SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Vascular Closure Device

Device Trade Name: Closer Vascular Sealing System (VSS)

Device Procode: MGB

Applicant's Name and Address:

Rex Medical, L.P.
555 E. North Lane, Suite 5035
Conshohocken, PA 19428

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150022

Date of FDA Notice of Approval: February 12, 2016

II. INDICATIONS FOR USE

The Closer VSS is indicated for percutaneous closure of femoral arterial access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular catheterization procedures utilizing 5, 6, or 7Fr procedural sheaths.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Rex Medical Closer VSS labeling.

V. DEVICE DESCRIPTION

1. Materials and Configuration

The Closer VSS consists of the 1) Closer Delivery System and the 2) Closer Access Kit (Dilator and Insertion Sheath), as shown in Figure 1. The Closer VSS delivers a fully absorbable sealing mechanism to the femoral arterial puncture site. The sealing mechanism consists of an intravascular patch (the sealing member) and 2 extravascular spheres connected via 2 strands of sutures. After deployment, the patch will remain intravascular,

and the 2 spheres will remain extravascular until absorbed. Hemostasis is achieved by mechanical means of the patch closing the arteriotomy from the inside of the puncture. The Closer VSS features a self-tightening mechanism that facilitates proper technique for delivery and deployment of the absorbable mechanism.

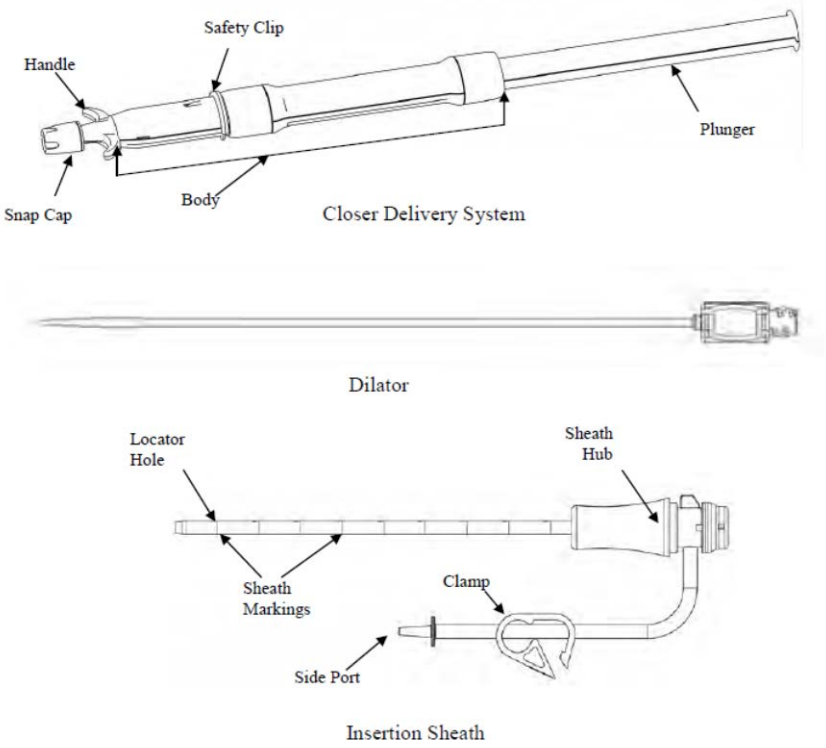

Figure 1. Closer VSS (Delivery System and Access Kit)

2. Operation

After completion of a diagnostic or interventional endovascular procedure, the existing procedural sheath is exchanged for the Closer VSS Insertion Sheath. The delivery system is then connected to the sheath. When the plunger is depressed on the delivery system, the patch is deployed inside the femoral artery. Once the patch is deployed, the sheath/delivery system is pulled out of the access site. During the removal process, the patch engages with the vessel wall. Next, the extravascular components (Spheres) are released from the delivery system into the extravascular tissue tract. The delivery system then applies tension on the sutures to tighten the spheres down to the vessel wall; the system tightens down each sphere individually minimizing the force exerted on the vessel wall. Once this operation is completed, hemostasis is achieved. When the spheres are tightened down to a predetermined load, the sutures are automatically released from the system. The delivery system achieves the entire deployment and tightening sequence while the user is removing the sheath/delivery system from the access site. The patch and spheres absorb within 90 days and the sutures absorb within 180 days.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for attaining hemostasis at an arterial puncture site post-catheterization including manual or mechanical compression, percutaneous suture delivery, PEG-based hemostatic devices, collagen plugs with resorbable foot plate, and staples. Pressure dressings and sandbags are routinely used in combination with compression methods to control oozing. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Closer VSS has not been marketed in the United States or any foreign country.

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 device:

- Access site closure-related bleeding requiring transfusion
- Vascular injury requiring repair (via surgery, ultrasound guided compression, transcatheter embolization or stent graft)
- New ipsilateral lower extremity ischemia causing a threat to the viability of the limb and requiring surgical or endovascular intervention, documented by subject symptoms, physical exam, and/or a decreased or absent blood flow on lower extremity angiogram
- Access site closure-related infection requiring intravenous antibiotics and/or extended hospitalization
- New onset access site closure-related neuropathy in the ipsilateral lower extremity requiring surgical repair
- Permanent access site closure-related nerve injury (> 30 days).
- Access site closure-related bleeding requiring greater than 30 minutes of continual manual compression to achieve initial arterial hemostasis
- Access site closure-related hematoma $\geq$ 6 cm
- Late access site closure-related arterial bleeding (following hospital discharge)
- Ipsilateral lower extremity arterial emboli
- Ipsilateral deep vein thrombosis
- Access site closure-related vessel laceration
- Access site wound dehiscence
- Localized access site infection treated with intramuscular or oral antibiotics
- Arteriovenous fistula not requiring treatment
- Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection
- Pseudoaneurysm not requiring treatment

- New onset of transient access site closure-related neuropathy in the ipsilateral lower extremity that is transient (≥ 24 hours and ≤ 30 days) and does not require surgical repair.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Bench testing was performed in accordance with design verification test protocols that were developed to verify that the device meets product specifications. Testing included the following:

Table 1: Engineering Testing

Purpose	Test	Acceptance Criteria	Results
Test the Vessel wall locator function of the system	Vessel Locator Flow Rate test	1) Sheath Tip seals on the Dilator, 2) Flow rate > 15 ml/min	Pass
Implant clamping force post deployment	Resorbable Implant Retention Strength	≥ 0.35lbf	Pass
Device deployment	Performance Testing Report	No complications or malfunctions during deployment.	Pass
Implant break test	Performance Testing Report	≥ 3.0 lbf	Pass
Sheath Joint Strength	Closure Sheath Strength and Integrity Test	ISO 11070	Pass
Sheath liquid leak Test	Closure Sheath Strength and Integrity Test	ISO 11070	Pass
Extravascular component failure force	Ball Countersink Breaking Force	≥ 3.0 lbf	Pass
Suture break test	Suture Elongation and Break Test	≥ 3.0 lbf	Pass
Drying requirement	Exposure Time/Dry Time Moisture Content Study	≤ 72 hrs	Pass
Packaging determination	Suture Tray/Lid Break Force Test	Comparison test between 2 packaging methods	N/A
Test the insertion of Dilator and sheath into mock vessel	Dilator/Sheath transition test	Smooth transition with no hangups	Pass

To evaluate the ability of the product to withstand exposure to temperatures at or above 98.2 °F (36.7°C) for 6 hours or more	Closer Device Elevated Temperature Exposure Test	Implant Performance & break test criteria must pass	Pass
To evaluate polymer degradation at multiple time points in accordance with ISO 15814	30 day degradation study	Parts remain intact over 30 day period	Pass

B. Sterilization

The Closer VSS Delivery System is sterilized using gamma radiation sterilization and has been validated per ANSI/AAMI/ISO 11137-2: 2012: "Sterilization of Health Care Products Radiation-Part 2: Establishing the sterilization dose." Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The Closer VSS Access Kit is sterilized using ethylene oxide (EO) sterilization and has been validated per AAMI/ISO 11135:2007 "Medical Devices Validation and Routine Control of Ethylene Oxide Sterilization." Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the amount of EO residual and bacterial endotoxins was verified to be within the specifications limits.

C. Biocompatibility

Biocompatibility testing was performed in accordance with ISO 10993-1. The Closer access kit and part of the delivery system is classified as an external communicating device that is in contact with circulating blood for limited exposure (less than 24 hours) following an arterial catheterization procedure. The patch and spheres are classified as an implant device for tissue/bone contact for a permanent duration (greater than 30 days) that has the potential for direct contact with circulating blood. Per ISO 10993-01, the following tests were performed on the Closer VSS delivery system and access kit:

Table 2: Biocompatibility Testing

Closer Device Introducer Sheath and Delivery System		
Biocompatibility Test	**Standard Method**	**Results**
Cytotoxicity	ISO 10993-5	Pass - Non-cytotoxic
Hemolysis	ISO 10993-4	Pass - Non-hemolytic
Complement Activation (C3a Assay)	ISO 10993-4	Pass - Non-activating
Complement Activation (SC5b-	ISO 10993-4	Pass - Non-activating

9 Assay)		
Maximum Sensitization	ISO 10993-10	Pass – Non-sensitizing
Intracutaneous Irritation Reactivity	ISO 10993-10	Pass - Non-Irritant
Acute Systemic Toxicity	ISO 10993-11	Pass - No mortality or evidence of systemic toxicity
Material Mediated Pyrogenicity	ISO 10993-11	Pass - Non-pyrogenic

Biocompatibility Summary for the Implantable Components		
Biocompatibility Test	**Standard Method**	**Results**
Cytotoxicity	ISO 10993-5	Pass - Non-cytotoxic
Maximum Sensitization	ISO 10993-10	Pass – Non-sensitizing
Intracutaneous Irritation Reactivity	ISO 10993-10	Pass - Non-Irritant
Acute System Toxicity	ISO 10993-11	Pass - No evidence of systemic toxicity
Subchronic Toxicity	ISO 10993-11	Pass - No evidence of toxicity
In Vitro Mouse Lymphoma	ISO 10993-3	Pass - Non-mutagenic
Bacterial Reverse Mutation Study	ISO 10993-3	Pass - Non-mutagenic
Mouse Peripheral Blood Micronucleus Study	ISO 10993-3	Pass - extracts do not induce micronuclei
Muscle Implantation Study (2 weeks)	ISO 10993-6	Pass – Non-irritating
Muscle Implantation Study (6 weeks)	ISO 10993-6	Pass – Non-irritating
Muscle Implantation Study (26 weeks)	ISO 10993-6	Pass – Non-irritating
Hemolysis	ISO 10993-4	Pass - Non-hemolytic
Partial Thromboplastin	ISO 10993-4	Pass - No evidence of coagulation abnormalities in the intrinsic pathway
Complement Activation (C3a Assay)	ISO 10993-4	Pass - Non-activating
Complement Activation (SC5b-9 Assay)	ISO 10993-4	Pass - Non-activating
Chronic Toxicity	ISO 10993-6	Pass – Non-toxic

All tests were successfully completed and all acceptance criteria were met for the delivery system, access kit and implant material. In conclusion, the biocompatibility testing performed on the Closer VSS device demonstrated that the requirements of ISO 10993-1 have been met.

D. Packaging Testing

The Closer VSS packaging was evaluated in accordance with ANSI/AAMI/ISO 11607 – part 1:2006. Testing included accelerated aging, testing of physical distribution environmental stresses, including testing for environmental conditioning, shock, vibration and compression hazards; evaluation of package strength using physical strength methods; and validation testing of package sterility using physical integrity detection, applying the appropriate standards.

The device passed the packaging simulations and confirmed the sterile barrier integrity and minimum seal strength for the Closer VSS packaging per the stated standard test methods. Following the shipping simulations, it was confirmed that the Closer VSS meets the performance specifications.

E. Shelf-life Testing

The Closer VSS Delivery System was evaluated to support a shelf life of four months. Devices were real time aged in a temperature controlled area for 120 Days. The testing demonstrated that devices that were aged for four months met the functional, visual, and performance requirements. No anomalies were found during testing. The Access Kit was exposed to accelerated aging to a time point of 180 Days per ASTM F1980-07. The aged samples were able to pass all acceptance criteria. As a result of the testing performed on the Closer VSS and packaging, the device is currently labeled with a shelf life of 4 months.

F. Animal Studies

GLP animal studies were performed to evaluate the acute and chronic performance of the Closer VSS in an ovine model. The table below shows the GLP animal studies performed with the Closer VSS, number of animals tested and survival time points. Studies were performed to evaluate the acute and chronic performance of the Closer VSS in an ovine model after access with a 6Fr & 7Fr procedural sheath. The delivery system performance and handling and the ability of the Closer VSS to achieve and maintain hemostasis were evaluated during the procedure. The animals were monitored for any adverse events during the survival period. The vascular and physiological response as well as the implant resorption was examined via histopathological evaluation at each survival time point. The outcome was compared to manual compression control. All animals achieved hemostasis with the Closer VSS device, and the studies were completed without major device related incidents or complications. The time to hemostasis for the Test Device was significantly shorter than for the control. The intravascular portion of the implant was completely resorbed between 60 and 90 days. The implant was completely resorbed by 180 days. The data support the overall safety of the device when used to perform vascular closure procedures in an animal model. The studies also demonstrate that the implant material safely biodegrades over time with no toxic effects.

Table 3: GLP Animal Study Timepoint Summary

Study type	Number of Animals	Length of study w/Timepoints
6 Fr Procedural sheath	Minimum of 6 animals at each time point	7, 30, 60, 90 and 180 day survival & evaluation time Point
7 Fr Procedural sheath	6 animals at each time point	7 and 30 day survival & evaluation time point

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of vascular closure with the Closer VSS device following endovascular procedures in the US under IDE # G130213. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between May 20, 2014 and January 28, 2015. The database for this PMA reflected data collected through February 27, 2015 and included 220 patients. There were 11 investigational sites.

The study was a multi-center, prospective, single-arm clinical study. The study was designed to evaluate the safety and effectiveness of Closer VSS in sealing femoral arterial access sites and specifically to facilitate hemostasis and ambulation, in comparison to Performance Goals based on historical manual compression (MC) data. The study population was defined as subjects undergoing cardiac or peripheral diagnostic or interventional catheterization procedures via the femoral artery approach when using a standard 5F, 6F or 7F introducer sheath. Of the 220 enrolled patients, there were 50 consecutive patients enrolled into an Ultrasound sub-study.

An independent combination Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) (the same group, designated as the Data Safety Monitoring Committee or DSMC) was responsible for systematic review and adjudication of any reported deaths, access site closure-related major or minor complications, and all potentially device- or procedure-related adverse events (i.e., events eligible for review). A core lab was used to independently evaluate the ultrasound sub-study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Closer VSS Trial was limited to patients who met the following pre-operative inclusion criteria:

1. 18 to 80 years of age
2. Provides informed consent and agrees to 30 day follow-up requirements

3. Acceptable candidate for an elective, non-urgent diagnostic or interventional endovascular procedure using a 5, 6 or 7 Fr introducer sheath, via femoral approach
4. Acceptable candidate for blood transfusion and/or emergent vascular surgery if necessary.

Patients were not permitted to enroll in the Closer VSS Trial if they met any of the following pre-operative exclusion criteria:

1. Evidence of active systemic infection
2. Pre-existing immunodeficiency disorder
3. Known allergies to polylactic acid (PLA), polyglyocolic acid (PGA) or polydioxanone (PDO) polymers
4. Significant history of bleeding diathesis or coagulopathy, or baseline platelet count < 100,000 cells/mm3, or baseline INR > 1.8 for subjects on warfarin
5. Baseline serum creatinine > 2.5 mg/dl
6. Baseline hemoglobin < 10 g/dl or hematocrit < 30%
7. Severe co-morbidities resulting in a life expectancy of less than 90 days
8. Currently involved in any other investigational clinical trials
9. Planned endovascular or surgical procedure within the next 30 days, prior to study exit
10. Planned ipsilateral femoral arteriotomy within next 90 days
11. Arteriotomy in the ipsilateral groin within the past 30 days with any residual hematoma, significant bruising or known associated vascular complication
12. Previous vessel closure device used in the ipsilateral groin within the past 90 days
13. Previous vascular surgery or repair in the vicinity of the target access site
14. Severe peripheral vascular disease in the ipsilateral limb requiring surgical or endovascular treatment within the previous 30 days or next 30 days, prior to study exit
15. Existing nerve damage in ipsilateral limb
16. Unilateral or bilateral lower extremity amputation(s)
17. Females of child bearing potential who are pregnant, planning to become pregnant within 3 months of the procedure, or lactating
18. Extreme morbid obesity (BMI greater than 45 kg/m2)
19. Unable to ambulate at least 20 feet without assistance at baseline
20. Administration of low molecular weight heparin (LMWH) within 8 hours of procedure

During the operation, patients were not permitted to enroll in the Closer VSS Trial if they met any of the following intra-operative exclusion criteria:

1. Use of an introducer sheath that is less than 5 Fr or greater than 7 Fr in diameter
2. Suspected bacterial contamination of the procedural sheath or surrounding tissues
3. Femoral artery diameter less than 5 mm at access site
4. Presence of arterial stenosis > 50%, anomalous branches, or vessel abnormalities in the vicinity of the access site
5. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, "back wall stick")
6. Angiographic evidence of severe calcium or stent within 1 cm of the puncture site
7. Placement of an ipsilateral venous sheath for procedure
8. Procedural sheath placement either through the superficial femoral artery and into the profunda femoris artery, or placement at or distal to bifurcation of the superficial femoral artery and the profunda femoris artery
9. More than one arterial femoral access site is required
10. Loss of distal pulses in the ipsilateral extremity during the procedure
11. ACT greater than 350 seconds in subjects receiving unfractionated heparin in the absence of a glycoprotein IIb/IIIa inhibitor or greater than 250 seconds in the presence of a glycoprotein IIb/IIIa inhibitor (may wait to remove introducer sheath until ACT level reaches the target value)
12. Intra-procedural bleeding around sheath, and/or suspected vascular complications
13. Procedures that may extend index hospitalization beyond 24 hours post-procedure (e.g., staged endovascular procedure, referred directly to CABG, significant neurovascular procedures, etc.)
14. Existing medical conditions that may extend index hospitalization beyond 24 hours post-procedure (e.g., MI, recurrent CHF, etc.)
15. Systemic hypertension (systolic BP greater than 180 mmHg) or hypotension (systolic BP less than 90 mmHg) just prior to enrollment
16. In the Investigator's opinion, any of the following circumstances are present:
    a. different method should be used to achieve hemostasis of the arterial access site
    b. the subject should not attempt ambulation according to the protocol requirements
    c. the subject may not comply with follow-up requirements for any reason

2. <u>Follow-up Schedule</u>

All patients were scheduled to return for follow-up examinations at 30 ± 7 days postoperatively.

Preoperatively, a medical history was obtained including a record of the subject's demographic (i.e., age, race, sex) and baseline information (i.e., height, weight). Subjects were evaluated for any significant previous history of lower extremity neuropathy in the ipsilateral limb, including an assessment of etiology, existing symptoms and severity, and any endovascular procedures performed within the past 90 days, or planned within the next 90 days. At the end of the endovascular procedure, with the procedural sheath in place and under fluoroscopic visualization, an injection of contrast was made to assess the anatomy of the access site to verify the intra-operative eligibility criteria. Sites were provided with calibrated study timers/clocks and source worksheets to facilitate consistent capture of study times. Postoperatively, the objective parameters measured during the study included any access site-related events or symptoms of lower extremity neuropathy in the ipsilateral limb that were not existing prior to the index procedure (i.e., paresthesias, numbness, weakness), including an assessment of severity. Adverse events and complications were recorded at all visits.

A sub-study was performed utilizing independent analysis of 30-day, non-invasive Duplex ultrasound (DUS) imaging in subjects treated with the Closer device in either diagnostic or interventional procedures. B-mode gray-scale, color Doppler and pulsed spectral Doppler images were obtained of the common femoral artery and veins in an area approximately 4 cm above to 4 cm below the access site to assess for iatrogenic injuries, pseudoaneurysm, hematoma, vessel injury or thrombosis, and arteriovenous fistula.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was the rate of combined access site closure-related major complications within 30 ± 7 days following the catheterization procedure. The secondary safety endpoint was the rate of combined access site closure-related minor complications within 30 ± 7 days following the procedure.

With regards to effectiveness, the primary effectiveness endpoint was time to hemostasis (TTH). The key secondary effectiveness endpoint was time to ambulation (TTA), and remaining secondary endpoints were time to discharge eligibility (TTDE), time to hospital discharge (TTD), procedure success and device success.

B. Accountability of PMA Cohort

At the time of database lock, of 220 patients enrolled in the PMA study, 219 (99.5%) patients were available for analysis at the completion of the study, the 30-day (± 7 days) post-operative visit. Below is an accountability table of the PMA cohort.

Table 4: Accountability of PMA Cohort

Disposition	Totals (number vs. %)	
Number completed study/enrolled	219/220	
Inclusion/Exclusion violation	3	1.4%
Successful device deployment	216	98.2%
Early Termination	1	0.5%
Protocol deviation	0	0
Investigator decision	0	0
Lost to follow-up	1	0.5%
Withdrew consent	0	0

C. Study Population Demographics and Baseline Parameters

1. Demographics and Baseline Parameters

The demographics of the study population are typical for a VCD study performed in the US. Of the 220 enrolled subjects, 109 underwent interventional procedures and 111 underwent diagnostic procedures. The mean age was 63.9 ± 9.5 years. The percentage of female subjects was 31.8% and the mean BMI was 30.3 kg/m^2.

Table 5: Subject Demographics and Baseline Parameters – Pivotal Subjects

	Diagnostic	Interventional	Total
Age			
N	111	109	220
Mean	63.2	64.7	63.9
Std Deviation	10.3	8.7	9.5
Median	65	65	65
Min	26	35	26
Max	80	80	80
Gender			
N	111	109	220
Female	45	25	70
Male	66	84	150
Ethnicity			
N	111	109	220
Hispanic or Latino	6	7	13
Not Hispanic or Latino	91	95	186
Unknown	14	7	21
Race			
N	110	107	217
Asian	4	4	8
Black or African American	6	10	16
Native Hawaiian or Pacific Islander	2	0	2

	Diagnostic	Interventional	Total
White or Caucasian	98	91	189
Unknown	0	2	2
BMI			
N	111	109	220
Mean	30.8	29.8	30.3
Std Deviation	5.7	4.9	5.3
Median	29.8	29.7	29.8
Min	18.3	16.2	16.2
Max	44.8	41.2	44.8
Systolic Blood Pressure			
N	111	109	220
Mean	135.3	133.7	134.5
Std Deviation	18.8	18.9	18.9
Median	135.0	133.0	135.0
Min	91	96	91
Max	179	181	181
Diastolic Blood Pressure			
N	111	109	220
Mean	73.1	73.3	73.2
Std Deviation	13.6	12.6	13.1
Median	72.0	71.0	72.0
Min	47	44	44
Max	113	103	113

2. Medical History

Baseline medical history and risk factors are summarized below.

Table 6: Medical History & Risk Factors

	Diagnostic		Interventional		Total / %	
N	111		109		220	
Hypercholesterolemia/Hyperlipidemia	84	75.7%	97	89.0%	181	82.3%
Hypertension	88	79.3%	84	77.1%	172	78.2%
Atherosclerotic Disease	63	56.8%	91	83.5%	154	70.0%
Coronary Artery Disease	57	51.4%	71	65.1%	128	58.2%
Peripheral Vascular Disease	12	10.8%	25	22.9%	37	16.8%
Carotid Disease	10	9.0%	17	15.6%	27	12.3%
Ever Smoker	59	53.2%	65	59.6%	124	56.4%
Current Smoker	19	17.1%	16	14.7%	35	15.9%
Diabetes Mellitus	35	31.5%	37	33.9%	72	32.7%
Current Treatment	35	31.5%	36	33.0%	71	32.3%
Insulin	7	6.3%	18	16.5%	25	11.4%
Diet	15	13.5%	21	19.3%	36	16.4%

Oral/SQ Hypoglycemics	26	23.4%	25	22.9%	51	23.2%
Lower Extremity Neuropathy in the Ipsilateral Limb	1	0.9%	3	2.8%	4	1.8%
Residual Symptoms or deficit at enrollment	0	0.0%	0	0.0%	0	0.0%
Complaint	0	0.0%	0	0.0%	0	0.0%
Localized	0	0.0%	0	0.0%	0	0.0%
Radiating	0	0.0%	0	0.0%	0	0.0%
Other	0	0.0%	0	0.0%	0	0.0%
Symptoms	0	0.0%	0	0.0%	0	0.0%
Paresthesia	0	0.0%	0	0.0%	0	0.0%
Numbness	0	0.0%	0	0.0%	0	0.0%
Weakness	0	0.0%	0	0.0%	0	0.0%
Pain	0	0.0%	0	0.0%	0	0.0%
Severity	0	0.0%	0	0.0%	0	0.0%
Mild	0	0.0%	0	0.0%	0	0.0%
Moderate	0	0.0%	0	0.0%	0	0.0%
Severe	0	0.0%	0	0.0%	0	0.0%
Clinically Significant	0	0.0%	0	0.0%	0	0.0%
Other significant medical history	82	73.9%	74	67.9%	156	70.9%
Any of the above Risk Factors	107	96.4%	107	98.2%	214	97.3%

3. Anti-coagulants and Antiplatelet Medications

Administration of oral anticoagulant/antiplatelet agents from 48 hours pre-procedure through hospital discharge was reported in 95% of Closer VSS cases, with 51.4% of total subjects receiving two or more oral agents. Over 65% of interventional subjects received bivalirudin. The table below summarizes oral and intravenous/subcutaneous agents by procedure type.

Table 7: Summary of Anti-coagulant and Anti-platelet Agents From 48 Hours Pre-Procedure Through Discharge

Oral Medications	**Diagnostic**		**Interventional**		**Total / %**	
N	111		109		220	
Aspirin	98	88.3%	108	99.1%	206	93.6%
Warfarin	1	0.9%	3	2.8%	4	1.8%
Ticlopidine	0	0.0%	0	0.0%	0	0.0%
Clopidogrel	20	18.0%	72	66.1%	92	41.8%
Prasugrel	1	0.9%	25	22.9%	26	11.8%
Pradaxa	0	0.0%	2	1.8%	2	0.9%
Ticagrelor	0	0.0%	12	11.0%	12	5.5%
Rivaroxaban	1	0.9%	0	0.0%	1	0.5%
Other*	2	1.8%	2	1.8%	4	1.8%
Any Oral Medication	101	91.0%	108	99.1%	209	95.0%
Subjects receiving $\geq$ 2 oral anti-	22	19.8%	91	83.5%	113	51.4%

platelet agents						
Peri-Procedural IV and SQ Medications						
N	111		109		220	
Any GP IIb/IIIa Inhibitors	0	0.0%	1	0.9%	1	0.5%
Integrilin	0	0.0%	0	0.0%	0	0.0%
Aggrastat	0	0.0%	1	0.9%	1	0.5%
ReoPro	0	0.0%	0	0.0%	0	0.0%
Other	0	0.0%	0	0.0%	0	0.0%
Bivalirudin (Angiomax)	2	1.8%	71	65.1%	73	33.2%
Unfractionated Heparin (bolus/infusion)	9	8.1%	39	35.8%	48	21.8%
Unfractionated Heparin (subcutaneous)	1	0.9%	3	2.8%	4	1.8%
Low Molecular Weight Heparin	2	1.8%	4	3.7%	6	2.7%
Any IV/Subcutaneous Medication	**14**	**12.6%**	**108**	**99.1%**	**122**	**55.5%**

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the implanted patient cohort of 219 patients available for the 1-month evaluation. The key safety outcomes and adverse effects are presented in the tables below.

The primary safety endpoint is the 30-day incidence rate of combined access site closure-related major complications. The trial was designed to demonstrate that the major access site closure-related major complication rate met Performance Goals based on historical manual compression (MC) data.

The access site closure-related major complication rate for all Closer VSS pivotal subjects was 0.0% (0/219). The upper limit of the Wilson Score 95% Confidence Interval is well below the Performance Goal of 6%, indicating a rejection of the null hypothesis that Closer VSS's major access site closure-related complication rate is greater than the Performance Goal of 6% ($p<0.0001$). The table below shows an event-based analysis, on an Intent-to-Treat (ITT) basis of the access site closure-related major complications reported in the pivotal Closer VSS subjects.

Table 8: Access Site Closure-Related Major Complications by Procedure Type at 30 Days

Access Site Closure-Related Major Complication	**Diagnostic (N=110)**		**Interventional (N=109)**		**Total (N=219)**	
Any Access Site Closure-Related Major Complication	0	0.0%	0	0.0%	0	0.0%
Wilson-Score, 95% Confidence Interval	0.00%	3.37%	0.00%	3.40%	0.00%	1.72%
Access site closure-related bleeding requiring transfusion	0	0.0%	0	0.0%	0	0.0%
Vascular injury requiring repair (via	0	0.0%	0	0.0%	0	0.0%

surgery, U/S guided compression, transcatheter embolization or stent graft)						
New ipsilateral lower extremity ischemia causing a threat to viability of limb an requiring surgical or endovascular intervention	0	0.0%	0	0.0%	0	0.0%
Access site closure-related infection requiring intravenous antibiotics and/or extended hospitalization	0	0.0%	0	0.0%	0	0.0%
New onset access site closure-related neuropathy in the ipsilateral lower extremity requiring surgical repair	0	0.0%	0	0.0%	0	0.0%
Permanent access site closure-related nerve injury (> 30 days)	0	0.0%	0	0.0%	0	0.0%

*1 diagnostic subject was lost to follow-up, so has been excluded from the denominator.

The combined rate of access site closure-related minor complications was the secondary safety endpoint. Analyses for access site closure-related minor complications were performed to demonstrate that the minor complication rates met predefined clinical acceptance criteria.

The minor complication rates observed in the study were 0/110 (0.0%) for diagnostic subjects and 3/109 (2.75%) for interventional subjects in the ITT population. Observed rates were well below the predetermined clinically acceptable rates of 5.2% for diagnostic subjects and 6.2% for interventional subjects. Table 6 shows an event-based analysis, on an Intent-to-Treat (ITT) basis of the access site closure-related minor complications observed in the pivotal Closer VSS subjects. The only reported minor complications were access site closure-related bleeding requiring > 30 minutes to achieve initial arterial hemostasis which was reported in 3 subjects, 2 of which did not have the patch deployed according to the IFU.

Table 9: Access Site Closure-Related Minor Complications by Procedure Type at 30 Days

Access Site Closure-Related Minor Complications	**Diagnostic[1] (N=110)**		**Interventional[2] (N=109)**		**Total (N=219)**	
Any Access Site Closure-Related Minor Complication	0	0.0%	3	2.75%	3	1.37%
Access site closure-related bleeding requiring > 30 min. of continual manual compression to achieve initial arterial hemostasis	0	0.0%	3	2.75%	3	1.37%
Late access site closure-related arterial bleeding (following hospital discharge)	0	0.0%	0	0.0%	0	0.0%
Access site closure-related hematoma $\geq$ 6 cm	0	0.0%	0	0.0%	0	0.0%
Ipsilateral lower extremity arterial emboli	0	0.0%	0	0.0%	0	0.0%
Ipsilateral deep vein thrombosis	0	0.0%	0	0.0%	0	0.0%
Access site closure-related vessel laceration	0	0.0%	0	0.0%	0	0.0%
Access site wound dehiscence	0	0.0%	0	0.0%	0	0.0%
Localized access site infection treated with intramuscular or oral antibiotics	0	0.0%	0	0.0%	0	0.0%

Arteriovenous fistula not requiring treatment	0	0.0%	0	0.0%	0	0.0%
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection	0	0.0%	0	0.0%	0	0.0%
Pseudaneurysm not requiring treatment	0	0.0%	0	0.0%	0	0.0%
New onset of transient access site closure-related neuropathy in the ipsilateral lower extremity that is transient (≥ 24 hrs. and ≤ 30 days) and does not require surgical repair	0	0.0%	0	0.0%	0	0.0%

[1] 1 diagnostic subject was lost to follow-up, so has been excluded from the denominator.
[2] Includes 1 case of known user error and 1 case of suspected user error, both resulting in failure to deploy the patch and subsequent prolonged hemostasis times.

In the 30-day ultrasound sub-study, an intraluminal defect adherent to the anterior wall of the common femoral artery wall was noted in 14 patients which was felt to be the Closer device as it continued to degrade and considered by the Data Safety Monitoring Committee to be of no clinical significance. All vessels were noted to be patent or < 50% stenosed. In 2 of these patients, the ultrasound exams also showed what the ultrasound core laboratory considered to be an arterial thrombus in the same location. These thrombi were subclinical. One of them was prophylactically treated with warfarin and not seen on a repeat femoral ultrasound done 1 month later and the other was not detected or treated by the site.

2. Effectiveness Results

The analysis of effectiveness was based on the 220 evaluable patients at discharge. Key effectiveness outcomes are presented in the tables below. The study was designed to test the primary null hypothesis that, combined over diagnostic and interventional procedures, the true population mean Closer VSS TTH is equal to or longer than a Performance Goal (PG) established from similar clinical trials for FDA approved vascular closure devices versus the alternative hypothesis that the true mean Closer VSS TTH is shorter than the Performance Goal. Therefore, hypotheses for the primary TTH analysis are as follows:

H_0: population mean Closer VSS TTH – PG ≥ 0,
H_A: population mean Closer VSS TTH – PG < 0,

where PG is specific to procedure type, 17 minutes for diagnostic procedures and 24 minutes for interventional procedures.

The primary effectiveness endpoint was TTH, defined as elapsed time between Closer VSS delivery system removal and first observed arterial hemostasis. The mean TTH for the diagnostic arm was 0.58 minutes (95% confidence interval 0.03-1.13 minutes) and the mean TTH for the interventional arm was 3.01 minutes (95% confidence interval 1.00-5.01 minutes). TTH for Closer VSS was statistically significantly less than predetermined Performance Goals (PG) in all three cases (diagnostic PG 17 min., interventional PG 24 min., and combined) by both t test and Wilcoxon's signed rank test ($p<0.0001$).

The key secondary effectiveness endpoint was TTA, defined as elapsed time between device removal and when subject stands and walks 20 feet without evidence of arterial re-bleeding from the access site. The mean TTA for the diagnostic arm was 1.92 hours (95% confidence interval 1.80-2.05) and the mean TTA for the interventional arm was 3.09 hours (95% confidence interval 1.00-5.01). TTA for Closer VSS was statistically significantly less than predetermined PGs in all three cases (diagnostic PG 6 hrs., interventional PG 11 hrs., and combined) by both t test and Wilcoxon's signed rank test ($p < 0.0001$).

Additional secondary effectiveness endpoints were TTDE, TTD, Procedure Success and Device Success. TTDE was defined as elapsed time between device removal and when subject is medically able to be discharged based solely on access site assessment. The mean TTDE was 2.83 ± 1.54 hours. Discharge eligibility was achieved in < 6 hours in 96.8% of the subjects. TTD was defined as elapsed time between device removal and when the subject was actually discharged from the hospital. The mean TTD was 13.12 ± 16.49 hours. Proportions of subjects achieving TTH, TTA, TTDE and TTD at fixed time points are shown in the tables below.

Table 10: Primary Effectiveness Endpoint TTH Results

Time to Hemostasis (minutes)	Diagnostic (n = 111)	Interventional (n = 109)	Total (n = 220)
Mean ± Standard Dev (95% C.I.)	0.58 ± 2.94 (0.03, 1.13)	3.01 ± 10.58 (1.00, 5.01)	1.78 ± 7.81 (0.74, 2.82)
Median (95% C.I.)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Range (Min, Max)	(0.00, 28.32)	(0.00, 85.28[1])	(0.00, 85.28[1])
Performance Goal (p-value)	17 (< 0.001)	24 (< 0.001)	N/A (< 0.001)

[1] One interventional subject did not have the patch deployed due to user error, resulting in an outlier TTH of 85.28 minutes.

Table 11: Secondary Effectiveness Endpoint TTA Results

Time to Ambulation (hours)	Diagnostic (n = 111)	Interventional (n = 109)	Total (n = 220)
Mean ± Standard Dev (95% C.I.)	1.92 ± 0.67 (1.80, 2.05)	3.09 ± 1.05 (2.89, 3.29)	2.50 ± 1.05 (2.36, 2.64)
Median (95% C.I.)	1.95 (1.80, 2.29)	2.90 (2.80, 3.01)	2.24 (2.14, 2.49)
Range (Min, Max)	(1.01, 6.02)	(1.99, 8.08)	(1.01, 8.08)
Performance Goal (p-value)	6 (< 0.001)	11 (< 0.001)	N/A (< 0.001)

Table 12: Secondary Effectiveness Endpoint TTDE Results

Time to Discharge Eligibility (hours)	Diagnostic (n = 111)	Interventional (n = 109)	Total (n = 220)
Mean ± Standard Dev (95% C.I.)	2.17 ± 0.67 (2.04, 2.29)	3.50 ± 1.86 (3.15, 3.85)	2.83 ± 1.54 (2.62, 3.03)
Median (95% C.I.)	2.16 (1.97, 2.25)	3.19 (3.01, 3.29)	2.51 (2.42, 2.75)
Range (Min, Max)	(1.22, 6.05)	(2.24, 19.32)	(1.22, 19.32)

Table 13: Secondary Effectiveness Endpoint TTD Results

Time to Discharge (hours)	Diagnostic (n = 111)	Interventional (n = 109)	Total (n = 220)
Mean ± Standard Dev (95% C.I.)	4.57 ± 6.35 (3.38, 5.77)	21.83 ± 18.93 (18.24, 25.43)	13.12 ± 16.49 (10.93, 15.32)
Median (95% C.I.)	2.97 (2.65, 3.36)	22.66 (20.86, 23.59)	4.74 (4.04, 6.64)
Range (Min, Max)	(1.44, 53.01)	(2.29, 122.01)	(1.44, 122.01)

Hemostasis was achieved in 0 seconds in 80.5% of Closer VSS subjects. Ambulation was achieved in $\leq$ 4 hours in 93.6% of the subjects.

Table 14: Proportions of Subjects Achieving Arterial Hemostasis at Fixed Time Points, ITT Population

	Diagnostic		Interventional		Total	
N	111		109		220	
0 minutes	97	87.4%	80	73.4%	177	80.5%
≤ 1 minute	103	92.8%	89	81.7%	192	87.3%
≤ 5 minutes	107	96.4%	96	88.1%	203	92.3%
≤ 10 minutes	110	99.1%	99	90.8%	209	95.0%
≤ 15 minutes	110	99.1%	103	94.5%	213	96.8%
≤ 30 minutes	111	100%	106	97.2%	217	98.6%
≤ 60 minutes	111	100.0%	108	99.1%	219	99.6%
≤ 90 minutes[1]	111	100.0%	109	100.0%	220	100.0%

[1] 1 interventional subject did not have the patch deployed due to user error, resulting in an outlier TTH of 85 minutes.

Table 15: Proportions of Subjects Achieving Ambulation at Fixed Time Points, ITT Population

	Diagnostic		Interventional		Total	
N	111		109		220	
≤ 1 hour	0	0.0%	0	0.0%	0	0.0%
≤ 2 hours	69	62.2%	2	1.8%	71	32.3%
≤ 3 hours	105	94.6%	65	59.6%	170	77.3%
≤ 4 hours	109	98.2%	97	89.0%	206	93.6%
≤ 5 hours	110	99.1%	102	93.6%	212	96.4%
≤ 7 hours	111	100.0%	107	98.2%	218	99.1%
≤ 9 hours	111	100.0%	109	100.0%	220	100.0%

Table 16: Proportions of Subjects Eligible for Discharge Based on Access Site Condition at Fixed Time Points, ITT Population

	Diagnostic		Interventional		Total	
N	111		109		220	

≤ 2 hours	47	42.3%	0	0.0%	47	21.4%
≤ 4 hours	109	98.2%	95	87.2%	204	92.7%
≤ 6 hours	110	99.1%	103	94.5%	213	96.8%
≤ 8 hours	111	100.0%	107	98.2%	218	99.1%
≤ 12 hours	111	100.0%	108	99.1%	219	99.6%
≤ 24 hours	111	100.0%	109	100.0%	220	100.0%

Table 17: Proportions of Subjects Discharged from Hospital at Fixed Time Points, ITT Population

	Diagnostic		**Interventional**		**Total**	
N	111		109		220	
≤ 2 hours	15	13.5%	0	0.0%	15	6.8%
≤ 4 hours	84	75.7%	10	9.2%	94	42.7%
≤ 6 hours	99	89.2%	21	19.3%	120	54.6%
≤ 8 hours	102	91.9%	28	25.7%	130	59.1%
≤ 12 hours	105	94.6%	29	26.6%	134	60.9%
≤ 24 hours	109	98.2%	73	67.0%	182	82.7%
≤ 48 hours	110	99.1%	105	96.3%	215	97.7%

3. Device Success

Device Success, defined as the ability to 1) deploy the delivery system, 2) deliver the implant, and 3) achieve hemostasis with the Closer VSS alone or with adjunctive compression, was achieved in 216 of the 220 subjects in which device deployment was attempted (98.2%). Table 18 shows the device success rate and associated 95% confidence intervals by procedure type.

Table 18: Device Success Rate

Procedure	Number of Subjects[1]	Number of Successes	Success Rate	95% Confidence Interval[2]	
Diagnostic	111	110	99.1%	95.1%	99.8%
Interventional	109	106	97.2%	92.2%	99.1%
Total	220	216	98.2%	95.4%	99.3%

[1]Includes 3 instances of known user error and subsequent failure to follow written Instructions for Use resulting in non-deployment of the patch. Excluding these 3 cases, Overall Device Success rates are 110/110 (100%) for the diagnostic group, 106/107 (99.1%) for the interventional group, and 216/217 (99.5%) for all subjects.

[2] 95% Exact Binomial Confidence Interval

4. Procedure Success

Procedure Success is defined as attainment of final hemostasis using any method and freedom from major vascular complications through 30 days. No major access site-related complications were reported, and therefore Procedure Success was achieved in 100% of cases. Table 19 shows the Procedure Success Rate and associated 95% confidence intervals by procedure type.

Table 19: Procedure Success Rate

Procedure	Number of Subjects[2]	Number of Successes	Success Rate	95% Confidence Interval[1]	
Diagnostic	110	110	100%	96.6%	100.0%
Interventional	109	109	100%	96.6%	100.0%
Total	219	219	100%	98.3%	100.0%

[1] 95% Exact Binomial Confidence Interval

[2] 1 diagnostic subject was lost to follow-up and was omitted from denominator for Procedure Success tabulation

5. Subgroup Analyses: Gender Bias

The preoperative characteristic of gender bias was evaluated for potential association with outcomes. There were 68.2% male subjects enrolled compared to 31.8% females. There was no statistically significant difference in the rate of major or minor complications for either gender. Similarly, there were no statistically significant differences in the effectiveness endpoints of time to hemostasis, ambulation, discharge eligibility or hospital discharge for either gender. An analysis of gender effects related to major complications was not performed as there were zero (0) major access site closure-related adverse events reported.

6. Overall Summary of Safety and Effectiveness Data

The results of the Closer VSS Trial successfully met the performance goals for the primary safety and effectiveness endpoints. The data support the claims of reduced Time to Hemostasis and Time to Ambulation in diagnostic and interventional subjects.

E. Financial Disclosure

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 37 investigators. 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.

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

In accordance with the provisions of section 515(c)(3) 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

The primary effectiveness endpoint was time to hemostasis, and the key secondary effectiveness endpoint was time to ambulation. The clinical study results show that patients treated with the Closer VSS achieved clinically acceptable hemostasis and ambulation times compared to performance goals based on manual compression data. This was observed in both diagnostic and interventional patients.

B. Safety Conclusions

The results from pre-clinical studies performed on the Closer VSS demonstrate that the device is safe for use. In vivo animal studies in sheep demonstrate that the Closer VSS is safe for femoral vascular closure. The results of the Closer VSS trial demonstrate adequate safety. The primary safety endpoint was the combined rate of access site closure-related major complications within 30 ± 7 days following the catheterization procedure. The secondary safety endpoint was the combined rate of access site closure-related minor complications within 30 ± 7 days following the catheterization procedure.

There were no access site closure-related major complications reported for either procedure type. In addition, the Closer VSS access site closure-related minor complication rate was 0.0% for diagnostic procedures and 2.75% for interventional procedures, which were also below the predetermined clinically acceptable rates.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Probable benefits include improved time to hemostasis, improved time to ambulation, and improved time to hospital discharge. The device success rate was 98% and the procedure success rate was 100%. There were no major complications and a low minor complication rate. In conclusion, given the available information cited above, the data support that for the percutaneous closure of femoral artery access sites in diagnostic and interventional patients utilizing 5, 6, and 7 Fr procedural sheaths, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data support the claims of reduced Time to Hemostasis and Time to Ambulation in diagnostic and interventional subjects.

XIII. CDRH DECISION

CDRH issued an approval order on February 12, 2016.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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.

XV. REFERENCES

None