SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Vascular Occluding Agent
Device Trade Name:	VenaSeal Closure System
Device Procode:	PJQ
Applicant's Name and Address:	Covidien llc 951 Aviation Parkway, Suite 900 Morrisville, NC 27560
Date(s) of Panel Recommendation:	Not Applicable
Premarket Approval Application (PMA) Number:	P140018
Date of FDA Notice of Approval:	February 20, 2015

II. INDICATIONS FOR USE

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).

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the VenaSeal system product labeling.

V. DEVICE DESCRIPTION

The VenaSeal 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.

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.

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

Laser markings on catheter

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.

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.

Introducer and Dilator

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

Introducer and Catheter

6. 3cc Syringe

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

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.

8. J-Wire Guidewire

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

Please refer to the Operator's Manual for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Currently, there are a number of treatment options available to patients with symptomatic venous reflux disease, including vein stripping surgery, sclerotherapy, and thermal ablation (i.e., endovenous laser ablation [EVLA] and radiofrequency ablation [RFA]). The goal of each of these treatment regimens is to eliminate the sources of reflux in order to improve current symptoms, control progression of the disease, promote ulcer healing, and prevent recurrence.

Vein stripping surgery removes the diseased vein. In sclerotherapy, a sclerosing agent is injected directly into the target vein, ablating the vein chemically. The injected agent produces endothelial damage which results in "sclerotic changes" in the vein wall eventually resulting in fibrosis across the vein lumen. During RFA and EVLA, a catheter is inserted into the target vein and heat is applied to ablate the target vein. The ablated vein does not allow blood flow.

Each alternative has its own advantages and disadvantages. The physician should fully discuss these alternatives with his/her patient to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The VenaSeal system has not been marketed previously in the United States

The VenaSeal system is commercially available outside the United States for use in the treatment of venous reflux disease. The product is currently distributed in Europe, Canada, Australia and Hong Kong. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. 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
- Neurological deficits including stroke and death
- Pain
- Paresthesia
- Phlebitis
- Superficial thrombophlebitis
- Urticaria or ulceration may occur at the site of injection
- Vascular rupture and perforation
- Visible scarring

For the specific adverse events that occurred in the VeClose clinical study please see **Section 10** below.

IX. SUMMARY OF PRECLINICAL STUDIES

A variety of non-clinical testing was performed with the VenaSeal Closure System to demonstrate that the product is suitable for its intended purpose. Testing focused on evaluating the features and performance criteria for closure of symptomatic truncal veins, such as the great saphenous vein (GSV), with the VenaSeal adhesive that is delivered endovenously using the VenaSeal delivery system components

A. Laboratory Studies

Characterization testing of the VenaSeal closure system was conducted via bench top studies. These activities were applied to the three major elements of the VenaSeal kit: (1) the VenaSeal adhesive; (2) the VenaSeal delivery system components; and, (3) the VenaSeal closure system kit itself (catalog number: VS-402). Tests were conducted, in isolation and/or in combination, to ensure that the finished (sterilized) VenaSeal system met and/or conformed to the stated criteria.

1. VenaSeal Adhesive Benchtop Testing

VenaSeal adhesive benchtop testing was performed to characterize the materials, the performance attributes of the adhesive, heat of polymerization, and degradation rate. The tests performed are outlined in **Table 1**.

Table 1: VenaSeal Adhesive Benchtop Testing

	Test	***Test Description***	***Acceptance Criteria***	***Results***
Material Characterization	Absolute Viscosity	Viscosity measured using a glass capillary viscometer at 25ºC (77°F)	Acceptable internal resistance to flow	Passed
	Composition	Chemicals characterization	Chemical constituents of the proprietary formulation meet pre-determined specifications	Passed

	Test	*Test Description*	*Acceptance Criteria*	*Results*
	Adhesive Set Time	Time to polymerization measured.	Adhesive setting time within 180 sec per test method	Passed
Adhesive Strength Characterization	Adhesive Lap Shear	Test per ASTM F2255-05, "Standard Method for Strength Properties of Tissue Adhesives by Lap-Shear Loading."	Lap shear 1 N/mm^2 minimum	Passed
	Pliability	Deflect polymerized VenaSeal adhesive through at least 180 degrees, visual inspection	The creased area of the adhesive shall be free of any visual evidence of cracks, deformities, or discolorations.	Passed
	Tensile Strength	Test per ASTM F2258-05, Standard Test Method for Strength Properties of Tissue Adhesives in Tension	These tests were conducted to characterize the VenaSeal adhesive. As such, no acceptance criteria are specified.	The test results showed the adhesive to have the predefined plastic type behavior.
	Peel Adhesion Strength	Test per ASTM F2458-05, Standard Test Method for Wound Closure Strength of Tissue Adhesives and Sealants and ASTM F2256-05, Standard Test Method for Strength Properties of Tissue Adhesives in T-Peel by Tension Loading	These tests were conducted to characterize the VenaSeal adhesive. These assessments do not reflect mechanical forces occurring in clinical use. As such, no acceptance criteria are specified.	The test results showed the adhesive to have the predefined plastic type characteristics.
Heat of Polymerization	Heat of Polymerization	Heat of polymerization was measured using differential scanning calorimetry (DSC).	Heat of Polymerization was measured in order to characterize this property of the VenaSeal adhesive. No acceptance criteria are specified.	The test results showed the adhesive heat of polymerization to be acceptable.
Degradation Rate	Hydrolytic Degradation	Hydrolytic degradation testing was performed to characterize extractables, leachables of and degradation by-products of VenaSeal adhesive per the recommendations outlined in the US FDA "Class II Special Controls Guidance Document: Tissue Adhesive for the Topical Approximation of Skin" (May 30, 2008). Samples were hydrolytically degraded in physiological saline and the extract was analyzed to quantify degradent concentrations.	This test was intended to generate and document degradation characterization data for clinically representative VenaSeal adhesive polymer.	The analysis evaluated the measured degradants and eluents, and concluded that there was little appreciable patient risk due to exposure from VenaSeal Adhesive degradants or leachants.

2. <u>VenaSeal Delivery System Components Benchtop Testing</u>

The VenaSeal delivery system components were tested to demonstrate mechanical design, and functionality. As demonstrated below, the results of all benchtop testing supports the conclusion that the VenaSeal delivery system components satisfy the desired product characteristics, comply with applicable sections of ISO 11070 and ISO 10555-1, and are safe and effective for the intended use. The tests performed for the delivery components are outlined in **Table 2**.

Table 2: VenaSeal Delivery System Component Benchtop Testing

Test	***Test Description***	***Acceptance Criteria***	***Results***
Catheter, Introducer, and Dilator			
Kink Resistance (Simulated Use Testing)	The catheter, introducer, and dilator (following preconditioning) were subjected to kink resistance testing by bending around a set diameter at the caudal, mid, and cephalad point of the samples	All samples shall be free of kinks during or following testing.	Pass
Leak Test	The catheter (following preconditioning) was subjected to a liquid leakage test under pressure in accordance with ISO 10555-1 Annex D.	All samples shall be free from leakage sufficient to form a falling drop.	Pass
Tensile Testing	The catheter, introducer, and dilator (following preconditioning) were subjected to tensile testing in accordance with ISO 11070 and ISO 10555-1 Appendix C and Appendix B respectively.	All sample tensile strengths shall be greater than the minimum tensile requirement as defined by ISO 11070 and ISO 10555-1. These acceptance criteria are appropriate given the low distance and tortuosity of the tracking path.	Pass
Dispenser Gun			
Adapter Tensile Testing	The adapter assembly inner and outer barrel adhesive joints were subjected to tensile testing at a rate of 300mm/min.	All samples tensile force strength data shall be greater than the minimum tensile requirement of 222 N (50 lbf).	Pass
Guidewire			
Strength of Union	This test is performed per ISO 11070. The coil attachment joints are individually placed in the appropriate fixture and pulled to breaking at a rate of 10mm/minute.	Unions must meet force required in ISO 11070.	Pass
Corrosion Resistance	This test is performed per ISO 11070. The test piece is placed in a beaker of pH buffered saline at a controlled temperature for 5 hours. It is then placed in boiling distilled or de-ionized water for 30 minutes. Water is cooled and held at 37°C for 48 hours. Test piece is removed and allowed to dry at room temperature, and then examined for evidence of corrosion.	No visible corrosion.	Pass

Test	*Test Description*	*Acceptance Criteria*	*Results*
Wire Fracture	Per ISO 11070, the distal end of guidewire is secured in fixture and then wrapped tightly around the appropriate sized dowel pin following multiple turns. Wire is unwrapped and removed from the fixture. Wire is examined for fractures.	Coating must adhere after multiple turns with no damage to wire or coating.	Pass
Wire Flexure	This test is performed per ISO 11070. Using the appropriate sized fixture, the distal end of the guide wire is placed around one former in one direction, and continued around the other former in the other direction. The guide is removed and re-positioned multiple times, then visually examined for damage in the device.	Coating must adhere after multiple cycles with no damage to wire or coating.	Pass
VenaSeal Closure System			
Delivery System Compatibility (Simulated Use Testing)	Evaluate compatibility of the interfaces between the catheter, introducer, dilator and guidewire following pre-conditioning. Evaluate compatibility of the interfaces between the syringe and dispenser guns.	The components shall meet the interface and compatibility requirements specified in the VenaSeal kit material specification and identified in the protocol and report.	Pass
Dispensing Performance Test	The VenaSeal delivery system shall be primed and VenaSeal adhesive dispensed per the product's instructions for use following pre-conditioning. The dispensed volume shall be weighed.	The average dispensing volume shall be within the specified range.	Pass

These bench tests demonstrate acceptable and reproducible safety and effectiveness of the VenaSeal closure system.

B. Animal Studies

Pre-clinical testing was performed in goat, swine, and rabbit models to validate the safety and performance of the product, including: (1) accuracy of the VenaSeal adhesive application procedure; (2) ability of acute & chronic vessel closure; and, (3) adhesive acute & chronic toxicity. Collectively, 51 animals were implanted with VenaSeal adhesive in the pre-clinical studies that evaluated product safety and performance in acute, sub-chronic, and chronic (180 day) time periods.

Each study met the established acceptance criteria, supporting that the device operates as intended. The VenaSeal system met performance and safety expectations when used as intended, supporting that the VenaSeal adhesive can coapt the vessels in a permanent manner; that the VenaSeal adhesive does not migrate from its implant location; and, that

the VenaSeal adhesive does not cause an unexpected immunological response. The tests performed are outlined in **Table 3**.

Table 3: VenaSeal System Animal Testing

Test	***Test Description***	***Acceptance Criteria***	***Results***
Sub-Chronic Systemic and Sub-Chronic Local Toxicity	Assess material for sub-chronic systemic and sub-chronic local toxicity. VenaSeal adhesive was injected directly into the subcutaneous tissues on each side of the dorsal midline where it polymerized *in vivo*. Rabbits were observed through 13 weeks. Prior to sacrifice, blood was taken for analysis of hematology, coagulation, and clinical chemistry. Macroscopic observations of the implant sites were obtained at necropsy. The implant sites and selected organs were weighed and evaluated for histopathology.	The test article shall generate sub-chronic systemic and sub-chronic local toxicity responses that are less than or equal to the toxicity responses observed for the Histoacryl Blue control.	The results support that VenaSeal adhesive does not result in any specific adverse systemic or local toxicological findings in the tissues examined.
Chronic Systemic and Chronic Local Toxicity	Assess material for chronic systemic and chronic local toxicity VenaSeal adhesive was injected directly into the subcutaneous tissues on each side of the dorsal midline where it polymerized *in vivo*. Rabbits were observed through 26 weeks. Prior to sacrifice, blood was taken for analysis of hematology, coagulation, and clinical chemistry. Macroscopic observations of the implant sites were obtained at necropsy. The implant sites and selected organs were weighed and evaluated for histopathology.	The test article shall generate chronic systemic and chronic local toxicity responses that are less than or equal to the toxicity responses observed for the Histoacryl Blue control.	The cumulative results support that VenaSeal adhesive does not result in any specific adverse systemic or local toxicological findings in the tissues examined.
Acute, Sub-Chronic, and Chronic GSV Occlusion	Assess for acute, sub-chronic and chronic GSV occlusion using VenaSeal adhesive per instructions for use. Right and left saphenous veins were treated in three goats (6 samples) each at 30 and 90 days, and two goats (4 samples) at 180 days. Prior to sacrifice, vein closure was assessed via ultrasound. Implant site samples were then evaluated for histopathology.	1. All animals shall be in good health for the test duration and show no signs of compromised mobility. 2. Treated vessels shall exhibit adhesive or fibrotic occlusion at all examination periods. Mature fibrotic occlusion shall be identified as the time period where no inflammation has resolved and fibrosis no longer progresses.	The results support that the VenaSeal adhesive provides chronic, mature occlusion of the GSV after 30 days via the comparison of fibrotic organization.
VenaSeal Adhesive Application Procedure Validation, Acute Vein Closure, Adhesive Stability	The VenaSeal closure system kit was used to apply VenaSeal adhesive per the IFU in swine. Vein closure and placement accuracy were analyzed via ultrasound acutely and 7-14 days after treatment. In addition, the lack of	1. Delivery procedure shall prepare the tools for presentation to the sterile field, position the introducer sheath tip caudal to the initial	Measurement of the adhesive location via ultrasonic analysis was not possible immediately following the

Test	*Test Description*	*Acceptance Criteria*	*Results*
	adhesive migration was evaluated by checking for the absence of embolization in the lungs.	compression location, prepare the delivery system, position the infusion catheter tip caudal to the initial compression location, dispense VenaSeal adhesive to the target vein without unanticipated fault conditions, safely and permanently close the wound. 2. After the procedure, the treated vein segment shall be closed and the adhesive shall not be present 5cm beyond the initial compression location. 3. After a period of 7-14 days, the treated vein segment shall be closed and no significant adhesive shall be present 5 cm beyond the initial compression location. The lungs shall show no signs of injury due to adhesive migration.	procedure due to the vessel collapsing as intended upon treatment. Adhesive location was analyzed in the sub-chronic vein closure analysis at 7-14 days. The results support that the VenaSeal adhesive provides procedure is appropriate and that the material does not migrate.

C. Additional Studies

1. Biocompatibility

Biocompatibility testing of the VenaSeal system patient contacting materials was coordinated per the requirements of ISO 10993-1. The VenaSeal adhesive was evaluated as permanent implant in contact with circulating blood, and the patient contacting delivery components were evaluated as an external communicating device in limited (< 24 hours) contact with circulating blood. Each of the VenaSeal components has been tested using test articles representative of final product subjected to material characterization and traceability and following simulated clinical use (i.e., wetted path).

The biocompatibility tests completed for the adhesive, in its polymerized and unpolymerized states, are presented in Table 4. As outlined, evaluations for subacute/subchronic toxicity implantation and chronic toxicity implantation were assessed within the animal studies (Table 3). Testing for carcinogenicity and reproductive/developmental effect were not performed as information available supported that the material is safe for its intended use. The biocompatibility tests completed for the patient-contacting delivery system components are presented in Table 5.

Table 4: Results of Biocompatibility Testing – VenaSeal Adhesive (Polymerized and Unpolymerized States)

Test	*Method Reference*	*Results*
Cytotoxicity (Elution Method)	ISO 10993-5	The cumulative results of the VenaSeal adhesive material cytotoxicity testing, in combination with assessments of toxicological risk and *in vivo* use, support an overall favorable cytotoxicity profile for the VenaSeal adhesive material per its intended use.
ISO Maximization Sensitization Study (Guinea Pigs)	ISO 10993-10	VenaSeal adhesive does not elicit a sensitization response
ISO Intracutaneous Reactivity	ISO 10993-10	The cumulative results support that the VenaSeal adhesive material does not cause intracutaneous reactivity
Material Mediated Rabbit Pyrogenicity	ISO 10993-5 US Pharmacopeia Section 151	The cumulative results support that the VenaSeal adhesive material is non-pyrogenic
Acute Systemic Toxicity	ISO 10993-11	The cumulative results support that the VenaSeal adhesive material is not considered to cause acute systemic toxicity
Subacute / Subchronic Toxicity Implantation (13 weeks)	ISO 10993-11 ISO 10993-6	The cumulative results support that the VenaSeal adhesive material does not result in any specific adverse systemic toxicological findings in the tissues examined
Genotoxicity (Bacterial Mutagenicity, *in vitro* Mouse Lymphoma Assay, Mouse Micronucleus Assay)	ISO 10993-3	The cumulative results support that the VenaSeal adhesive material is non-mutagenic
Hemo-compatibility (Hemolysis, Complement Activation, Partial Thromboplastin Time, Platelet and Leukocyte Count)	ASTM F-756-08 ISO 10993-4	The cumulative results support that the VenaSeal adhesive material is non-hemolytic.
Chronic Toxicity Implantation (26 Weeks)	ISO 10993-11 ISO 10993-6	The cumulative results support that VenaSeal adhesive does not cause any significant adverse systemic or local toxicity in the tissues examined

Table 5: Results of Biocompatibility Testing – Delivery System Components

Test	*Method Reference*	*Results (pass/fail)*
Introducer, Dilator, and Catheter		
Cytotoxicity (Elution Method)	ISO 10993-5	No cytotoxic effects observed
ISO Maximization Sensitization Study (Guinea Pigs)	ISO 10993-10	No evidence of delayed dermal contact sensitization.
ISO Intracutaneous Reactivity	ISO 10993-10	No evidence of significant irritation.
Systemic Toxicity	ISO 10993-11	No mortality or systemic toxicity.
Material Mediated Pyrogenicity (Rabbit)	ISO 10993-11	Non-pyrogenic
Hemocompatibility/Hemolysis (Hemolysis, Platelet and Leukocyte Counts, Partial Thromboplastin Time)	ISO 10993-4	Non-hemolytic and non-compliment activating.
Guidewire		
Cytotoxicity (Elution Method)	ISO 10993-5	No cytotoxic effects observed
ISO Maximization Sensitization Study (Guinea Pigs)	ISO 10993-10	No evidence of delayed dermal contact sensitization.
ISO Intracutaneous Reactivity	ISO 10993-10	No evidence of significant irritation.
Systemic Toxicity	ISO 10993-11	No mortality or systemic toxicity.
Material Mediated Pyrogenicity (Rabbit)	ISO 10993-11	Non-pyrogenic
Hemocompatibility/Hemolysis (Hemolysis, Lee & White Coagulation, Prothrombin Time, Unactivated Partial Thromboplastin Time, Complement Activation)	ISO 10993-4	Non-hemolytic and non-compliment activating.
Implantation (1 & 4 weeks)	ISO 10993-6	Non-irritating

The data from the biocompatibility evaluations support the overall conclusion that the VenaSeal closure system product is biocompatible for its intended use and duration, has a safe biodegradation profile, similar to other approved n-BCA based medical devices, and has an acceptable toxicological profile for raw materials and degradants.

2. Sterilization

The VenaSeal system is provided to the user labeled as sterile and for single-patient use only. There are two discrete sterilization processes employed in the manufacture of the VenaSeal closure system kit; an in-process sterilization of the VenaSeal adhesive packaged within its 6 mL vial and a terminal sterilization of the fully packaged kit.

The filled VenaSeal adhesive vial is sterilized using dry heat to a minimum sterility assurance level (SAL) of 1×10^{-6}. The dry heat sterilization process has been validated per ANSI/AAMI ISO 20857 to demonstrate that the method results in a finished product that is sterile to a SAL of 1×10^{-6} and that the adhesive maintains acceptable behavior.

The assembled kit, which includes one dry-heat sterilized vial of VenaSeal adhesive, is terminally sterilized by exposure to ethylene oxide (EtO) to a minimum SAL of 1×10^{-6}. The EtO sterilization process has been validated per ISO 11135-1 to demonstrate that the finished product is sterile to a SAL of 1×10^{-6} and that all components, including the VenaSeal adhesive, exhibit acceptable EtO desorption kinetics that are less than the limits set forth in ISO 11135-1.

3. Packaging Validation

Packaging validation testing was performed to show the VenaSeal closure system device packaging and labeling met established specifications. The tests performed are outlined in **Table 6**.

Table 6: VenaSeal Kit Package Testing

Test	*Purpose*	*Acceptance Criteria*	*Results*
Shipping Container Test (Simulated Transit per ASTM D4169-09 Distribution Cycle 13): • Header Bag Burst Test per ASTM F1140-07 • Header Bag and Tyvek Lid Dye Penetrant Testing per ASTM F1929 • Tyvek Lid Peel Testing	The purpose of this testing is to validate the VenaSeal closure system sterile barrier following simulated transit.	Following ASTM D4169 testing, all packaging shall visually appear to be intact with no apparent breach of sterile barriers. All subsequent sterile barrier tests must pass.	Pass
VenaSeal Adhesive Sterile Barrier Validation: • Vacuum Testing per ASTM D5094 /D5094M Method B.	The VenaSeal adhesive is sterilized via dry heat prior to being placed within the kit packaging. The purpose of this testing is to demonstrate the functional effectiveness of the adhesive sterile barrier for the period of time that the sterilized adhesive may be stored in manufacturing inventory prior to kit assembly. Once the adhesive is packaged and EtO sterilized with the VenaSeal closure system kit, the vial no longer serves as a sterile barrier.	All samples shall appear intact with no apparent breach of sterile barriers as evidenced by dye outside of the sample vial.	Pass

4. Shelf Life Validation

Accelerated and real-time aging testing was conducted to demonstrate the device packaging can maintain a sterile barrier and that the VenaSeal system functions as intended with a shelf life of 24 months from the date of adhesive sterilization or 24 months from the date of kit manufacture, whichever is shorter. The shelf life of the VenaSeal closure system is predicated on the validated longevity of its three major elements:

1. The VenaSeal Adhesive;
2. The VenaSeal Delivery System;
3. The VenaSeal Closure System kit packaging materials.

The tests performed are outlined in **Table 7**.

Table 7: VenaSeal System Shelf Life Testing

Test	*Test Method*	*Acceptance Criteria*	*Result*
VenaSeal Adhesive Material Shelf Life	*24 Month Accelerated Aging* • Adhesive Viscosity • Adhesive Lap Shear • Adhesive Setting Time • Adhesive Composition • Adhesive Pliability *24 Month Real-time Aging* • Adhesive Viscosity • Adhesive Lap Shear • Adhesive Setting Time • Adhesive Composition • Adhesive Pliability	The VenaSeal adhesive shall meet all its material characterization requirements. Specific acceptance criteria for these characterizations are provided in **Table 1**.	Pass
VenaSeal Adhesive Sterile Barrier	*24 Month Accelerated Aging* • Vacuum Testing per ASTM D5094 /D5094M Method B • Visual Inspection	All packaging shall visually appear to be intact with no apparent breach of sterile barriers. There shall be no evidence of dye outside of the test sample vials.	Pass

Test	*Test Method*	*Acceptance Criteria*	*Result*
VenaSeal Delivery System Components (excluding the guide wire)	*24 Month Accelerated Aging* • Visual Inspection • Delivery System Compatibility • Delivery System Kink Resistance • Catheter Leak Test • Dispenser Performance Test Catheter Component Tensile Testing *24 Month Real-time Aging* • Visual Inspection • Delivery System Compatibility • Delivery System Kink Resistance • Catheter Leak Test • Dispenser Performance Test Catheter Component Tensile Testing	The VenaSeal delivery system components shall meet all their laboratory test requirements. Specific acceptance criteria for these tests are provided in **Table 2**.	Pass
VenaSeal Guide Wire Component	*5 Year Aging* • Bench Testing per ISO 11070	The guidewire shall meet all its laboratory test requirements. Specific acceptance criteria for these tests are provided in **Table 2.**	Pass
VenaSeal Kit Sterile Barrier	*24 Month Accelerated Aging* • Tyvek Lid and Header Bag Dye Penetrant Test • Header Bag Burst Test • Tyvek Lid Peel Test *24 Month Real-time Aging* • Tyvek Lid and Header Bag Dye Penetrant Test • Header Bag Burst Test • Tyvek Lid Peel Test	Any wicking of the dye through the pouch seal within 20 seconds from application of dye to seal shall constitute a test failure. The 95/95 lower tolerance limit for the Header Bag burst strength shall be greater than 40 inches of H_2O without evidence of weld creep upon pouch purse for all tested units. The 95/95 lower tolerance limit for the peel strength of the tray to Tyvek lid seal shall be greater than or equal to 1.19N (4.3 ozf).	Pass

X. 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 8**. 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 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 8: VenaSeal System Clinical Studies

	Feasibility	eSCOPE	VeClose Pivotal
Study Title	Sapheon™ Closure System First-In-Man Study	European Sapheon™ Closure System Observational Prospective (eSCOPE) Study	VenaSeal Sapheon Closure System vs. Radiofrequency Ablation for Incompetent Greater Saphenous Veins (VeClose)
Objective	Assess safety and effectiveness in a first in man setting	To assess the role of the Sapheon Closure System in closure of incompetent great saphenous veins in a routine clinical setting	To demonstrate safety and effectiveness of the VenaSeal for the treatment of lower extremity truncal reflux compared to RFA performed using the Covidien ClosureFast system
Study Design	Prospective, single arm, single center, OUS clinical study	Prospective, multicenter, single-arm, observational, OUS, post-market study	Prospective, multi-center, randomized, US pivotal clinical study
Post-procedure compression stockings	No	No	Yes
# of Subjects	38	70	242 (20 roll-in, 108 VenaSeal, 114 RFA)
Primary Endpoint	Vein closure at 6 months, no discrete segment of patency > 5 cm), assessed by Investigator	Vein closure at 6 months (no discrete segment of patency > 10 cm), assessed by Investigator	Vein closure at 3 months (no discrete segment of patency > 5 cm), assessed by independent vascular ultrasound core laboratory
Effectiveness Results	94.7% closure at 6 Months (95% CI: 87.9 – 100)	94.3% closure at 6 Months (95% CI: 89.0 – 99.9%)	3M results (LOCF): VenaSeal 107/108 (99.1%) RFA 109/114 (95.6%) 12M results (CC): VenaSeal 92/95 (96.7%) RFA 91/94 (96.8%)

	Feasibility	eSCOPE	VeClose Pivotal
Safety Results	Subjects followed for 36 Months: • 24 AEs reported in 17 subjects • 1 DVT at 31 months post-treatment in a hypercoagulable subject (unknown device relationship, not related to the procedure) • No PEs or deaths	Subjects followed for 12 Months: • 33 AEs reported in 20 subjects • No PEs, DVTs or deaths	Subjects followed for 12 Months: • 1 access site burn in a RFA subject • 2 access site infections (1 VenaSeal, 1 RFA) • 7 events of paresthesia in the treatment zone (1 roll-in, 3 VenaSeal, 3 RFA) • 1 event of paresthesia not in treatment zone (RFA) • 1 DVT at 6 months in a RFA subject • No skin ulcerations, PEs, or deaths
AE – adverse event; CC – Complete Case; CI – confidence interval; DVT – deep venous thrombosis; LOCF - Last Observation Carried Forward;;OUS – outside United States; PE – pulmonary embolism; RFA – radiofrequency ablation; US – United States;			

A. Primary Clinical Study (VeClose)

1. 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 system 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 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 two secondary endpoints, intraoperative pain and ecchymosis at Day 3, were analyzed to demonstrate standard statistical superiority of VenaSeal system over RFA. The Holm stepdown method was used to adjust for multiplicity in the 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.

The control group was an active control group receiving treatment using a legally marketed device with similar indications for use.[3]

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

[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).

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 of 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

b. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at:

Day 3 (can occur Day 4 or 5 if Day 3 falls on a weekend);
Month 1 (± 7 days);
Month 3 (± 4 weeks);
Month 6 (± 6 weeks);

Month 12 (± 8 weeks);
Month 24(± 8 weeks); and
Month 36 (± 8 weeks).

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) 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.

The key time points are summarized in **Table 9** shown below.

Table 9: VeClose Study Follow Up time points

Visit (acceptable visit window)	Screening	Baseline	Procedure	Discharge	Day 3[1]	Mo 1 (± 7d)	Mo 3 (± 4 wks)	Mo 6 (± 6 wks)	Mo 12 (± 8 wks)	Mo 24 (± 8 wks)	Mo 36 (± 8 wks)
Medical history	X	X				X[5]	X[5]				
Physical examination / ecchymosis	X	X[2]			X[2]						
Procedure-related pain			X		X						
CEAP	X						X	X	X	X	X
VCSS		X			X	X	X	X	X	X	X
AVVQ		X				X	X	X	X	X	X
EQ-5D	X					X	X	X	X	X	X
Satisfaction with treatment			X				X	X	X	X	X
Duplex Ultrasound	X		X[3]		X[4]	X[4]	X[4]	X[4]	X[4]	X	X
Adverse event assessment			X	X	X	X	X	X	X	X	X
Procedure-related information			X								
Adjunctive therapy							X[6]				

1. The Day 3 assessment can occur on the Day 4 or 5 if Day 3 falls on a weekend
2. Ecchymosis assessed at baseline and Day 3
3. Duplex only for review of GSV and to assess access site.
4. All follow-up U/S exams evaluate only closure and thrombus
5. Primarily an assessment of paresthesia
6. Details of any adjunctive procedures performed will be captured on CRFs.

c. Clinical Endpoints

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.

Although the study was not statistically powered for safety as ablation techniques of the varicose veins are relatively benign procedures with very few serious adverse events, safety of this study was assessed by the occurrence rate of each of the following specific adverse events:

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

The study was designed with a non-inferiority hypothesis for the primary effectiveness endpoint for anatomical closure at 3 months and these results were also assessed at 12 months to ensure long-term closure. 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). Complete closure was defined as Doppler ultrasound showing vein closure along entire treated vein segment with no discrete segments of patency exceeding 5 cm.

The study employed a non-inferiority approach to analysis with a 10% non-inferiority delta:

H_0: $C_V \leq C_{RFA} - 10\%$
H_a: $C_V > C_{RFA} - 10\%$

where C was the proportion of treated subjects with closure of the target GSV given a particular treatment.

The following secondary efficacy endpoint assessments were performed:

- Pain during the procedure, rated using a 0-10 NRS
- Ecchymosis at Day 3 following the procedure, rated on a 0-5 ordinal scale

At 12 months, an additional analysis of effectiveness (i.e., complete closure of the target GSV) was reported based on the Investigator and Vascular Technologist's assessment (site reported).

At each study visit subjects were examined and specifically assessed for the occurrence specific symptoms or events as defined in the protocol. Reporting of safety events was verified by monitoring procedure-specific and systemic adverse events. Adverse event analyses were compared across groups.

2. Accountability of PMA Cohort

At the time of database lock, of 242 patients enrolled in the PMA study, 85.5% (207) patients are available for analysis at the completion of the 12 month post-operative study visit. The study enrollment is presented in **Table 10**.

Table 10: VeClose Study Subject Disposition

	Roll-In Phase	Randomized Phase		All
Visit	**VenaSeal**	**VenaSeal**	**RFA**	
Day 0	20	108	114	242
Day 3	20 (100%)	108 (100%)	114 (100%)	242 (100%)
Month 1	20 (100%)	105 (97.2%)	110 (96.5%)	235 (97.1%)
Month 3	19 (95.0%)	104 (96.3%)	108 (94.7%)	231 (95.5%)
Month 6	17 (85.0%)	101 (93.5%)	105 (92.1%)	223 (92.1%)
Month 12	17 (85.0%)	95 (88.0%)	95 (83.3%)	207 (85.5%)
Active Subjects	17 (85.0%)	99 (91.7%)	106 (93.0%)	222 (91.7%)
Discontinued/Withdrawn prior to Month 3	1 (5.0%)	2 (1.9%)	4 (3.5%)	7 (2.9%)
Discontinued Subjects To Date	3 (15.0%)	9 (8.3%)	8 (7.0%)	20 (8.3%)

Notes: Fisher's exact test for number discontinued/withdrawn prior to Month 3 is p=0.6839 across randomized groups and p=0.4020 between VenaSeal randomized and roll-in groups. Fisher's exact test for number discontinued/withdrawn prior to Month 12 is p=0.8031 across randomized groups and p=0.3991 between VenaSeal randomized and roll-in groups.

3. Study Population Demographics and Baseline Parameters

The demographics and baseline parameters of the study population are typical for a varicose vein study performed in the US (see **Tables 11-14**). 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 11: 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 12: 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 13: 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 14: 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			

4. 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).

5. Safety and Effectiveness Results

a. 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

A total of 42.2% of VenaSeal-treated subjects (9 roll-in and 45 randomized) and 34.2% of 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. **Table 15** presents a summary of all AEs reported in this study.

Table 15: Summary of Adverse Events

	Roll-in Phase		Randomized Phase			
	VenaSeal (n=20)	Event n	VenaSeal (n=108)	Event N	RFA (n=114)	Event n
Deaths	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
Unanticipated Adverse Device Effect	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0
Serious Adverse Event	1 (5.0%)	1	3 (2.8%)	3	4 (3.5%)	4
Any Adverse Event	9 (45.0%)	12	45 (41.7%)	63	39 (34.2%)	56

There have been no reports of deep venous thrombosis (DVT) occurring on the study limb or pulmonary embolus (PE) in the study. As shown above, there were 8 SAEs in total and all were determined to be unrelated to the procedure or treatment by the Data Safety and Monitoring Board (DSMB) and the Clinical Events Committee (CEC). These SAEs include 2 neoplasms (thyroid cancer – VenaSeal; breast cancer –RFA) and 1 instance each of ischemic colitis, acute myocardial infarction in a patient with a history of coronary disease, cellulitis due to a pre-existing condition, bone pain due to pre-existing osteoarthritis, small intestinal obstruction, and orthostatic hypertension.

In addition, there have been no deaths or unanticipated adverse device effects reported and, to date, there have been no reported allergic reactions to the VenaSeal adhesive (cyanoacrylate).

The incidence of clinically-relevant Adverse Events by Study-Specific Dictionary is presented in **Table 16.** The incidence of paresthesia occurring in the treatment zone was 2.8% for the VenaSeal group and 2.6% for the RFA group; all cases were resolved or improved by 3 months. 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. Other adverse events not referenced in the tables below include hyperpigmentation, stocking irritation, and other AEs not associated with the target limb or procedure (dizziness, nausea, musculoskeletal pain, etc.).

Table 16: 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

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 17**).

Table 17: 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.

Phlebitis and superficial vein thrombophlebitis are commonly reported side effects in vein treatments, including VenaSeal and RFA. Phlebitis (combining all reports of in the treatment zone and not in the treatment zone) was the most common target GSV related adverse event reported in the study. In both groups phlebitis/superficial vein thrombophlebitis events typically occurred within the first 30 days as a result of the inflammatory phase of the vein healing post-procedure in the RFA group and the foreign body response in the VenaSeal group. 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 not in the treatment zone that underwent a procedure to drain the coagulum.

b. 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 18 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 18: 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 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). Statistical 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 19**. No effect of gender on the primary effectiveness endpoint was found.

Table 19: 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 Endpoints

Secondary endpoints were:

1. **Pain experienced during the procedure.** Pain during the procedure was reported by the subject immediately after the study procedure on a 0-10 numeric rating scale (NRS), where 0 represents no pain whatsoever and 10 represents worst imaginable pain.
2. **Ecchymosis along the treated area at Day 3**. Ecchymosis along the treated area was reported by the Investigator using the scale shown in **Table 20**. For this assessment, the treatment area is defined as the area of skin overlying the treated vein, excluding the 5 cm of skin immediately adjacent to the access site.

Table 20: Scale for Ecchymosis Assessment

Rating	Definition
0	None
1	<25%
2	25-50%
3	50-75%
4	75-100%
5	Extension above or below the treatment segment

Pain and ecchymosis were selected as secondary endpoints due to their importance to subject's undergoing treatment for varicose veins. **Table 21** summarizes the results of the secondary endpoints. Study data supported one of the two study's secondary endpoints. There was less bruising (ecchymosis) in the treatment area for subjects treated with VenaSeal system compared to RFA. This outcome is likely because RFA, unlike the

VenaSeal procedure, requires tumescent anesthesia. Injections of tumescent anesthesia puncture small veins and varicosities while the needle is advanced into the fascial plane. Additionally the target vein can be punctured during this process. Both of these can produce subcutaneous hemorrhage, resulting in ecchymosis. Both VenaSeal and RFA subjects reported very low pain levels. There was no statistically significant difference for the secondary effectiveness endpoint of pain during the procedure.

Table 21 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 Analyses

As a result of effective closure following treatment with VenaSeal, the source of reflux is eliminated. Thus, clinical symptoms related to venous reflux disease and quality of life scores improve (VCSS, AVVQ, EQ-5D).

VCSS: At baseline all subjects had a VCSS indicative of symptomatic venous reflux disease. At the first post-procedure visit (Day 3) the VCSS decreased, indicating improvement in venous disease. Improvements in VCSS were seen over time in subjects, as shown in Figure 1 below (numbers indicate sample size per group).

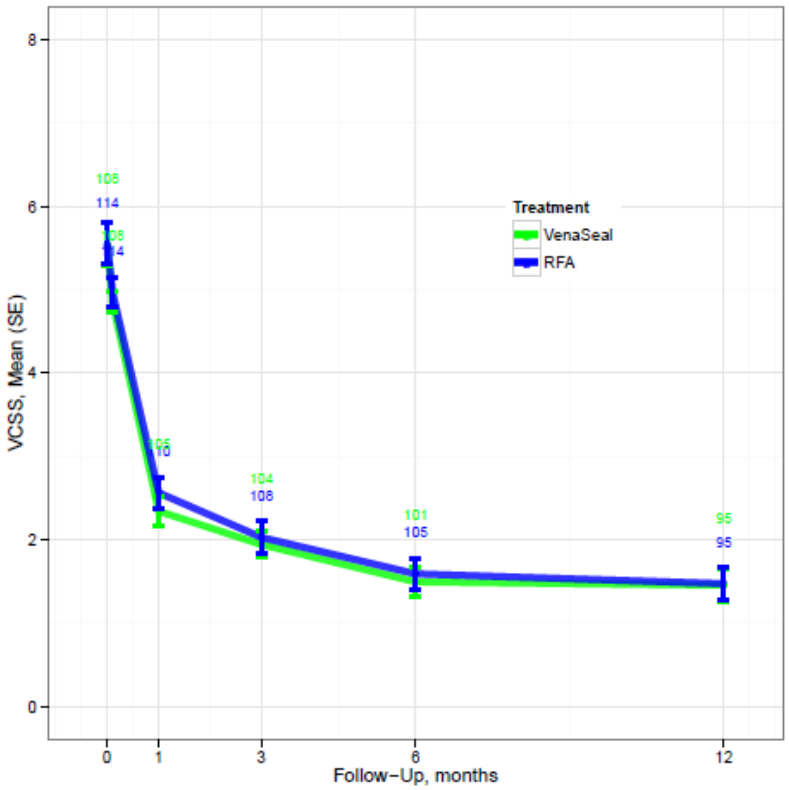

Figure 1 VCSS Scores Over Time

AVVQ: Subjects reported similar impact of their venous disease on QoL, with a mean AVVQ score at baseline of approximately 19. Over time subjects reported a decrease in AVVQ score, indicating lessening impact of venous disease on QoL (**Table 22**).

Table 22: AVVQ Total Score (CC Population)

Visit	VenaSeal			RFA		
	N	Mean (SD)	Mean Change from Baseline (SD)	N	Mean (SD)	Mean Change from Baseline (SD)
Baseline	107	18.9 (9.0)	--	111	19.4 (9.9)	--
Month 1	102	12.0 (7.1)	-6.7 (7.4)	109	12.6 (8.3)	-6.5 (8.7)
Month 3	104	11.6 (7.5)	-7.3 (8.1)	108	10.7 (8.6)	-8.3 (9.0)
Month 6	100	10.2 (7.2)	-8.8 (6.7)	105	9.1 (6.9)	-10.0 (8.8)
Month 12	95	9.8 (7.0)	-8.8 (7.5)	90	8.4 (6.2)	-10.1 (8.4)

EQ-5D: Subjects were generally in a good overall health status as baseline (mean 83.5 VenaSeal and 84.9 RFA) and reported small improvements over time.

NSAID use: As reported at Day 3, 15.7% and 19.3% of VenaSeal and RFA subjects took a NSAID in the previous 24 hours. For these subjects, the total dose of NSAID taken in the previous 24 hours ranged from 200-1800 mg.

CEAP: All subjects had a Clinical classification status of C2 or higher at baseline and improvement was seen over time (more subjects with C0 or C1), as shown in **Table 23** below.

Table 23: CEAP Status (Unblinded CC Population)

Clinical Category	VenaSeal				RFA			
	Baseline (n=108)	**Month 3 (n=104)**	**Month 6 (n=101)**	**Month 12 (n=95)**	**Baseline (n=114)**	**Month 3 (n=108)**	**Month 6 (n=105)**	**Month 12 (n=95)**
C0	0 (0%)	2 (1.9%)	20 (19.8%)	13 (13.7%)	0 (0%)	4 (3.7%)	12 (11.4%)	9 (9.5%)
C1	0 (0%)	25 (24.0%)	41 (40.6%)	48 (50.5%)	0 (0%)	32 (29.6%)	48 (45.7%)	49 (51.6%)
C2	61 (56.5%)	56 (53.8%)	27 (26.7%)	22 (23.2%)	64 (56.1%)	60 (55.6%)	34 (32.4%)	28 (29.5%)
C3	32 (29.6%)	10 (9.6%)	4 (4.0%)	3 (3.2%)	36 (31.6%)	4 (3.7%)	3 (2.9%)	1 (1.1%)
C4a	13 (12.0%)	11 (10.6%)	9 (8.9%)	9 (9.5%)	12 (10.5%)	7 (6.5%)	7 (6.7%)	7 (7.4%)
C4b	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	2 (1.8%)	1 (0.9%)	1 (1.0%)	1 (1.1%)

Device Failures and Replacements:
No technical complications or device malfunctions were reported in the VenaSeal procedures (0/128, 0%). There were a total of 5 intra-procedural technical complications in RFA subjects (5/114, 4.4%). In 4 RFA procedures technical complications were reported (i.e., cases which required the use of additional devices and their maneuvers). In one additional RFA procedure, the Investigator had difficulty placing the 7 Fr access introducer. However, all RFA procedures were subsequently successfully completed.

6. Financial Disclosure (VeClose Study)

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 10 active investigational sites. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

B. Supplemental Clinical Information

1. Feasibility Study

The Feasibility study was a prospective, single-arm, single center feasibility study conducted at the Canela Clinic (La Romana, Dominican Republic) in two enrollment phases, referred to as DR-1 (8 subjects) and DR-2 (30 subjects). Following treatment, subjects were followed at 24-72 hours post-procedure and at 1, 3, 6, 12, 24 and 36 months. A duplex ultrasound was performed at each follow-up visit from the saphenofemoral junction (SFJ) to the distal treatment point on each subject. Target GSV closure was assessed by Investigator assessment of duplex ultrasounds. Success was defined as duplex ultrasound proven vein closure along the entire treated vein segment with no discrete segments of patency ≥ 5 cm. During follow up, 2 subjects presented with recanalization of more than a 5 cm length at 1 and 3 months respectively. The rate of closed target GSV at 6 months (defined study endpoint) was 94.7%, and no subsequent recanalizations occurred during the follow-up period (up to 36 months). A cumulative occlusion rate of 95% - 97% at 12 months after treatment is comparable to contemporary thermal ablation results[4,5]. VCSS quickly improved in all 38 subjects of this study and the improvement persisted through 12 months follow-up with an average improvement from 6.1 (± 2.7) at baseline to 1.5 (± 1.5) at 12 months. A total of 24 adverse events were reported in 17 of the 38 subjects (44.7%). No deaths or serious treatment related adverse events occurred. There was 1 episode of DVT, reported at day 934; however, given the late onset of the DVT, the study's Medical Monitor assessment was that the event was unrelated to both the study device and study procedure and was idiopathic. Additionally, this subject was diagnosed as hypercoagulable with a protein C deficiency. Overall adverse events were mild or moderate and typical for subjects undergoing an endovenous procedure.

2. eSCOPE Study

The European Sapheon Closure System Observational Prospective (eSCOPE) study is an ongoing prospective, multicenter single-arm post-market clinical trial. Following treatment, 70 subjects were followed at 24-72 hours post-procedure and at 1, 3, 6, 12, 24 and 36 months. The primary effectiveness endpoint was closure of the target GSV as measured by duplex ultrasound by Month 6 and assessed by the study investigator. Complete closure was defined as no discrete segment of patency > 10 cm. During follow-up, 5 subjects showed a > 10 cm opening of the target GSV (24-72 hours: 2 cases, 3 months: 2 cases, and 6 months: 1 case). Using life-table methods, the 12-month closure rate was 92.9% (95% CI 87.0 – 99.1%), which met the pre-defined requirement for study success. There were no failures after month 6. No serious and device related adverse events were reported in the study. Through completion of 12 month follow-up visits, 33

4 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.

5 van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. *J Vasc Surg*. 2009;49(1):230-9.

adverse events have been reported in 20 subjects. One unrelated serious adverse event has been reported in the study (prostate cancer). Adverse events related directly to the procedure or study device were light or moderate in severity; the majority occurred within 15 days post treatment and most resolved quickly.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Non-clinical testing performed during the design and development of the VenaSeal system confirmed the product design characteristics, specifications, and intended use. In all studies the VenaSeal system operated as intended, vessels remained closed, and the performance characteristics for the product components and outcomes were acceptable. The results of this testing demonstrate that the VenaSeal system is designed to be effective for its intended use.

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. The non-inferiority (10% delta) of VenaSeal to RFA for complete closure of the target GSV at 3 months was established. The primary endpoint hypothesis test was performed using the ITT population and missing values were imputed using several pre-specified models (LOCF, pessimistic, optimistic and predictive). Additionally, a complete case (CC) cohort analysis was also performed. All pre-specified models and the CC cohort demonstrated non-inferiority of VenaSeal system to RFA (**Table 24**).

Table 24: 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 for the risk difference (from SAS PROC FREQ)..
[c] Asymptotic p-value for superiority test from StatExact Proc.

Two secondary effectiveness endpoints were also evaluated. There was less bruising (ecchymosis) in the treatment area for subjects treated with VenaSeal compared to RFA (p=0.0013). There was no significant difference in subject-reported pain during treatment (mean pain score of 2.16 for VenaSeal, 2.35 for RFA; p=0.5359).

In addition, 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 as assessed by clinical sites.

B. Safety Conclusions

Non-clinical testing performed for the VenaSeal system including biocompatibility and simulated-use testing. These design and development studies were essential in establishing the product design characteristics and specifications. In all studies of the VenaSeal system, the healing response and immunological reactions were acceptable. The results of this testing demonstrates that the VenaSeal system is designed to be safe for its intended use.

Although the study was not statistically powered for safety as ablation techniques of the varicose veins are relatively benign procedures with very few serious adverse events, the primary safety endpoint of this study was the occurrence rate of each of the following specific adverse events: deep venous thrombosis (DVT), clinically significant pulmonary embolus (PE), paresthesia, skin burn, skin ulceration and infection/cellulitis. There were no deaths or unanticipated adverse device effects observed in any of the studies. The primary safety concern was incidence and rate of DVT and PE. There have been no incidents of PE in the 3 clinical studies. There was a DVT reported in the Feasibility

study, occurring at 31 months post-VenaSeal treatment and was assessed by the study's Medical Monitor to be idiopathic. There was also a DVT reported in the VeClose study, occurring in the non-study limb of a RFA-treated subject. The most common adverse events (phlebitis) were mild and self-limited, and the incidence in the VenaSeal treated cohorts was infrequent and similar to the laser ablation devices. In the clinical studies, type, frequency and severity of adverse events observed across all three clinical studies are consistent with that for typical thermal ablation treatments for venous reflux disease.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in the VeClose study as well as the two OUS studies. This data was used to support PMA approval. The use of VenaSeal to treat venous reflux disease in the GSV, a superficial truncal vein, resulted in high closure rates, and these results are consistent with the reported closure success rates with thermal ablation treatments (i.e., RFA, EVLA). In addition, the VenaSeal device addresses some downsides associated with current thermal ablation technologies such as less bruising (ecchymosis) and rapid return to normal activities without the need for compression stockings following treatment. The risks are similar to RFA, which is currently the standard of care and control group used for the VeClose study.

In conclusion, given the available information above, the data support that for use in the treatment of lower extremity symptomatic varicose veins, the probable benefits of the VenaSeal Closure System outweigh the probable risks.

D. Overall Conclusions

Results of the randomized, prospective, multi-center clinical trial demonstrated that the VenaSeal Closure System was non-inferior to RFA control with respect to three-month primary effectiveness endpoint, and similar to the RFA control with respect to safety.

The non-clinical studies indicate that the VenaSeal Closure System meets or exceeds safety and performance specifications.

Data from non-clinical testing and the clinical trial provide a reasonable assurance that the VenaSeal Closure System is safe and effective for use in the treatment of lower extremity symptomatic varicose veins when used in accordance with its labeling.

XIII. 13. CDRH DECISION

CDRH issued an approval order on February 20, 2015. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facility(ies) has/have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. 14. APPROVAL SPECIFICATIONS

Directions for use: See device labeling. *(See General hints)*

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.