SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name: Vascular Hemostasis Device

Device Trade Name: Matrix VSG™ System

Applicant: AccessClosure, Inc.
645 Clyde Avenue
Mountain View, CA 94043

Premarket Approval Application (PMA) Number: P040044

Date of Panel Recommendation: None

Date of Notice of Approval to Applicant: AUG 17 2005

II. Indications for Use

The Matrix VSG™ System is indicated for use to seal femoral arterial access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F, or 7F procedural sheath.

III. Contraindications

There are no known contraindications for the Matrix VSG™ System.

IV. Warnings and Precautions

The Warnings and Precautions can be found in the Matrix VSG™ System labeling.

V. Device Description

A. Materials and Configuration

Matrix VSG™ System Components

The Matrix VSG™ System is comprised of a polyethylene glycol (PEG) hydrogel that is delivered extra vascularly using a balloon catheter to seal femoral arterial access site punctures. The Matrix VSG™ System is provided sterile in a sealed pouch and consists of a Polymer Kit and a Catheter Kit. The system components are:

- Polymer Kit contains the polymer precursor powders to produce the synthetic polyethylene glycol (PEG)

- Catheter Kit contains
  - Balloon catheter
  - Buffer syringe assembly containing borate and phosphate buffers
  - Tensioner
  - Inflation/Deflation syringe
  - Static mixer
  - Insertion sleeve

B. Principles of Operation for the Matrix VSG™ System:

At the end of the endovascular procedure (diagnostic or interventional), the Matrix VSG intravascular balloon catheter is inserted through the existing introducer sheath in the femoral artery to provide temporary hemostasis at the arteriotomy site. Upon deployment, the balloon catheter temporarily seals the arteriotomy from inside the artery. The two synthetic polyethylene glycol (PEG) powder precursors are reconstituted with the appropriate buffers provided in the pre-filled syringes. The reconstituted liquid precursors are then drawn up into the precursor delivery syringes and injected through the introducer sheath at the arteriotomy site and into the subcutaneous tissue tract. The two precursor solutions crosslink at the arteriotomy site and within the tissue tract to form a flexible and tissue-adherent sealant that provides local hemostasis. After delivery of the precursors and subsequent formation of the hydrogel, the balloon catheter is deflated and removed along with the introducer sheath. The formed hydrogel will resorb completely within 30 days.

VI. Alternative Practices and Procedures

Alternative practices for achieving hemostasis of the femoral artery puncture site post-catheterization include manual compression, mechanical compression, collagen-based hemostasis devices, and percutaneous delivery of sutures to the femoral artery access site. Pressure dressings and sandbags are routinely used in combination with compression methods to control oozing.

VII. Marketing History

The Matrix VSG™ System has not been marketed in the United States or any foreign country.

VIII. Potential Adverse Effects of the Device on Health

The Matrix VSG™ System, Model 100-CM5, was evaluated in a controlled, multi-center, randomized clinical trial designed to evaluate the safety and effectiveness of the device in sealing femoral arterial access sites when compared to compression. The study was conducted in the United States at 13 institutions involving 500 patients randomized to

either Matrix VSG™ System or manual compression using a 2:1 ratio. Of the 500 randomized patients, 336 (67%) were randomized to the device and 164 (33%) were randomized to standard compression. Of the patients randomized to the device, 168 patients (50%) underwent diagnostic catheterization procedures and 168 patients (50 %) underwent interventional catheterization procedures. Of the patients randomized to standard compression, 83 patients (51%) underwent diagnostic catheterization procedures and 81 patients (49%) underwent interventional catheterization procedures. Patients eligible for participation included candidates for early ambulation and patients who were clinically indicated for a diagnostic or an interventional endovascular procedure involving access through the femoral artery using a 5F, 6F, or 7F sheath.

Table 1 summarizes the Major and Minor complications (Event-Based) reported for all patients during the 30-day follow-up period. Tables 2 & 3 stratify the patients to Diagnostic or Interventional procedure.

Table 1 Reported Major and Minor Complications (Event-Based) All Patients

Complication	Matrix (n=336) % (n)	Compression (n=164) % (n)	p-value
Major Complications:[1]			
Pseudoaneurysm requiring intervention[2]	0.3% (1)	0.0% (0)	1.00
Leg Ischemia	0.3% (1)	0.0% (0)	1.00
Localized Infection Treated with IV Antibiotics	0.3% (1)	0.0% (0)	1.00
Inflammation Treated with IV Antibiotics or Extended Hospitalization[3]	1.2% (4)	0.0% (0)	0.31
Total	2.1% (7)	0.0% (0)	0.10
Minor Complications:[1]			
Pseudoaneurysm not requiring treatment	0.6% (2)	0.0% (0)	1.00
Pseudoaneurysm treated with thrombin injection	0.9%(3)	0.0% (0)	0.55
Hematoma ≥ 6 cm	1.2% (4)	0.6% (1)	1.00
Bleeding Requiring > 30 min Compression	0.0% (0)	0.6% (1)	0.33
Bleeding Following Hospital Discharge	0.3% (1)	0.0% (0)	1.00
Ipsilateral Lower Extremity Emboli	0.3% (1)	0.0% (0)	1.00
Ipsilateral Deep Vein Thrombosis	0.3% (1)	0.0% (0)	1.00
Inflammation Treated with PO Antibiotics	1.5% (5)	0.0% (0)	0.18
Total	5.1% (17)	1.2% (2)	0.04

[1] Those protocol-stipulated major and minor complications that are not listed in the table did not occur in either the Matrix or the compression patients

[2] Pseudoaneurysm requiring ultrasound guided compression

[3] Treatment with IV antibiotics (n=3) or treatment with oral antibiotics and re-hospitalization for incision and drainage (n=1)

Table 2 Reported Major and Minor Complications (Event-Based) Diagnostic Patients

Complication	Matrix (n=168) % (n)	Compression (n=83) % (n)	p-value
Major Complications:[1]			
Pseudoaneurysm requiring intervention	0.0% (0)	0.0% (0)	NA
Leg Ischemia	0.0% (0)	0.0% (0)	NA
Localized Infection Treated with IV Antibiotics	0.0% (0)	0.0% (0)	NA
Inflammation Treated with IV Antibiotics or Extended Hospitalization	1.2% (2)	0.0% (0)	1.00
Total	1.2% (2)	0.0% (0)	1.00
Minor Complications:[1]			
Pseudoaneurysm not requiring treatment	0.6% (1)	0.0% (0)	1.00
Pseudoaneurysm treated with thrombin injection	0.0% (0)	0.0% (0)	NA
Hematoma ≥ 6 cm	0.6% (1)	1.2% (1)	0.55
Bleeding Requiring > 30 min Compression	0.0% (0)	0.0% (0)	NA
Bleeding Following Hospital Discharge	0.6% (1)	0.0% (0)	1.00
Ipsilateral Deep Vein Thrombosis	0.0% (0)	0.0% (0)	NA
Inflammation Treated with PO Antibiotics	1.2% (2)	0.0% (0)	1.00
Total	3.0% (5)	1.2% (1)	0.67

[1] Those protocol-stipulated major and minor complications that are not listed in the table did not occur in either the Matrix or the compression patients

Table 3 Reported Major and Minor Complications (Event-Based) Interventional Patients

Complication	Matrix (n=168) % (n)	Compression (n=81) % (n)	p-value
Major Complications:[1]			
Pseudoaneurysm requiring intervention	0.6% (1)	0.0% (0)	1.00
Leg Ischemia	0.6% (1)	0.0% (0)	1.00
Localized Infection Treated with IV Antibiotics	0.6% (1)	0.0% (0)	1.00
Inflammation Treated with IV Antibiotics or Extended Hospitalization	1.2% (2)	0.0% (0)	1.00
Total	3.0% (5)	0.0% (0)	0.18
Minor Complications:[1]			
Pseudoaneurysm not requiring treatment	0.6% (1)	0.0% (0)	1.00
Pseudoaneurysm treated with thrombin injection	1.8% (3)	0.0% (0)	0.55
Hematoma ≥ 6 cm	1.8% (3)	0.0% (0)	0.55
Bleeding Requiring > 30 min Compression	0.0% (0)	1.2% (1)	0.33
Bleeding Following Hospital Discharge	0.0% (0)	0.0% (0)	NA
Ipsilateral Lower Extremity Emboli	0.6% (1)	0.0% (0)	1.00
Ipsilateral Deep Vein Thrombosis	0.6% (1)	0.0% (0)	1.00
Inflammation Treated with PO Antibiotics	1.8% (3)	0.0% (0)	0.55
Total	7.1% (12)	1.2% (1)	0.07

[1] Those protocol-stipulated major and minor complications that are not listed in the table did not occur in either the Matrix or the compression patients

The combined rate of major complications was the primary safety endpoint of the trial. A major complication was defined as vascular repair: surgically treated or permanent nerve injury at the access site: access site-related transfusion: any new ipsilateral lower extremity ischemia: access site-related infection treated with intravenous (IV) antibiotics or extended hospitalization: inflammatory reaction treated with IV antibiotics, surgical intervention, or extended hospitalization: and generalized infection or septicemia treated with IV antibiotics. There were seven (7) reported major complications in the Matrix group compared to no reports of major complications in the compression group.

The combined rate of minor complications was the secondary safety endpoint. A minor complication was defined as pseudoaneurysm or AV fistula not requiring treatment, pseudoaneurysm treated with thrombin injection, hematoma ≥ 6 cm, access site-related bleeding requiring > 30 minutes to re-achieve hemostasis, late access site-related bleeding, ipsilateral lower extremity arterial emboli, transient loss of ipsilateral lower extremity pulse, ipsilateral deep vein thrombosis, transient access site-related nerve injury, access site-related vessel laceration, access site wound dehiscence, access site infection treated with intramuscular or oral antibiotics, and access site inflammation treated with oral antibiotics. There were seventeen (17) reports of minor complications in the Matrix group compared to two (2) in the compression group.

None of the complications were considered unanticipated events. The observed rates of major and minor complications support the trial hypotheses that the combined rate of major complications and the combined rate of minor complications for the Matrix arm are non-inferior to those of the compression group. There were no deaths during the study.

Potential complications of allergic reaction, foreign body reaction, nerve injury, bleeding requiring transfusion, vessel laceration or wound dehiscence were not observed during this study.

IX. Summary of Preclinical Studies

Bench and *In-vitro* Device Characterization Testing

A. Biocompatibility

Biocompatibility testing of the Matrix VSG™ System was conducted in accordance with FDA's-modified matrix of ISO 10993-1, "Biological Evaluation of Medical Devices, Part 1 Evaluation and Testing". As seen in the Table 4 below, all testing passed and results concluded that the Matrix VSG™ System is non-toxic, non-sensitizing, non-irritant, non-mutagenic, non-hemolytic and non-pyrogenic.

Table 4 Matrix VSG™ System Biocompatibility Tests and Results

Biocompatibility Test Test Article – Matrix VSG Polymer Catheter	Specification	Result
Cytotoxicity Study using ISO Elution Method (*in vitro*)	No evidence of cell lysis or toxicity	PASS

Maximization Sensitization Study (*in vivo*)	No evidence of causing delayed dermal contact sensitization in the guinea pig	PASS
Intracutaneous Reactivity Study (*in vivo*)	No evidence of significant irritation	PASS
USP and ISO Systemic Toxicity Study (*in vivo*)	No mortality or evidence of systemic toxicity	PASS
Genotoxicity Bacterial Reverse Mutation Assay (DMSO Extract and Saline Extract) (*in vitro*)	Non-mutagenic to *Salmonella typhimurium*	PASS
Genotoxicity Chromosomal Aberration Study (*in vitro*)	Non-genotoxic to Chinese Hamster Ovary cells in the presence or absence of S9 metabolic activation	PASS
Genotoxicity. Mouse Bone Marrow Micronucleus Study (*in vitro*)	No clastogenic activity, negative in the micronucleus Non-genotoxic to the mouse	PASS
Subcutaneous Implantation Study 2, 4, and 6 week. (*in vivo*)	Nonirritant, more than half absorbed at 2 weeks and completely absorbed by 4 weeks	PASS
Hemolysis Study (Modified ASTM-Extraction Method) (*in vitro*)	Non-hemolytic	PASS
Pyrogenicity - Catheter only	Non-pyrogenic	PASS

B. Functionality

A series of *in-vitro* tests were conducted to characterize the mechanical performance of the Matrix VSG™ System. Results from the mechanical tests demonstrated that the Matrix VSG™ System met the acceptance criteria for each test. See Tables 5 & 6 for the testing and results.

Table 5 Matrix VSG™ System Functional Test Table

Item	Test	Sample Size	MX100 (PS0760) Acceptance Criteria per PS0760 or as specified	Results
Packaging Integrity				
1	Seal Strength Integrity Catheter Pouches	30	≥ 1.0 lbf/in	LCL = 1.47 mm ACI LCL = 6.14 mm Vendor PASS
2	Seal Strength Integrity Polymer Pouches	30	1.0 lbf/in	LCL = 2.55 mm ACI LCL = 2.35 mm Vendor PASS
3	Packaging Leak Test Catheter Pouches	10	No Bubbles	9 passed, 1 failed
4	Packaging Leak Test Polymer Pouches	10 elevated dose	No Bubbles	PASS
Catheter Functional Testing				
5	Balloon OD	30/10 normal/elevated dose	6.00 ± 0.25 mm measured at nominal pressure range (30 - 40 psi)	LCL = 5.80 mm UCL = 6.14 mm Mean = 5.95 mm SD = 0.04 mm PASS
6	Balloon Length	30/10 normal/elevated dose	3 - 7 mm - measured at nominal pressure range (30 - 40 psi)	LCL = 4.0 mm UCL = 5.6 mm Mean = 4.8 mm SD = 0.26 mm

Item	Test	Sample Size	MX100 (PS0760) Acceptance Criteria per PS0760 or as specified	Results
				PASS
7	Balloon Crossing Profile	30/10 normal elevated dose	0.035" Max	UCL = 0.035" Mean = 0.034" SD = 0.0005" PASS
8	Distal Shaft OD	30/10 normal elevated dose	0.021" Max	UCL = 0.020 Mean = 0.019 SD = 0.0002 PASS
9	Proximal Shaft OD	30/10 normal elevated dose	0.065" Max	UCL = 0.058" Mean = 0.057" SD = 0.0004" PASS
10	Length (hub to proximal balloon)	30/10 normal/elevated dose	18 cm Min	LCL = 19.9 cm Mean = 20.1 cm SD = 0.09 cm PASS
11	Length (distal marker to proximal balloon)	30/10 normal/elevated dose	13.5 cm Max	UCL = 12.6 cm Mean = 12.5 cm SD = 0.07 cm PASS
12	Balloon Inflation Time	30/10 normal/elevated dose	≤ 3 seconds	UCL = 0.8 sec Mean = 0.70 sec SD = 0.05 sec PASS
13	Balloon Deflation Time	30/10 normal/elevated dose	≤ 3 seconds	UCL = 1.09 sec Mean = 0.87 sec SD = 0.06 sec PASS
14	System Fatigue (Catheter & Syringe)	30/10 normal/elevated dose	4 inflation/deflation cycles to 30-40 psi	All units passed 10 cycles
15	Inflated Balloon Tensile	30/10 normal/elevated dose	Shall withstand 1 lbf load for 1 minute	PASS
16	Catheter Rupture Strength	30/10 normal/elevated dose	≥ 60 psi	LCL = 101 psi Mean = 115 psi SD = 5.4 psi PASS
17	Catheter Tensile Strength – All critical joints	30/10 normal/elevated dose	≥ 5 N	All joints PASS
Tensioner, Mixer, Syringe				
18	Tensioner Spring Rate	30/10 normal/elevated dose	0.12 ± 0.01 lbf/cm	LCL = 0.12 lbf/cm UCL = 0.13 lbf/cm Mean = 0.13 lbf/cm SD = 0.003 lbf/cm PASS
19	Tensioner Joint Tensile Strength (Top Foot & Wire form Snap)	30/10 normal/elevated dose	10 N	All PASS
20	Mixer Tensile Strength	30/10 normal/elevated dose	≥ 15 N	LCL = 41 N Mean = 47 N SD = 2.8 N PASS
21	Syringe Pullout Integrity	30/10 normal/elevated	30 N	LCL = 404 N Mean = 413 N

Item	Test	Sample Size	MX100 (PS0760) Acceptance Criteria per PS0760 or as specified	Results
		dose		SD 16 % PASS
Polymer Kit				
22	Gel Time	29/10 normal elevated dose	t=0 minutes after reconstitution 3.5sec	LCL 4.4 sec Mean 5.1 sec SD 0.62 sec PASS
		(One unit lost due to handling)	t=15 minutes after reconstitution 8.5 sec	LCL 8.0 sec Mean 6.6 sec SD 0.97 sec PASS
23	Gel Volume	30/10 normal elevated dose	Post reconstitution precursor syringe must contain ≥ 2.0cc	All PASS

Table 6 Comparative Balloon Rupture Test Data Functional Test Table

	MX-100 (new version) (TPR1246-02)	**100-CM5 (original) (TPR0671)**
Mean	118 psi	104 psi
σ	5.4 psi	6.1 psi
Min	105	92 psi
Max	128	116 psi
n	30	15
Failure Mode	Balloon material failure	Balloon material failure

C. Animal Studies

A series of acute and chronic animal studies were performed to characterize the safety and effectiveness of the Matrix VSG System. Ovine and porcine models were used to evaluate vascular and physiologic responses to the Matrix VSG System. The peripheral and vasculature and cardiovascular system in these animal species are well suited and understood with respect to the study of interventional cardiology devices. The availability of these species is adequate and the sizes of the major vascular structures such as femoral arteries are appropriate. The studies were performed at two institutions. Several characterization studies were performed.

One chronic study was performed to characterize the dilution sensitivity profile of the PEG polymer where post procedure angiograms indicated an absence of polymerization of the PEG polymer in flowing blood. There were no reports of any abnormalities or adverse events.

A second study was performed to measure the activated clotting time (ACT) of porcine blood spiked with amine and ester precursor solutions compared to control. The purpose of the study was to characterize the effect (if any) that each of the precursor solutions has on the ACT in these conditions. Both amine and ester precursor solutions met the acceptance criteria as there is no statistical difference between the test articles and control. Based on the results of this

study, the inadvertent introduction of the amine or ester precursor solutions into flowing blood should not modify ACTs in a clinical setting.

A third study was conducted to evaluate the inadvertent intravascular injection of the Matrix hydrogel into the tissue tract. There were no post procedural events when the mixed precursor solutions were injected in the femoral arteries in both acute and chronic timeframes. Creatinine phosphokinase (CPK) levels did not indicate any permanent tissue damage.

An acute study was conducted to validate the modifications to the Matrix VSG System by evaluating safety and efficacy parameters including ease of use factors There was no evidence of intra or post procedural major events and the time to hemostasis met the acceptance criteria.

D. Cadaver Study

The purpose of the cadaver study was to characterize the dispersal pattern of the Matrix VSG System hydrogel following injection into the tissue surrounding an arteriotomy. The results from this study indicated that larger amounts of hydrogel were evident immediately above the femoral artery and the hydrogel dissipated to smaller amounts as the sections progressed further proximally and distally. The hydrogel appeared to be well-integrated into the existing anatomy.

E. Sterilization and Shelf Life

The Polymer Kit and Catheter Kit are sterilized separately using electron beam irradiation. The system has been validated and approved for a 9 month shelf life

X. Clinical Studies

A. Matrix VSG System Single Center European Trial

A total of 55 patients were enrolled in this study with data available for 52 patients and 3 patients were lost to follow-up. Five patients were considered as roll-in patients. The objectives of this investigation were to assess the safety and performance of the Matrix VSG device to achieve hemostasis of femoral arterial access sites following diagnostic or interventional endovascular procedures. The distribution of patients undergoing diagnostic and interventional procedures were performed 58% and 42% respectively. Patients were evaluated at screening, during the procedure, post-procedure, pre-discharge and underwent a 30 day follow-up (range from 3 to 6 weeks).

Table 7 Single Center European Trial Results

Parameter	Results
Performance (n=50)	
Time to hemostasis (n=48*)	2.72 ± 0.25 minutes
Time to ambulation (n=44*)	2.01 ± 0.09 hours
Procedural success	96% (48/50)
Safety analysis (n=55)	

Major events	0/55 (0%)
Minor events	6/55(10.9%)

*Missing values

Another six (6) patients experienced device-related minor events including pain/discomfort (n=3) and pain/discomfort and CK elevation (n=3). The CK elevations were attributed to the device as no other cause could be identified. Ten (10) patients also experienced pain/discomfort or other minor adverse events that were either considered as related to the endovascular procedure or the relationship was undetermined.

B. Matrix VSG System Multi-Center European Trial

A prospective study was conducted at three investigational sites in Europe to evaluate the performance and safety of the Matrix VSG System following diagnostic or interventional endovascular procedures. A total of fifty-eight (58) patients were treated with the Matrix VSG™ System, data was available for 57 patients and 10 patients were part of roll-in phase of the study.
Patients were evaluated at screening, procedure, post-procedure, pre-discharge, and three to six-week follow-up.

Table 8 Multi Center European Trial Results

Parameter	Results
Performance (n=47)	
Time to hemostasis	3.11 ± 3.3 minutes
Time to ambulation	2.00 ± 0.57 hours
Procedural success	89.4% (42/47)
Safety analysis (n=57)	
Major events	2/57 (3.5%)
Minor events	11/57(17.5%)

The two major events included one case of peripheral arterial occlusion and one case of pseudoaneurysm requiring vascular repair.

C. Matrix VSG System U.S. IDE Multi-Center, Randomized Clinical Trial

The Matrix VSG System IDE trial was a prospective, multi-center, randomized clinical investigation to evaluate the safety and effectiveness of the Matrix VSG System, Model 100-CM5, to achieve hemostasis in femoral arterial access sites in patients undergoing percutaneous endovascular procedures using a 5, 6, or 7F sheath. Patients were randomized based on a 2:1 ratio into a treatment group which received the Matrix VSG System (n=336) or a control group treated with standard compression methods (n=164). Patients were further stratified based on the type of catheterization procedure so that each group included 50% diagnostic and 50% interventional procedures.

Enrollment at 13 investigational sites was initiated in December 2003 and the final randomized patient was enrolled in July 2004. The primary safety endpoint

was the combined rate of major complications within 30 days (± 7) and the primary effectiveness endpoints included time to hemostasis and ambulation. Secondary endpoints included time to hospital discharge and discharge eligibility, and combined rate of minor complications within 30 days (± 7)

Patients were required to be at least 18 years of age, to have signed an Informed Consent Form, and to have undergone a catheterization procedure through the femoral artery. Patients were excluded if they presented with clinically significant peripheral vascular disease; prior procedure in the ipsilateral common femoral artery < 30 days; known allergy to contrast medium or device materials; a myocardial infarction ≤ 72 hours prior to procedure, uncontrolled hypertension; existing bleeding disorder; common femoral artery diameter < 6.5 mm; pre-existing hematoma, intraluminal thrombus, pseudoaneurysm, AV fistula, or any type of dissection; fibrotic, calcified, or > 50% stenotic femoral artery; puncture below or at the common femoral artery bifurcation, or in the profunda femoris or superficial femoral artery; pre-existing bleeding around the arterial sheath; ipsilateral venous sheath; multiple arterial sticks; suspected posterior femoral arterial wall puncture; antegrade puncture; ACT > 350 seconds at the conclusion of the endovascular procedure; current treatment with glycoprotein IIb/IIIa inhibitors; or planned extended hospitalization.

Demographics

The majority of the patients were male [72.4% (362/500)] with all patients' ages ranging from 28.4 to 87.8 years. Of the 500 patients enrolled, 50% were diagnostic patients and the remaining 50% were interventional patients. With respect to the baseline patient demographic data, patient risk factors, concomitant therapy, and procedural variables, the two study groups are very similar. There were no statistically significant differences with respect to the variables included in the analysis of the two groups. The two groups are both representative of the patient population undergoing endovascular diagnostic or interventional procedures (Table 9).

Table 9 - Patient Demographic Data

	MATRIX	Standard Compression	p-value
Male	71.7% (241/336)	73.8% (121/164)	ns
Age (mean ± standard deviation)	64.1±11.5 (336)	64.0±13.2 (164)	ns
Body Mass Index (mean ± standard deviation)	28.5±4.3 (336)	29.3±4.8 (164)	ns
Diabetes	23.8% (80/336)	18.3% (30/164)	ns
Tobacco Use Within Last 6 Months	17.9% (60/336)	17.1% (28/164)	ns
History of Cardiovascular Disease	63.4% (213/336)	56.1% (92/164)	ns
History of Peripheral Vascular Disease	5.4% (18/336)	5.5% (9/164)	ns
History of Renal Failure	1.2% (4/336)	2.4% (4/164)	ns
Hypertension Requiring Medication	67.0% (225/336)	70.1% (115/164)	ns
Ankle Brachial Index (mean ± standard deviation)	1.1±0.2 (304)	1.1±0.2 (150)	ns
Femoral Bruit	1.5% (5/335)	1.2% (2/163)	ns

Access Site			
-Left Femoral Artery	14.3% (48/336)	10.4% (17/164)	ns
-Right Femoral Artery	85.7% (288/336)	89.6% (147/164)	
ACT at End of Procedure (mean ± standard deviation)	244.2±79.7 (222)	237.5±77.5 (102)	ns
Sheath Size			ns
-5F	13.7% (46/336)	12.8% (21/164)	
-6F	74.1% (249/336)	76.2% (125/164)	
-7F	12.2% (41/336)	11.0% (18/164)	

ns = not significant

Safety Data

In this clinical study, safety of the Matrix VSG System was evaluated through a comparison of various safety endpoints between the Matrix VSG System (treatment) and the Standard Compression (control) groups. The combined rate of major complications was the primary safety endpoint. The combined rate of minor complications was the secondary safety endpoint. Additionally, other adverse events and effectiveness measures were also evaluated during the Matrix VSG System clinical study. An independent Clinical Events Committee (CEC) adjudicated all reported complications. Table 1 displays the combined rate of major complications and the combined rate of minor complications comparing the Matrix treatment group to the control group.

Overall the primary safety endpoint hypothesis for this study was tested by placing a one-sided 95% upper confidence bound on the observed difference in the combined rate of major complications (Matrix VSG System rate minus the standard compression rate) using exact methods. An upper confidence bound of less than 5.0% supported that the combined major complication rate for the Matrix VSG System was non-inferior to that of standard compression. In the Matrix VSG System IDE study, the difference in rates between the Matrix VSG System group and the standard compression groups was 2.1% with an upper 95% confidence bound of 3.9% and therefore the Matrix VSG System treatment group was determined to be non-inferior to the standard compression control group. For the combined minor complication rate, the difference in rates between the two study groups was 3.9%. The p-value for the difference in combined major complication rates between the two study groups was 0.10 which indicates that the difference is not statistically or clinically significant. The p-value for the difference in combined minor complication rates between the two study groups was 0.04, which indicates that the difference is statistically significant. However, this statistically significant difference is not clinically significant since individually there were no clinically significant differences in the rates of minor complications. In conclusion, the results observed in the Matrix VSG System IDE trial established that the Matrix VSG System treatment group is non-inferior to the standard compression group with respect to the rate of major complications. The observed complication rates reported in the study were within the expected range and the primary safety endpoint in the study was met.

Effectiveness Data

The results of the effectiveness measures are summarized in Table 10 for all study patients. Table 11 & 12 include the effectiveness measures for patients undergoing diagnostic procedures and patients undergoing interventional procedures, respectively

Table 10 Effectiveness Results All patients

Effectiveness Measures	Matrix* n=336	Compression* n=164	P-value
Time to Hemostasis (mins)	n=335	n=161	
Mean ± SD	5.3 ± 13.4	25.4 ± 16.2	<0.0001
Median (25th, 75th)	2.0 (2.0,3.0)	20.0 (15.0, 30.0)	<0.0001
Range (min, max)	(1.0, 165.0)	(6.0, 120.0)	
Time to Ambulation (hrs)	n=336	n=160	
Mean ± SD	3.9 ± 6.1	7.4 ± 4.8	0.0001
Median (25th, 75th)	2.1 (2.0, 2.7)	6.0 (4.5, 7.4)	0.0001
Range (min, max)	(1.0, 71.8)	(1.6, 26.9)	
Time to Discharge - Actual (hrs)	n=334	n=160	
Mean ± SD	19.6 ± 26.3	20.1 ± 36.1	0.87
Median (25th, 75th)	18.1 (4.1, 24.0)	14.8 (6.3, 22.0)	0.21
Range (min, max)	(1.7, 216.6)	(2.6, 404.8)	
Time to Discharge Eligibility (hrs)	n=330	n=159	
Mean ± SD	14.7 ± 21.5	13.0 ± 11.5	0.25
Median (25th, 75th)	5.6 (3.1, 21.2)	7.3 (5.5, 18.9)	<0.005
Range (min, max)	(1.7, 214.1)	(2.4, 106.9)	

*The number of patients used to calculate effectiveness measures differ from overall study sample size due to missing values

Table 11 Effectiveness Results Diagnostic patients

Effectiveness Measures	Matrix n=168	Compression n=83	P-value
Time to Hemostasis (mins)	n=168	n=83	
Mean ± SD	3.6 ± 6.3	23.6 ± 17.1	<0.0001
Median (25th, 75th)	2.0 (2.0,3.0)	19.0 (14.0, 25.0)	<0.0001
Range (min, max)	(1.0, 60.0)	(6.0, 120.0)	
Time to Ambulation (hrs)	n=168	n=82	
Mean ± SD	2.7 ± 3.9	5.4 ± 2.7	<0.0001
Median (25th, 75th)	2.1 (2.0, 2.2)	5.2 (4.3, 6.1)	<0.0001
Range (min, max)	(1.0, 52.1)	(1.6, 26.9)	
Time to Discharge - Actual (hrs)	n=167	n=82	
Mean ± SD	8.8 ± 19.4	17.3 ± 47.6	0.13
Median (25th, 75th)	4.2 (3.2, 5.5)	6.3 (5.4, 7.3)	<0.0001
Range (min, max)	(1.7, 192.3)	(2.6, 404.8)	
Time to Discharge Eligibility (hrs)	n=166	n=83	
Mean ± SD	5.5 ± 10.9	9.6 ± 13.7.5	0.02
Median (25th, 75th)	3.1 (2.6, 4.2)	6.0 (4.9, 6.7)	0.001
Range (min, max)	(1.7, 214.1)	(2.4, 106.9)	

Table 2 Efficacy Results – Interventional patients

Effectiveness Measures	Matrix	Compression	P-value
	n=168	n=81	
Time to Hemostasis (mins)	n=167	n=78	
Mean ± SD	7.1 ± 17.8	27.3 ± 15.2	0.0001
Median (25th, 75th)	2.0 (2.0, 4.0)	25.0 (19.0, 30.0)	
Range (min, max)	(1.0, 165.0)	(10.0, 120.0)	
Time to Ambulation (hrs)	n=168	n=78	
Mean ± SD	5.1 ± 7.4	9.4 ± 5.6	0.0001
Median (25th, 75th)	2.2 (2.0, 4.4)	7.1 (5.5, 11.8)	
Range (min, max)	(1.3, 71.8)	(2.5, 22.3)	
Time to Discharge - Actual (hrs)	n=167	n=78	
Mean ± SD	30.3 ± 28.0	23.0 ± 16.9	0.13
Median (25th, 75th)	23.5 (20.4, 26.3)	20.6 (17.0, 23.4)	
Range (min, max)	(3.8, 216.6)	(3.0, 140.0)	
Time to Discharge Eligibility (hrs)	n=164	n=76	
Mean ± SD	24.0 ± 25.3	16.7 ± 6.8	< 0.0001
Median (25th, 75th)	20.7 (17.8, 23.6)	17.5 (13.5, 20.6)	
Range (min, max)	(1.9, 214.1)	(3.0, 38.4)	

Time to hemostasis and time to ambulation were the primary effectiveness endpoints of the trial. Time to hemostasis was defined as the time from sheath removal to when hemostasis was first observed. Time to ambulation was defined as the time from sheath removal to the time a patient walks at least 20 feet. The mean ± standard deviation (median) time to hemostasis was 5.3 ± 13.4 minutes (2 minutes) for the Matrix VSG group compared to 25.4 ± 16.2 minutes (20 minutes) for the compression group with $p < 0.0001$. The mean ± standard deviation (median) time to ambulation was 3.9 ± 6.1 hours (2 hours) for the Matrix VSG group compared to 7.4 ± 4.8 hours (6 hours) for the compression group with $p < 0.0001$. These results support the study hypotheses that the Matrix VSG System reduced the time to hemostasis and ambulation when compared to standard compression.

Time to discharge and discharge eligibility were secondary effectiveness endpoints of the trial. Time to discharge was defined as the time from sheath removal to hospital discharge. Time to discharge eligibility was defined as the time from sheath removal to the time when the patient is medically able to be discharged based solely on the assessment of the access site, as determined by the patient's physician. The mean ± standard deviation (median) time to discharge for the Matrix VSG group was 19.6 ± 26.3 hours (18.1 hours) compared to 20.1 ± 36.1 hours (14.8 hours) for the compression group with $p = 0.87$. The mean ± standard deviation (median) time to discharge eligibility for the Matrix VSG group was 14.7 ± 21.5 hours (5.6 hours) compared to 13.0 ± 11.5 hours (7.3 hours) for the compression group with $p = 0.25$

Table 13 includes the cumulative time to hemostasis, ambulation, discharge, and discharge eligibility for the two study groups

Table 13 Cumulative Distributions of Time Variables

VARIABLE	MATRIX	Standard Compression
Time to Hemostasis		
≤ 2 min	66.9% (224/335)	0.0% (0/161)
≤ 5 min	85.7% (287/335)	0.0% (0/161)
≤ 10 min	89.9% (301/335)	5.0% (8/161)
≤ 15 min	94.9% (318/335)	26.7% (43/161)
≤ 20 min	96.4% (323/335)	53.4% (86/161)
≤ 50 min	98.5% (330/335)	94.4% (152/161)
Time to Ambulation		
≤ 2 hours	14.9% (50/336)	1.3% (2/160)
≤ 3 hours	77.7% (261/336)	3.8% (6/160)
≤ 4 hours	81.5% (274/336)	12.5% (20/160)
≤ 5 hours	87.5% (294/336)	35.6% (57/160)
≤ 10 hours	93.8% (315/336)	83.8% (134/160)
≤ 24 hours	98.5% (331/336)	99.4% (159/160)
Time to Actual Hospital Discharge		
≤ 2 hours	0.3% (1/334)	0.0% (0/160)
≤ 3 hours	7.5% (25/334)	1.3% (2/160)
≤ 4 hours	22.8% (76/334)	3.1% (5/160)
≤ 5 hours	35.3% (118/334)	11.3% (18/160)
≤ 10 hours	45.8% (153/334)	44.4% (71/160)
≤ 24 hours	75.1% (251/334)	85.0% (136/160)
≤ 48 hours	93.4% (312/334)	94.4% (151/160)
Time to Discharge Eligibility		
≤ 2 hours	4.2% (14/330)	0.0% (0/159)
≤ 3 hours	23.6% (78/330)	1.3% (2/159)
≤ 4 hours	38.5% (127/330)	3.8% (6/159)
≤ 5 hours	47.0% (155/330)	17.6% (28/159)
≤ 10 hours	54.2% (179/330)	54.1% (86/159)
≤ 24 hours	87.3% (288/330)	92.5% (147/159)
≤ 48 hours	96.1% (317/330)	99.4% (158/159)

Procedure success was defined as successfully achieving hemostasis using any method with freedom from major complications. Device success was defined as the ability to deploy the Matrix VSG delivery system, inject the Matrix VSG precursors, and achieve hemostasis at the femoral artery puncture site. Table 14 includes a summary of procedure and device success for the two study groups The procedure success rate was 97.9% for the Matrix VSG group and 100% for the control group, demonstrating no statistically significant difference between the two groups (p=0.10). The device success rate for the Matrix VSG group was

90.5%. Procedure and device success rates are also stratified by type of endovascular procedure (diagnostic versus interventional procedure)

Table 14 Procedure and Device Success

Effectiveness Measures	Matrix	Compression	P-value
All Patients			
Device Success	90.5% (304/336)		
Procedure Success	97.9% (329/336)	100% (164/164)	0.10
Diagnostic Patients			
Device Success	94.0% (158/168)		
Procedure Success	98.8% (166/168)	100% (83/83)	1.00
Interventional Patients			
Device Success	86.9% (146/168)		
Procedure Success	97.0% (163/168)	100% (81/81)	0.18

Gender Bias Analysis

A higher number of male patients were enrolled in the study (72.4%) male vs. (27.6%) female, which is a reflection of the general referral pattern for patients undergoing interventional and diagnostic procedures. There were no statistically significant differences in the rates of major or minor complications between genders. There were no statistically significant differences in time to hemostasis, ambulation, discharge, or discharge eligibility between genders.

XI. Conclusions Drawn from Studies

Results of the biocompatibility testing, *in vitro* bench testing, animal studies, cadaver study and clinical investigations provide valid scientific evidence and reasonable assurance that the Matrix VSG System is safe and effective when used in accordance with its Instructions for Use. The safety of the device has been demonstrated by the fact that the incidence of major complications in the randomized clinical investigation was equivalent for both treatment arms (Matrix VSG System compared to standard compression). The effectiveness of the Matrix VSG System was demonstrated by a significant reduction in the times to hemostasis and ambulation in both diagnostic and interventional patients treated with the Matrix VSG System compared to those treated with standard compression. In addition, diagnostic patients treated with the Matrix VSG System had a significant reduction in time to discharge eligibility. Thus, valid scientific evidence demonstrates that the Matrix VSG System is safe and effective for achievement of hemostasis at the femoral access site post diagnostic and interventional catheterization procedures performed via a 5, 6, or 7 Fr sheath when used in accordance with device labeling.

XII. Panel Recommendation

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 the panel.

XIII. CDRH Decision

FDA performed an inspection of the manufacturing facilities on August 2 and 3, 2005, and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820). FDA issued a PMA approval letter to AccessClosure, Inc. on August 17, 2005.

XIV. Approval Specifications

A. Instructions for Use: See the labeling.

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

C. Post Approval Requirements and Restrictions: See approval order.