the study with venous disease in the study limb classified as C2. There were slightly more subjects with the left leg treated (53%). Aching and pain were the two most frequently reported dominant symptoms, with over 25% of subjects reporting these symptoms. The pre-procedure mean vein diameters as assessed by ultrasound at both the proximal and mid-thigh GSV were similar between VenaSeal™ and RFA, with almost 80% of all subjects with a GSV proximal diameter of < 8 mm and over 90% of subjects with a GSV mid-thigh diameter of < 8 mm. There were no statistically significant differences in the demographics or baseline parameters between the randomized groups (VenaSeal and RFA) or the VenaSeal™ groups (randomized and roll-in).

Table 2 Demographics (Intent-to-Treat (ITT) Population)

	Roll-in Phase	Randomized Phase		
Parameter	**VenaSeal™ (n=20)**	**VenaSeal (n=108)**	**RFA (n=114)**	**All (n=242)**
Gender				
Female	17 (85%)	83 (77%)	93 (82%)	193 (80%)
Male	3 (15%)	25 (23%)	21 (18%)	49 (20%)
p-value – VenaSeal™ groups	0.6064			
p-value - Randomized	0.4821			
Age (years)				
Mean (SD)	53.1 (9.2)	49.0 (11.8)	50.5 (10.5)	50.1 (11.0)
Median (range)	55.1 (36 - 65)	50.3 (26 – 70)	51.8 (25 – 70)	51.2 (25 -70)
p-value – VenaSeal groups	0.0927			
p-value - Randomized	0.3390			
Body Mass Index				
Mean (SD)	27.9 (5.1)	27.0 (5.1)	27.0 (5.7)	27.1 (5.4)
Median (range)	27.2 (17.8 -37.8)	26.7 (17.4 – 44.5)	27.0 (17.0 – 46.7)	26.7 (17.0 -46.7)
p-value – VenaSeal groups	0.4860			
p-value - Randomized	0.9499			
Ethnicity				
Hispanic	0 (0%)	4 (4%)	8 (7%)	12 (5%)
Not Hispanic	20 (100%)	104 (96%)	106 (93%)	230 (95%)
p-value – VenaSeal groups	0.8612			
p-value - Randomized	0.4269			
Race				
White	19 (95.0%)	102 (94.4%)	106 (93.0%)	227 (93.8%)
Black / African American	1 (5.0%)	1 (0.9%)	4 (3.5%)	6 (2.5%)
Asian	0 (0%)	2 (1.9%)	0 (0%)	2 (0.8%)
American Indian / Alaska Native	0 (0%)	0 (0%)	1 (0.9%)	1 (0.4%)
Other	0 (0%)	3 (2.8%)	3 (2.6%)	6 (2.5%)
p-value – VenaSeal groups	0.4370			
p-value - Randomized	0.3175			

Notes: Percentages are based on the number of subjects per column. P-value for VenaSeal groups compared the VenaSeal™ roll-in and VenaSeal™ randomized subjects.

Table 3 Baseline Clinical CEAP Status of Study Limb (ITT Population)

	Roll-in Phase	Randomized Phase		
Clinical Classification	**VenaSeal™ (n=20)**	**VenaSeal (n=108)**	**RFA (n=114)**	**All (n=242)**
C2	12 (60.0%)	61 (56.5%)	64 (56.1%)	137 (56.6%)
C3	7 (35.0%)	32 (29.6%)	36 (31.6%)	75 (31.0%)
C4a	1 (5.0%)	13 (12.0%)	12 (10.5%)	26 (10.7%)
C4b	0 (0%)	2 (1.9%)	2 (1.8%)	4 (1.7%)
p-value– VenaSeal™ groups	0.5785			
p-value - Randomized	0.9560			

Table 4 Treatment Limb Characteristics (ITT Population)

	Roll-in Phase	Randomized Phase		
Parameter	**VenaSeal™ (n=20)**	**VenaSeal (n=108)**	**RFA (n=114)**	**All (n=242)**
Target leg				
Right	11 (55%)	47 (44%)	56 (49%)	114 (47%)
Left	9 (45%)	61 (56%)	58 (51%)	128 (53%)
p-value– VenaSeal™ groups	0.4821			
p-value - Randomized	0.4825			
Dominant symptom				
Pain	6 (30.0%)	33 (30.6%)	24 (21.1%)	63 (26.0%)
Aching	7 (35.0%)	32 (29.6%)	39 (34.2%)	78 (32.2%)
Itching	0 (0%)	2 (1.9%)	5 (4.4%)	7 (2.9%)
Burning	0 (0%)	5 (4.6%)	3 (2.6%)	8 (3.3%)
Sensitivity	1 (5.0%)	1 (0.9%)	2 (1.8%)	4 (1.7%)
Heaviness	2 (10.0%)	14 (13.0%)	16 (14.0%)	32 (13.2%)
Swelling	2 (10.0%)	17 (15.7%)	18 (15.8%)	37 (15.3%)
Other	2 (10.0%)	4 (3.7%)	7 (6.1%)	13 (5.4%)
p-value– VenaSeal groups	0.6391			
p-value - Randomized	0.6536			

Table 5 Pre-Procedure Ultrasound Measurements (ITT population)

	Roll-In Phase	Randomized Phase		
	VenaSeal™ (n=20)	**VenaSeal (n=108)**	**RFA (n=114)**	**All (n=242)**
Proximal Vein Diameter	**20**	**108**	**113**	**241**
Mean (SD) (mm)	6.9 (1.6)	6.3 (2.1)	6.6 (2.1)	6.5 (2.1)
< 8 mm	14 (70.0%)	89 (82.4%)	88 (77.2%)	191 (78.9%)
≥ 8 mm	6 (30.0%)	19 (17.6%)	25 (21.9%)	50 (20.7%)
Not Done	0 (0%)	0 (0%)	1 (0.9%)	1 (0.4%)
p-value (t-test) – VenaSeal™ groups	0.1499			
p-value (t-test) - Randomized	0.3026			
Mid-Thigh Vein Diameter	**20**	**107**	**110**	**237**
Mean (SD) (mm)	5.3 (1.4)	4.9 (1.5)	5.1 (1.5)	5.0 (1.5)
< 8 mm	19 (95.0%)	104 (96.3%)	104 (91.2%)	227 (93.8%)
≥ 8 mm	1 (5.0%)	3 (2.8%)	6 (5.3%)	10 (4.12%)
Not Done	0 (0%)	1 (0.9%)	4 (3.5%)	5 (2.1%)
p-value (t-test) – VenaSeal groups	0.2193			
p-value (t-test) - Randomized	0.2759			

Procedural Data

The duration of the procedure, from accessing the leg through withdrawal of the catheter, and including administration of the tumescent anesthesia for the RFA subjects, averaged 24 minutes for VenaSeal™ system and 19 minutes for RFA. The mean difference in procedure duration was 5.4 minutes and this difference was statistically significant, $p<0.0001$. The vein access site (above knee, below knee, at knee) distribution was similar between VenaSeal system and RFA with slightly more VenaSeal system procedures with vein access below the knee compared to RFA (52.8% vs 45.6%, respectively). The mean amount of lidocaine used was lower for the VenaSeal system group vs. the RFA group (1.61 vs. 2.69 cc, $p = 0.0961$). Mean tumescent anesthesia volume was 272 cc in the RFA group. The mean (SD) volume of VenaSeal™ adhesive administered was 1.21 mL (0.41).

Safety and Effectiveness Results

Safety Results

Safety of this study was assessed by the occurrence rate of each of the following clinically related adverse events:

- Deep venous thrombosis (DVT)
- Clinically significant pulmonary embolus (PE)
- Paresthesia
- Skin burn
- Skin ulceration
- Infection/cellulitis

There have been no reports of deep venous thrombosis (DVT) occurring on the study limb or pulmonary embolus (PE) in the study. The incidence of paresthesia occurring in the treatment zone was 2.8% for the VenaSeal™ group and 2.6% for the RFA group. The incidence of skin burns was 0% for the VenaSeal group and 0.9% for the RFA group. The incidence of access site infection was 0.9% for both VenaSeal and RFA groups. The incidence of Adverse Events by Study-Specific Dictionary is presented in **Table 6**.

Table 6 Incidence of Adverse Events* by Study-Specific Dictionary

Coded Term	Roll-in (n=20)	VenaSeal™ (n=108)	RFA (n=114)
Access site burn	0 (0%)	0 (0%)	1 (0.9%)
Access site infection	0 (0%)	1 (0.9%)	1 (0.9%)
Deep vein thrombophlebitis**	0 (0%)	0 (0%)	1 (0.9%)
Paresthesia in the treatment zone	1 (5.0%)	3 (2.8%)	3 (2.6%)
Paresthesia not in treatment zone	0 (0%)	0 (0%)	1 (0.9%)
Pulmonary embolus	0 (0%)	0 (0%)	0 (0%)
Skin ulceration	0 (0%)	0 (0%)	0 (0%)

*Clinically relevant adverse events as pre-defined by the clinical protocol

**Deep vein thrombophlebitis occurred in the non-index leg

A total of 42.2% VenaSeal™-treated subjects (9 roll-in and 45 randomized) and 34.2% RFA-treated subjects (39) reported at least 1 adverse event (AE). A total of 131 events were reported, 75 in VenaSeal-treated subjects (12 roll-in, 63 randomized) and 56 in RFA-treated subjects.

In addition:

- There have been no deaths or unanticipated adverse device effects reported.
- There were 8 subjects (1 roll-in, 3 VenaSeal™ system and 4 RFA) that reported a serious adverse event (SAE) during the study. All SAEs were unrelated to the respective device(s) or procedures as confirmed by the Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC).
- To-date, there have been no reported allergic reactions to the VenaSeal™ adhesive (cyanoacrylate).

Two events occurred more frequently in VenaSeal-treated subjects (roll-in and randomized) compared to RFA-treated subjects: phlebitis (all locations) and superficial thrombophlebitis (**Table 7**). Phlebitis and superficial vein thrombophlebitis are commonly reported side effects in vein treatments, including VenaSeal™ and RFA. These AEs were generally mild in severity and typically required either no treatment or medical treatment, consisting of typical Non-Steroidal Anti-Inflammatory Drugs (NSAID). There were two AEs in the VenaSeal group for superficial vein thrombophlebitis phlebitis not in the treatment zone that underwent a procedure to drain the coagulum.

Table 7 **Phlebitis and Superficial Vein Thrombophlebitis Adverse Events by Study-Specific Dictionary**

Coded Term	Roll-in (n=20)	VenaSeal™ (n=108)	ALL VenaSeal (n=128)	RFA (n=114)
Phlebitis in both treatment and non-treatment zones	0 (0%)	1 (0.9%)	1 (0.8%)	1 (0.9%)
Phlebitis in treatment zone	2 (10.0%)	12 (11.1%)	14 (10.9%)	10 (8.8%)
Phlebitis not in treatment zone	1 (5.0%)	11 (10.2%)	12 (9.4%)	5 (4.4%)
All Phlebitis Events	**3 (15.0%)**	**24 (22.2%)**	**27 (21.1%)**	**16 (14.0%)**
Superficial vein thrombophlebitis	**3 (15.0%)**	**5 (4.6%)**	**8 (6.3%)**	**3 (2.6%)**

Notes: The event rate (# of events divided by # of subjects at risk) is presented.

Primary Effectiveness Results

As of October 8, 2014, 207 subjects have completed the 12-month visit, 15 subjects have not yet completed the 12-month visit and 20 subjects have discontinued from the study.

The primary endpoint of the study was complete closure of the target vein at 3 months after index treatment as judged by the Core Lab. Complete closure was defined as duplex ultrasound showing closure along entire treated target vein segment with no discrete segments of patency exceeding 5 cm. In instances where a Month 3 duplex ultrasound exam was not available (e.g., images missing, unreadable, visit not done), the Month 1 (or Day 3) and/or Month 6 duplex ultrasound images were transmitted and assessed by the Core Lab. The time points prior to Month 3 (i.e., Day 3 or Month 1) were used to impute missing data for the last observation carried forward (LOCF) model of the primary effectiveness endpoint.

The primary endpoint hypothesis test was performed using the ITT. For the ITT cohort, missing values were imputed using the following techniques:

- Last observation carry forward (LOCF)
- Pessimistic, which assumes that all missing data are failures for the primary endpoint
- Optimistic, which assumes that all missing data are successes for the primary endpoint
- Predictive, in which logistic regression based on selected baseline parameters, if predictive of complete occlusion, are used to predict whether the missing value is likely to be a success or failure

Additionally, a complete case (CC) cohort analysis was also performed.

Table 8 presents the results of the primary effectiveness endpoint analyses (performed with SAS) with missing data imputed by the 4 pre-specified models, as well as the CC cohort. All pre-specified models and the CC cohort demonstrated non-inferiority of VenaSeal™ system to RFA.

Table 8 Analyses for Primary Effectiveness Endpoint at Month 3 (ITT Population)

Model	Success Rate VenaSeal™ (n=108)	Success Rate RFA (n=114)	Rate Difference (95% CI)[a]	P-value for Non-inferiority[b]	P-value for Superiority[c]
LOCF	107/108 (99.1%)	109/114 (95.6%)	3.5% (-0.7 – 7.6%)	**<0.0001**	0.0560
Pessimistic	92/108 (85.2%)	93/114 (81.6%)	3.6 (-6.2 – 13.4)	**0.0032**	0.2356
Optimistic	107/108 (99.1%)	109/114 (95.6%)	3.5 (-0.7 – 7.6%)	**<0.0001**	0.0560
Predictive	98.9%	95.5%	3.5 (-0.8 – 7.7%)	**<0.0001**	0.0660
CC cohort	92/93 98.9%)	93/95 94.9%	4.0 (-0.8 – 8.9%)	**0.0001**	0.0054

[a] Asymptotic confidence limits for the proportion difference
[b] Wald test of non-inferiority test for the risk difference (from SAS PROC FREQ)
[c] Asymptotic p-value for superiority test from StatExact Proc.

Treatment failures (> 5 cm opening in the treated vein) occurred in a total of 6 subjects (1 VenaSeal™ system and 5 RFA) at Month 3. A thorough review of the collected data from the treatment failures did not suggest any obvious failure mode(s). Modeling was not performed for the VenaSeal™ arm, since the number of failures was too small. Recurrence of patency in treated veins is often attributed to new tributary varicosities or disease progression.

Similarly, target GSV closure was also assessed by the clinical site at the Month 3 and Month 12 visit. At Month 3, 103/104 (99.0%) of VenaSeal system subjects and 103/108 (95.4%) of RFA subjects had target GSV closure. The rates of target GSV closure at 12 months remained high across both treatment groups with 92/95 (96.8%) VenaSeal system and 91/94 (96.8%) RFA.

Gender Analysis

The primary effectiveness endpoint was examined for differences in outcome between genders. The target GSV closure rate at Month 3 by gender is shown in **Table 9**. No effect of gender on the primary effectiveness endpoint was found.

Table 9 Complete Closure at Month 3 by Core Lab Ultrasound Assessment by Gender (ITT population, LOCF model)

Gender	Statistics	Male		Female	
		VenaSeal™	RFA	VenaSeal	RFA
Success Rate	n (%)	25/25 (100%)	18/21 (85.7%)	82/83 (98.8%)	91/93 (97.8%)
Difference in Success Rate	Point estimate, 95% CI	14.3%		0.9%	

Notes: Two-sided 95% CI calculated with Wilson method (in R: "prop.test, correct=F"). This method was shown to have conservative Type 1 error rates with success rates in the 90-100% range and sample sizes of 110 per group.

Secondary Effectiveness Results:

There was less ecchymosis (i.e., bruising) at Day 3 in VenaSeal™-treated subjects (p=0.0013, Wilcoxon test). More VenaSeal-treated subjects had no ecchymosis at Day 3 than RFA patients (67.6% vs. 48.2%, p=0.0035, chi-squared test) (**Table 10**).

VenaSeal-treated subjects reported a mean intraoperative pain score of 2.16 (SD 2.23) and RFA-treated subjects reported a mean pain during treatment score of 2.35 (SD 2.18). There was no statistical significance in subject reported pain scores (p=0.5359).

Table 10 Summary of Secondary Effectiveness Endpoints

Endpoint Description	Statistic	VenaSeal™	RFA	P-Value
Pain During Treatment	Mean (SD)	2.16 (2.23)	2.35 (2.18)	0.5359
Ecchymosis at Day 3	None (%)	67.6%	48.2%	**0.0013**
	< 25% (%)	26.9%	33.3%	
	25-50% (%)	2.8%	14.0%	
	50-75% (%)	1.9%	3.5%	
	75-100% (%)	0.9%	0.9%	

Additional Effectiveness
Results of the VCSS, clinical classification CEAP, AVVQ and EQ-5D improved markedly in both VenaSeal™-treated subjects and RFA-treated subjects from baseline to Month 12 with no difference across treatment groups.

Similarly, target GSV closure was also assessed by the clinical site at the Month 3 and Month 12 visit. At Month 3, 103/104 (99.0%) of VenaSeal™ system subjects and 103/108 (95.4%) of RFA subjects had target GSV closure. The rates of target GSV closure remained high across both treatment groups at Month 12 (92/95 (96.8%) VenaSeal system and 91/94 (96.8%) RFA).

9. HOW SUPPLIED

The VenaSeal™ closure system is a medical device provided as a sterile, single patient kit comprised of the VenaSeal™ adhesive and VenaSeal™ delivery system components.

The kit is designed to be used as a system, and its contents are not intended for use as individual components. The VenaSeal adhesive, an n-butyl-2-cyanoacrylate (n-BCA) based formulation, is a clear, free-flowing liquid that is provided sterile following exposure to dry heat. The VenaSeal adhesive polymerizes in the vessel via an anionic mechanism (i.e., VenaSeal adhesive begins to polymerize into a solid material upon contact with body fluids or tissue). This acute coaptation halts blood flow through the insufficient vein until the implanted adhesive becomes fibrotically encapsulated to establish a durable, chronic occlusion of the treated vein. The VenaSeal delivery system components facilitate the placement and delivery of VenaSeal adhesive within the target vessel. The VenaSeal system kit is provided sterile by exposure to ethylene oxide (EtO).

1. VenaSeal™ Adhesive

Five (5) cc of the VenaSeal™ adhesive (a specially formulated n-butyl-2-cyanoacrylate) is contained within a screwed-capped vial.

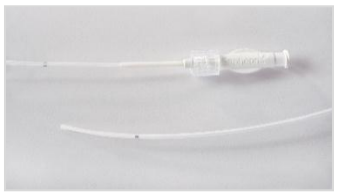
Figure 2: VenaSeal™ Adhesive

2. Dispenser Gun

The dispenser gun consists of a pistol type, ergonomic handle with an integrated barrel and trigger. Each depression of the trigger delivers a controlled 0.10 cc (range: 0.06–0.12 cc) amount of adhesive.

Figure 3: Dispenser Gun

3. Catheter, 4. Introducer, and 5. Dilator



The catheter is 5 Fr with an effective length of 91 cm, laser markings at 3 cm and 85 cm from the tip, and high echogenic visibility.

Figure 4: Laser markings on catheter

The introducer is 7 Fr with an effective length of 80 cm and 10 mm spaced, circumferential markings along its length for measuring retraction length during the VenaSeal™ procedure.

Figure 5: Introducer and Dilator

The dilator is 5 Fr with an effective length of 87 cm.

Figure 6: Introducer and Catheter

6. 3cc Syringe

The 3-cc syringes are graduated Monoject™ Luer Lock Syringes, each with a standard threaded luer lock connector.

Figure 7: 3cc Syringe

7. Dispenser Tips

The dispenser tips are each comprised of a stainless steel, 1.5 mm ID, 3.8 cm length hypotube with a luer lock connector.

Figure 8: Dispenser Tip

8. J-Wire Guidewire

The guidewire is a 0.035-inch, 180-cm J-wire guidewire.

Figure 9: J-Wire Guidewire

10. STORAGE AND HANDLING

The VenaSeal™ system should be stored in its dispenser box carton at room temperature and humidity. The kit should only be opened and the components removed from the carton only upon use.

11. DIRECTIONS FOR USE

Recommended Accessories
The VenaSeal™ system is not a procedure pack and will require the use of the following non-supplied, commercially available components:

- 5 Fr Micro-Access Kit (or equivalent)
    - 21-gauge Guidewire Insertion Needle
    - 0.018-inch Micro-Access Kit Guidewire
    - Micro-Access Sheath
    - Micro-Access Dilator
- Flushing Syringe
- Sterile Saline

REMINDER: Covidien requires physicians to be trained on the VenaSeal™ system prior to independent commercial use. Serious, including fatal, consequences could result with the use of the VenaSeal system without adequate training. Contact your Covidien sales representative for information on training.

PATIENT PREPARATION
Prior to use, perform baseline ultrasound to map incompetent vein to be treated.

Use sterile technique. Use local anesthetic at the access site.

RECOMMENDED PROCEDURE

1. The physician should review the preliminary ultrasound map of the incompetent vein to be treated and perform a final assessment using duplex ultrasound with the subject in the supine position.
2. Under ultrasound guidance, locate the target vein for treatment and locate its most distal location.

    Note: For treatment of the great saphenous vein (GSV) or anterior accessory great saphenous vein (AAGSV), locate the target vein and saphenofemoral junction (SFJ). Trace the vein to determine a site at its distal end for access. *The following instructions are specific to treating the GSV.*

    Note: For treatment of the small saphenous vein (SSV), locate the target vein and

saphenopopliteal junction (SPJ). Trace the vein to determine a site at its distal end for access.

3. Prepare and drape the selected access site as required per standard procedures.
4. Administer local anesthetic at the selected access site.
5. Under ultrasound guidance, access the target vein with a 21-gauge guidewire insertion needle from a 5 Fr micro-access kit or equivalent using Seldinger technique.
6. Advance a 0.018-inch micro-access kit guidewire into the vein and confirm venous access using ultrasound.
7. Remove the guidewire insertion needle and advance the micro-access sheath/dilator over the micro-access kit guidewire and into the vein.
8. Remove the micro-access kit guidewire and micro-access dilator.
9. Advance the 0.035-inch 180-cm J-wire guidewire through the micro-access sheath and into the lumen of the vein.
10. Under real-time ultrasound, position the J-wire guidewire just caudal to the saphenofemoral junction (SFJ).
11. Confirm J-wire guidewire positioning with ultrasound. After confirmation, remove the micro-access sheath and advance the 7Fr introducer/dilator from the VenaSeal™ system over the J-wire guidewire to the SFJ.
12. Remove the 0.035-inch J-wire guidewire and dilator.
13. Flush the introducer through the luer injection port with sterile saline using a flushing syringe. Leave the syringe in place.
14. Under real-time ultrasound guidance, position the introducer tip 5 cm (range 4–6 cm) caudal from the SFJ.
15. Attach a dispenser tip to the 3-cc syringe from the VenaSeal™ system.
16. Utilize the dispenser tip/3-cc syringe combination to extract the VenaSeal™ adhesive from its vial into the 3-cc syringe. Purge visible air from the 3-cc syringe.
17. Once the 3-cc syringe is filled with the VenaSeal adhesive, remove the dispenser tip and connect the 3-cc syringe to the 5 Fr catheter.
18. Lock the 3-cc syringe attached to the catheter into place within the dispenser gun. Care should be taken to avoid kinking the catheter.

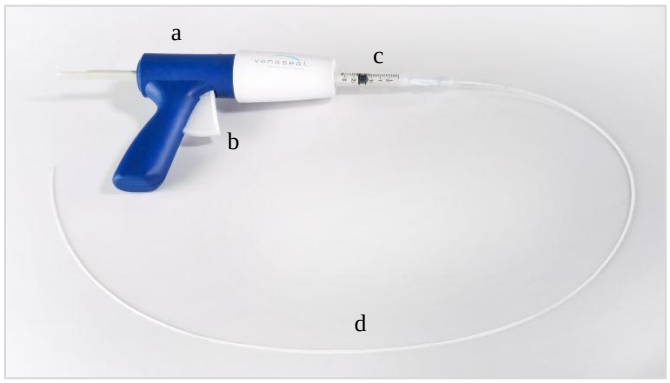


Figure 10:
Illustration of the Dispenser Gun, 3-cc Syringe, and Catheter Assembly

a. Dispenser Gun
b. Trigger
c. 3-cc Syringe
d. Catheter

19. Prime the catheter by pulling the trigger on the dispenser gun to advance the VenaSeal adhesive to within 3 cm (range 2–4 cm) of the distal catheter tip. The distal laser mark denotes 3 cm from the catheter tip. Do not advance the adhesive to the catheter tip during priming.
20. Remove the saline-filled flushing syringe from the introducer.
21. Insert the primed catheter into the introducer and advance until the laser mark on the catheter is at the hub of the introducer. Care must be taken to avoid kinking the catheter.
22. Pull the introducer back caudal another 5 cm. Advance the catheter cephalad and lock the introducer to the catheter with the spin-lock mechanism. This will expose the catheter tip, positioning it 5 cm (range 4–6 cm) caudal to the SFJ junction. Verify catheter tip is 5 cm from SFJ with ultrasound imaging.
23. Using a transverse ultrasound plane, position the ULTRASOUND transducer just cephalad (2–3 cm) to the catheter tip and APPLY ADEQUATE PRESSURE to compress the GSV near the SFJ as depicted in Figure 11 below.

Figure 11:
Ultrasound transducer position for initial injection of the VenaSeal™ adhesive

24. While applying compression with the ultrasound transducer, deliver 0.10 cc (range 0.06–0.12 cc) of the VenaSeal adhesive in the vein by pulling the trigger of the dispenser gun once. Hold the dispenser gun trigger for 3 seconds after the trigger pull to completely inject the 0.10 cc of the VenaSeal adhesive. Immediately pull back 1 cm and deliver another 0.10 cc of the VenaSeal™ adhesive in the vein with an additional trigger pull, again holding the dispenser gun trigger for 3 seconds after the trigger pull.
25. Following this second injection, immediately (within 3 seconds) pull back the connected introducer and catheter 3 cm holding the transverse compression with the ultrasound transducer for a minimum of 3 minutes. During the compression time, utilize a free hand caudal to the transducer to add light compression as depicted in Figure 12 below.

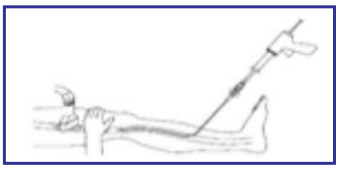


Figure 12:
Pressure application in VenaSeal™ procedure

26. After the compression time, locate the catheter tip under ultrasound guidance.
27. After confirming the catheter tip position, apply compression on the vein caudal to the previous injection and cephalad to the catheter tip with the ultrasound transducer in a transverse plane.
28. Deliver 0.10 cc (range 0.06–0.12 cc) of the VenaSeal adhesive in the vein by pulling the trigger of the dispenser gun once and holding the trigger for 3 seconds.
29. Following the injection, immediately (within 3 seconds) pull back the connected introducer/catheter 3 cm and hold transverse compression (with the ultrasound transducer) for a minimum of 30 seconds. During the compression time, utilize a free hand caudal to the transducer to add light compression as depicted in Figure 12 above.
30. Repeat steps 26–29 to treat the entire length of the target vein segment to a point 5 cm cephalad from the access site. Injections should all be located within the target vein.

Additional injections can be given during treatment at the site of tributaries or focal dilatation.

31. After the final VenaSeal adhesive injection, remove the introducer/catheter and hold hand pressure as long as necessary to achieve hemostasis.
32. Confirm vein closure along the treated segment with ultrasound. Note: The exact application procedure is to be determined by the medical provider.
33. Dispose of the VenaSeal™ system as per protocol for biohazardous medical devices.

In the event the primed catheter needs to be withdrawn from the introducer prior to completion, take the following steps:

1. If the VenaSeal adhesive has not been injected through the distal end of the catheter (Procedure Steps 20–23).
    a. Check to make sure there is no adhesive that has been injected out the catheter tip.
    b. If (a) has not occurred, the catheter can be unscrewed from the introducer and withdrawn.
2. If the adhesive has been injected through the distal end of the catheter (After Procedure Step 23).
    a. Withdraw introducer with attached catheter. The following steps are performed outside the body.
    b. Push the white button on top of the dispenser gun and pull back the plunger rod.
    c. Unlock and release the syringe with attached catheter from the dispenser gun.
    d. Pull back gently on the syringe plunger to draw the adhesive back in to the catheter.
    e. Adhesive should be drawn at least 5–10 cm from the distal laser mark on the catheter.
    f. Using sterile gauze, repeatedly wipe any residual adhesive off the tip of the catheter.
    g. After confirming the tip is cleaned of adhesive, the catheter can be unscrewed from the introducer and withdrawn.
    h. Flush the introducer sheath with sterile saline prior to advancing over the guidewire.
3. To re-introduce the catheter back into the introducer, follow steps 10–23 above.

Total Amounts of VenaSeal™ Adhesive Expected for Use in Vein Treatments

The amount of adhesive delivered is related to length of the target GSV. The VenaSeal™ Instructions for Use describe the application of 0.10 cc of the VenaSeal™ adhesive every 3 cm in the target vein. In addition, the first delivery consists of 0.20 cc. The table below shows a calculation of the total expected amount of adhesive delivered as a function of target treatment length. Additional injections could be administered at sites of dilatation and junctions with tributaries. The exact application procedure and dosage is to be determined by the physician.

Table 11: Total amount of adhesive delivered as a function of planned treatment length
FOR REFERENCE ONLY

Planned treatment length (cm)	Initial delivery (cc)	Subsequent # of deliveries	Total amount of adhesive (cc)
10	0.2	3	0.5
15	0.2	5	0.7
20	0.2	7	0.9
25	0.2	8	1
30	0.2	10	1.2
35	0.2	12	1.4
40	0.2	13	1.5

45	0.2	15	1.7
50	0.2	17	1.9
55	0.2	18	2
60	0.2	20	2.2
65	0.2	22	2.4
70	0.2	23	2.5
75	0.2	25	2.7
80	0.2	26	2.8
85	0.2	28	3.0
90	0.2	30	3.2

M
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12. SYMBOL LEGEND

IQ Sterilized Using Ethylene Oxide	g Batch Code	i Consult Instructions For Use	H Use By Date
L Do Not Use If Package is Damaged	M Manufacturer	h Catalogue Number	℞ ONLY Caution: Federal Law restricts this device to sale by or on the order of a physician
IS Sterilized Using Steam or Dry Heat	D Do Not Re-Use	B Do Not Resterilize	

13. LIMITED WARRANTY TO PURCHASER

Covidien warrants to the Purchaser that, for the earlier of one (1) year or until the Product is used by Purchaser, the Products will be free from defects in materials and workmanship when stored and used in accordance with the instructions for storage and use provided by Covidien and in accordance with applicable regulatory requirements. Descriptions or specifications appearing in Covidien's literature are meant to generally describe the Products and do not constitute any express warranties. In the event that Covidien gives technical advice with respect to the Products, it is agreed that such advice is given without any liability on Covidien's part. Covidien does not warrant conformity of Products with any samples provided. Any guarantee of specific properties of or in the Products shall only be effective if and to the extent specifically confirmed by Covidien in writing. These warranties shall not apply for Product failure or deficiency due to improper storage, alteration, or the consequences of uses for which the Product was not designed or that adversely affect its integrity, reliability, or performance. THE WARRANTIES, OBLIGATIONS, AND LIABILITIES OF COVIDIEN AS SET FORTH HEREIN ARE EXCLUSIVE AND IN SUBSTITUTION FOR, AND PURCHASER HEREBY WAIVES, ALLOTHER WARRANTIES, EXPRESS OR IMPLIED, ARISING BY LAW OR OTHERWISE, WITH RESPECT TO THE PRODUCTS AND ANY OTHER GOODS OR SERVICES DELIVERED UNDER THIS AGREEMENT, INCLUDING, BUT NOT LIMITED TO: (1) ALL OTHER EXPRESS AND IMPLIED WARRANTIES, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND (2) ANY IMPLIED WARRANTY ARISING FROM COURSE OF PERFORMANCE, COURSE OF DEALING, OR USAGE OF TRADE.