SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Vascular Closure Device

Device Trade Name: Celt ACD® Vascular Closure Device

Device Procode: MGB

Applicant's Name and Address: Vasorum, Ltd
Trinitas House
2012 Orchard Avenue
Citywest Business Campus
Dublin 24, Ireland

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150006

Date of FDA Notice of Approval: July 20, 2016

II. INDICATIONS FOR USE

The Celt ACD® Vascular Closure Device is indicated for the percutaneous closure of common femoral artery puncture sites while reducing time-to-hemostasis in patients who have undergone diagnostic or interventional intra-arterial catheterization procedures where either 5F or 6F introducer sheaths have been used.

III. CONTRAINDICATIONS

The Celt ACD® Vascular Closure Device is contraindicated in patients with a known allergy to 316LVM stainless steel.

IV. WARNINGS AND PRECAUTIONS

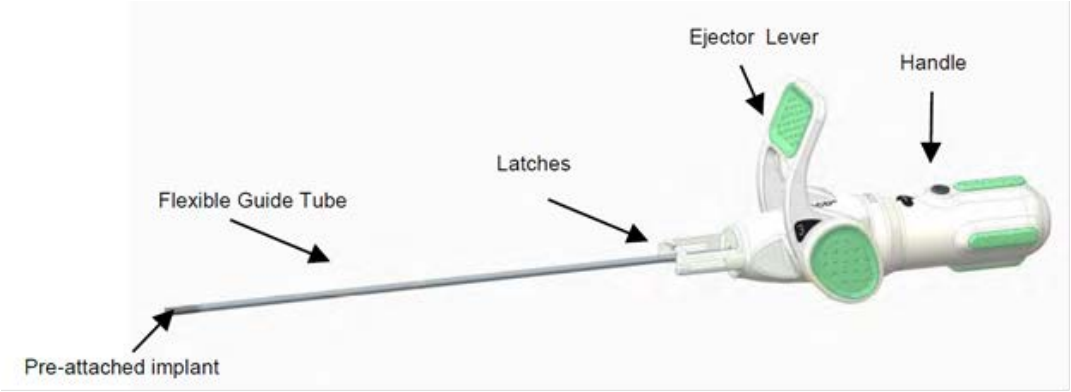
The warnings and precautions can be found in the Celt ACD® labeling.

V. DEVICE DESCRIPTION

The Celt ACD® Vascular Closure Device (VCD) is a single use puncture site closure device which is radiopaque and if required can be visualized under fluoroscopic control during all phases of deployment. The device is manufactured as either a 5F or 6F delivery system, with a pre-mounted implant on its tip. During deployment, the delivery system is activated and delivers a small stainless steel (316LVM) implant into the arterial wall thereby closing the puncture site.

The Celt ACD® consists of the following:

1. A delivery system



2. Pre-attached implant

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are many other alternatives for achieving closure or hemostasis of the femoral artery puncture site after catheterization. These alternatives include manual compression, mechanical compression, adjunctive pads and patches for helping to achieve hemostasis, and closure devices using a suture or sutures, collagen sponge or patch, collagen-thrombin procoagulant mixture, porcine small intestinal submucosa patch, nitinol clip, or polymer hydrogel, plug, or patch. 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 Celt ACD® VCD has been marketed in Europe (in particular in UK, Germany, Switzerland, Slovakia, the Czech Republic, Benelux and Austria) by Vasorum Ltd since June 2012. Vasorum Ltd initiated a voluntary limited recall of three lots of 6F devices from the European market in June 2013. These lots were found to have an out-of-specification subassembly component following the reporting of an adverse incident. The subassembly component was modified to correct the problem. No further such incidents have been reported from the market place since the modification was implemented.

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:

- Bruising, oozing or bleeding at the puncture site.
- Hematoma or Ecchymosis.
- Pain, discomfort or transitory local irritation and inflammation at the puncture site.
- Access-site related nerve injury, vascular spasm, local pulse deficits, ischaemia or access-site wound dehiscence.
- Infection at the procedure site.
- Failure of the device to deploy correctly in the artery.
- Vaso-vagal response.

Other events that could possibly occur, but are considered extremely unlikely include:

- Occlusive intraluminal thrombus and/or emboli formation at the Celt ACD® Vascular Closure Device implant site.
- Partial or complete occlusion of the arterial lumen.
- Damage of the arterial wall including stenosis/narrowing.
- Swelling of the treated limb.
- Embolization (device, thrombus, tissue, air or calcific debris).
- Pseudoaneurysm, arterial or deep vein thrombosis or arteriovenous fistula.
- Corrective intervention, including transfusion and/or surgery, due to any of the above complications.

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

IX. SUMMARY OF NONCLINICAL 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: Bench testing performed

Test	Purpose	Acceptance Criteria	Results
Deployment and Removal	Determine the maximum force applied to the thumb activated lever which should not exceed the pinch grip force range for males and females of 86N	The device is designed with a maximum force to activate the lever of ≤ 86N	Pass
Distal wing strength	Determine the force required to withstand the pull of the distal wings through a puncture hole	The device is designed to withstand a pullback force of 1 lb. (4.4N)	Pass
Bond Joint Strength	Verify the strength of the bond between the guide tube and body front	Torque: 3.6 Ncm(5F); 6.6 Ncm (6F) Compression: 210 N	Pass
Weld Strength	Verify the strength of the weld joint between the core pin and occluder anchor.	Torque: 3.6 Ncm(5F); 6.6 Ncm (6F) Compression: 57 N (5F) 77.4 N (6F)	Pass
Lever Strength	Verify the strength of the plastic lever for implant deployment.	78.12 N (3x maximum measured ejection force load)	Pass

B. Sterilization

The Celt ACD® device is sterilized using e-beam 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}.

C. Biocompatibility

Biocompatibility testing for the Celt ACD® device was performed in accordance with ISO 10993-1 as well as additional chemical characterization methods. The Celt ACD 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 stainless steel implant is 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. The following biocompatibility tests were performed on the Celt ACD® system.

Table 2: Biocompatibility tests performed on the whole device

Test Type	Standardized Method	Test	Results
Cytotoxicity	ISO 10993-5	L929 Neutral Red Uptake Cytotoxicity Test	Pass
Hemocompatibility	ISO 10993-4	Hemolysis – Human Blood-Autian Method	Pass

Hemocompatibility	ISO 10993-4	Coagulation – Prothrombin Assay	Pass
Hemocompatibility	ISO 10993-4	Coagulation – Unactivated Partial Thromboplastin Time Assay	Pass
Irritation	ISO 10993-10	Intracutaneous Injection Test	Pass
Sensitization	ISO 10993-10	Kligman Maximization Test	Pass
Systemic Toxicity	ISO 10993-11	Systemic Injection Test	Pass
Systemic Toxicity	ISO 10993-11	Rabbit Pyrogen Test (material mediated)	Pass
Genotoxicity	ISO 10993-3	Ames Reverse Mutation	Pass

Table 3: Biocompatibility tests performed on the implant only

Test Type	Standardized Method	Test	Results
Cytotoxicity	ISO 10993-5	Cytotoxicity – Elution Test	Pass
Hemocompatibility	ASTM756-13	Hemolytic Properties of Materials (indirect and direct contact)	Pass
Chemical Characterization	ISO 10993-18 ISO 10993-17	Leachable Substances Assessment	Pass
Implantation	N/A	Implantation into the abdominal aorta of pigs to determine the short and medium term effects of the tissue-material interactions	Pass

All tests were successfully completed and all acceptance criteria were met for the delivery system and implant. In conclusion, the biocompatibility of the Celt ACD device has been adequately demonstrated.

D. Packaging Testing

The Celt ACD® packaging was evaluated in accordance with ISO 11607–1:2009. 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 Celt ACD® packaging per the stated standardized test methods. Following these simulations, it was confirmed that the Celt ACD® meets the performance specifications.

E. Shelf-Life Testing

The Celt ACD® device was evaluated to support a shelf life of three (3) years. Devices were subjected to accelerated aging equivalent to three years per ASTM F1980. The testing demonstrated that devices that were aged in this way met the functional, visual, and performance requirements. No anomalies were found during testing. As a result of

the testing performed on the Celt ACD® and packaging, the device is currently labeled with a shelf life of three years.

F. Magnetic Resonance Imaging (MRI) Compatibility Testing

Testing of this device in magnetic fields of 1.5 and 3.0 Tesla showed that the device is MR Conditional. The Celt ACD® device can be scanned safely under the following conditions:

- Static magnetic field of 3 Tesla or less
- Spatial gradient field of 1500 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 4 W/kg in the First Level Controlled Mode for the MR system for 15 minutes of scanning

G. Animal Studies

A series of animal studies in porcine abdominal aortic arteries were conducted during the development of the Celt ACD® device. Acute studies evaluated the deployability, functionality and effectiveness of the device. The porcine implant work shows that Celt ACD® provides immediate hemostasis in the aorta of fully anticoagulated animals. Chronic porcine implant studies have also been carried out where the animals were survived following implantation of Celt ACD®. The aorta was harvested five (5) weeks, eight (8) weeks and 16 weeks after implantation. One animal was evaluated at each of these chronic time points. Pathology and histology findings showed that Celt ACD® remained *in situ* with no evidence of haemorrhage/thrombosis. The intimal surface overlying the implant is totally covered with cells within five weeks. Also at five (5) weeks endoluminal endothelialisation of the implant in the arterial wall occurred with the vessel showing healing.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of puncture site closure with the Celt ACD® VCD for percutaneous closure of a common femoral artery puncture in adult patients after an interventional procedure in the US, Germany and Ireland under IDE # G110061. 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 21, 2012 and September 16, 2014. The database for this PMA reflected data collected through November 27, 2014 and included 207 patients. There were four (4) investigational sites.

The study was a prospective, multi-center, two-arm, randomized clinical study. The objective of the Celt ACD® VCD clinical study was to evaluate the safety and effectiveness of the 6F Celt device to achieve hemostasis of the common femoral artery access site in fully anticoagulated patients undergoing percutaneous cardiac or peripheral vascular interventional procedures using a 6F sheath. The device and control groups were compared using frequentist statistical analysis methods.

The study was monitored by an independent Data Safety Monitoring Committee (DSMC), which also served as a Clinical Events Committee (CEC) to adjudicate adverse events.

The control group consisted of patients who were treated with manual compression.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the CELT ACD® pivotal study was limited to patients who met the following inclusion criteria:

   1. Over 18 years of age.
   2. Each patient, or his or her guardian or legal representative, is willing to give informed consent.
   3. Clinically indicated for an intra-arterial procedure involving access through the common femoral artery and conducted through an access sheath size between 5F and 6F inclusive.

   Patients were not permitted to enroll in the CELT ACD® pivotal study if they met any of the following exclusion criteria:

   1. Patients with known allergy to any of the materials used in the device.
   2. Severe acute non-cardiac systemic disease or terminal illness with a life expectancy of less than one year.
   3. Evidence of systemic bacterial or cutaneous infection, including groin infection.
   4. Patients suffering with definitive or potential coagulopathy or platelet count < 100,000/µl.
   5. Use of systemic thrombolytic agents within 24 hours prior to or during the catheterisation procedure which cause the concentration of fibrinogen to be < 100 mg/dl *or* if post-thrombolytic fibrinogen (in case of thrombolysis within 24 hours or intra-procedural) cannot be measured.
   6. Patients in whom an introducer sheath smaller than 5F or greater than 6F have been used.
   7. Currently participating in another investigational device or drug study.
   8. Patients with severe claudication, iliac or femoral artery diameter stenosis greater than 50% or previous bypass surgery or stent placement in the vicinity of the access site.
   9. If puncture site is via a vascular graft.
   10. If a palpable haematoma is observed during the procedure.

11. Patients in whom there is any indication that puncture has been made in the profunda femoris artery or superficial femoral artery, or adjacent to the bifurcation.
12. Patients with a common femoral artery lumen diameter of less than 5 mm for 5F and 6F sheaths.
13. Patients that have any amputation from an access site limb.
14. Patients that have undergone a percutaneous procedure using a vascular closure device for hemostasis within the previous 30 days or using manual/mechanical pressure for hemostasis within the prior 30 days in the same leg.
15. Patients with a systolic blood pressure reading below 90 mmHg.
16. Patients with an active haematoma, arteriovenous fistula, or pseudoaneurysm.
17. Patients with a very superficial artery where the depth from skin to the artery surface at the access site is less than 4 mm.
18. Morbidly obese patients (Body Mass Index > 35kg/m^2).
19. Patients with a stent ≤ 1 cm of the puncture site that would interfere with placement of the device implant.
20. Patient is known or suspected to be pregnant, or is lactating.
21. Patients in whom there has been an antegrade puncture.
22. Patients in whom there has been difficulty in obtaining vascular access resulting in multiple arterial punctures and/or posterior arterial wall puncture.
23. Patients who have undergone prior or recent use of an intra-aortic balloon pump through the arterial access site.
24. Patients with uncontrolled hypertension (BP ≥ 180/110 mmHg) at time of vascular closure.
25. Patients with acute ST-elevation myocardial infarction ≤ 48 hours before catheterization procedure.
26. Patients with cardiogenic shock (hemodynamic instability requiring intravenous medication or mechanical support) experienced during or immediately post- catheterization.
27. Patients who are unable to ambulate at baseline.
28. Patients known to require an extended hospitalization (e.g., patient is undergoing cardiac surgery).
29. Patient has already participated in the trial.
30. Patient is unavailable for follow-up.

2. Follow-up Schedule

All patients were scheduled to return for a follow-up examination 30 ± 7 days postoperatively. The clinical study protocol stipulated that a minimum of 30 patients (20 device and 10 control patients) at one (1) study site would undergo femoral artery Duplex ultrasound examinations of the access site prior to hospital discharge and at the 30-day follow-up visit to assess for access site complications. A total of 47 patients were recruited into the Ultrasound Sub-Study and data from

35 patients (25 device and 10 manual compression patients) were available for analysis.

Preoperatively, a medical history was obtained including a record of the subject's demographic and baseline information, a physical examination including groin assessment was performed, and the following blood labs were evaluated:

- hemoglobin
- hematocrit
- platelet count
- fibrinogen (if patient was on thrombolytic therapy)

Postoperatively, the objective parameters for the study were measured along with the activated clotting time. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

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

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

With regard to success/failure criteria, the device group was evaluated for non-inferiority with a 4% margin to the control group for the safety endpoints and for superiority for the effectiveness endpoints.

B. Accountability of PMA Cohort

At the time of database lock, of 207 patients enrolled in the PMA study, 100% (207) patients were available for analysis at the completion of the study, the 30-day post-operative visit.

Despite the 100% patient compliance at the 30-day follow-up evaluation the following effectiveness data was missing:

- 11.9% (7) of control patients did not have TTH recorded

- 31.8% (47) of device patients and 25.4% (15) of control patients did not have TTA recoded
- 52.0% (77) of device patients and 50.8% (30) of control patients did not have TTD recorded.

Note: The original randomization process (2:1 randomization) continued until 181 individuals had been randomized (122 to Celt ACD® and 59 to manual compression). Following discussion and approval by the FDA there was an alteration in the randomization process for the remaining 26 individuals who were not randomized but were directly allocated to the Celt ACD® group. This resulted in 148 patients in the Celt ACD® group and 59 patients in the manual compression group (2.5:1 ratio).

C. Study Population Demographics and Baseline Parameters

The demographics and characteristics of the study population are shown in Table 4 and are typical for a VCD study performed in the US.

Table 4: Celt ACD Clinical Study Patient Characteristics

	CELT ACD (n=148)	Manual compression (n=59)	Total (n=207)	p-value
Age in years (mean, 95% CI) (SD, Range)	66.75 (65.01, 68.49) (SD=10.8; 42, 92)	67.44 (64.39, 70.49) (SD=11.7; 40, 92)	66.95 (65.44,68.45) (SD=11.0; 40, 92)	0.69#
Height in cm (mean, 95% CI) (SD, Range)	172.9 (171.3, 174.5) (SD=9.56; 145, 197)	171.7 (169.4, 173.9) (SD=7.82; 155,187)	172.5 (171.1, 173.9) (SD=9.12; 145, 197)	0.30#
Weight in kg (mean, 95% CI) (SD, Range)	85.38 (79.76, 91.0) (SD=16.22; 40,154)	82.78 (78.88, 86.68) (SD=14.83; 54.4,117)	84.65 (80.48, 88.82) (SD=15.80;40, 154)	0.93#
BMI (kg/m2)[1] (mean, 95% CI) (SD, Range)	27.75 (27.00, 28.50) (SD=4.47;14.2, 47.5)	28.18 (26.97, 29.38) (SD=4.41; 19.5,40.9)	27.87 (27.00, 28.50) (SD=4.45; 14.2,47.5)	0.55#
Male (N, %)	112 (75.7%)	47 (79.66%)	159 (76.81%)	0.54~
Sheath size: 6F, N (%) 7F, N (%)	144 (97.3%) 4 (2.7%)	57 (96.6%) 2 (3.4%)	201 (97.1%) 6 (2.9%)	1.0$
Femoral artery site: Right N (%) Left N (%)	142 (95.9%) 6 (4.1%)	57 (96.6%) 2 (3.4%)	199 (96.1%) 8 (3.9%)	1.0$
Type of catheterization: Cardiac Peripheral	144 (97.3%) 4 (2.7%)	57 (96.6%) 2 (3.4%)	201 (97.1%) 6 (2.9%)	1.0$
History of mild/moderate PVD	148 (100%)	59 (100%)	207 (100%)	n/a
Use of antiplatelet/ anticoagulant pre/post procedure	148 (100%)	59 (100%)	207 (100%)	n/a

Type anticoagulant: **Bivalirudin** **Unfractionated heparin** **Warfarin**	 35 (23.6%) 112 (75.7%) 1 (0.7%)	 18 (30.5%) 41 (69.5%) 0 (0%)	 53 (25.6%) 153 (73.9%) 1 (0.5%)	0.32[@]
Systolic blood pressure (pre) (mean, 95% CI) (SD, Range)	N=137 141.4 (137.9,145.0) (SD=20.9; 94, 204)	N=55 141.5 (135.3,147.8) (SD=23.1;105,203)	N=192 141.45 (138.4,144.5) (SD=21.5; 94,204)	0.98[#]
Diastolic blood pressure (pre) (mean, 95% CI) (SD, Range)	N=137 76.8 (74.9,78.8) (SD=11.6;46,111)	N=55 76.0 (72.2.79.8) (SD=14.1;54,144)	N=192 76.6 (74.8,78.4) (SD=12.4;46,144)	0.67[#]
Activated clotting time (ACT) in secs (mean, 95% CI) (SD, Range)	N=100 249.6 (233.0,266.2) (SD=83.8;104,481)	N=36 244.5 (212.8,276.2) (SD=93.7; 113,428)	N=136 248.3 (233.6,262.9) (SD=86.2;104,481)	0.76[#]
Hypertensive	113 (76.9%)[&]	51 (86.4%)	164 (79.6%)[&]	0.12[~]
Diabetes	35 (23.7%)	17 (28.8%)	52 (25.1%)	0.44[~]

[#] - Independent t-test
[$] - Fishers Exact test
[~] - Chi-Square test
[@] - Chi-Square test without warfarin
[&] - Missing on one individual
[1] - N=10 participants had BMI>35

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the intent-to-treat (ITT) cohort of 207 patients available for the 30-day evaluation. The key safety outcomes and adverse events are presented below.

The major complications reported are shown in Table 5. All three (3) complications were categorized as 'Other.' The major complication reported in the Celt ACD® group was embolization of the Celt ACD® implant in the right leg following proper functioning of the delivery system. The event was most likely a result of inadequate proximal wing positioning outside the artery at the puncture site secondary to the device not being pulled back sufficiently prior to opening the proximal wings of the implant. The embolized implant was successfully retrieved radiologically with a snare with access through the left femoral artery and was deposited in the subcutaneous tissue outside the left femoral artery access site. The major complications in the manual compression group were: one patient reporting syncope during the follow-up period and one patient suffering brain stem ischemia.

There was a lower major complication rate with the Celt ACD® compared to the manual compression group and the upper limit of the 95% confidence interval was within the 4% non-inferiority margin.

Table 5: Major complications reported in the Celt ACD Clinical Study

Major Complications	Celt ACD (N=148)	Manual Compression (N=59)	Total (N=207)
Vascular repair or the need for vascular repair (via surgery, ultrasound -guided compression, transcatheter embolization, or stent-graft).	0	0	0
Retroperitoneal bleeding.	0	0	0
Access-site-related infection requiring intravenous antibiotics and/or extended	0	0	0
Permanent access site-related nerve injury.	0	0	0
Surgery for access site-related nerve injury.	0	0	0
Access site related bleeding requiring transfusion.	0	0	0
Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram.	0	0	0
Any complication requiring surgery, vascular repair, or transfusion is a major complication and not a minor complication.	0	0	0
Other			
Syncope during the follow-up period.	0	1	1
Brain Stem Ischemia.	0	1	1
Device embolization from the femoral artery access point.	1	0	1
Total Major Complications – N (%)	1 (0.68%)	2 (3.39%)	3 (1.45%)
Difference in Major Complication Rate (95% CI)	-2.71% (-7.09%, 1.66%)		
p-value[&]	0.0013		

[$] - Farrington-Manning 95% confidence limits

[&] - Farrington-Manning method (test for margin of 4%, z=3.01)

Overall in the study, there were a total of 12 minor complications reported with seven in the Celt ACD® group and five (5) in the manual compression group. The reported minor complications are shown in Table 6. Of the seven (7) minor complications reported in the Celt ACD® group, three (3) were related to access site bleeding which required more than 30 minutes to achieve hemostasis. One (1) was related to an access site hematoma of greater than 6 cm and another to ecchymosis of greater than 5 cm. Another patient reported pain in the right groin which was resolved at follow-up. Another reported right-sided weakness and confusion which were not device-related.

In the manual compression group the five (5) minor complications were reported across four (4) patients. Three (3) patients were reported to have access site hematomas of greater than 6 cm and one reported ecchymosis of greater than 5 cm. One (1) patient reported decreased power to the right leg patient which had resolved at follow-up.

There was a lower minor complication rate with the Celt ACD® compared to the manual compression group and the upper limit of the 95% confidence interval was within the 4% non-inferiority margin.

Table 6: Minor complications reported in the Celt ACD Clinical Study

Minor Complications	Celt ACD (N=148)	Manual Compression (N=59)	Total (N=207)
Access site hematoma ≥ 6 cm.	1	3	4
Ecchymosis > 5 mm.	1	1	2
Locally induced vasovagal episode requiring therapy.	0	0	0
Pseudoaneurysm, documented by ultrasound that does not require intervention.	0	0	0
Arteriovenous (AV) fistula documented by ultrasound that does not require intervention.	0	0	0
Access site-related bleeding requiring > 30 minutes to re-achieve hemostasis.	3	0	3
Late access site-related bleeding (i.e. following hospital discharge).	0	0	0
Transient loss of ipsilateral lower extremity pulse.	0	0	0
Ipsilateral deep vein thrombosis.	0	0	0
Transient access site-related nerve injury.	0	0	0
Access site-related vessel laceration (not requiring surgical repair or intervention).	0	0	0
Access site wound dehiscence.	0	0	0
Localized access site infection treated with intramuscular or oral antibiotics.	0	0	0
Pseudoaneurysm treated with ultrasound-guided thrombin injections or ultrasound-guided fibrin adhesive injection.	0	0	0
Ipsilateral lower extremity arterial emboli.	0	0	0
Other			
Pain to the right groin.	1	0	1
Confusion; Right side weakness.	1	0	1
Decreased power to the right leg.	0	1	1
Total Minor Complications – N (%)	7 (4.73%)	5 (8.47%)	12 (5.80%)
Difference in Major Complication Rate (95% CI)	-3.74% (-10.43%, 2.94%)[$]		
p-value[&]	0.012		

[$] - Farrington-Manning 95% confidence limits

[&] - Farrington-Manning method (test for margin of 4%, z=2.27)

To provide a further assessment of safety of Celt ACD® a Doppler Ultrasound (DUS)-based quantitative and qualitative analysis of the Common Femoral Artery (CFA) was carried out in a sub-study. The sub-study was designed to determine if there were any changes in the vessel and blood flow related to Celt ACD® implantation. This was assessed by comparing vessels in which Celt ACD® was deployed to vessels in which manual compression was used to achieve hemostasis. Patient selection was on a first come basis and all of the ultrasounds were done at one of the study sites in Germany. In the sub-study data from a total of 35 patients was available for analysis. These were a sub-set of the patients recruited in the Pivotal Trial. Using 2 Dimensional grey scale and color-Doppler ultrasound (Siemens Sanoline G40 and GE Healthcare Vivid 7) a DUS evaluation

of the inguinal region of the CFA from 1 cm proximal to 1 cm distal of the arterial puncture site was carried out.

The continuous variables of CFA diameter (cm) and Peak Systolic Velocity (PSV) (cm-sec) were measured and analyzed. Both pre- and post-procedure vessel internal diameter data were available for a total of 35 patients recruited into the study (Celt ACD® N=25, Manual Compression N=10). The median diameter (and inter-quartile range) at the puncture site pre- and post-procedure is shown in Table 7, along with the difference in pre- and post-procedure measures, between the manual compression and Celt ACD® randomized groups. As the data were non-normal, a Mann Whitney test was applied and no statistically significant difference was found between the randomized groups for change in internal diameter of the common femoral artery.

Table 7: Doppler Ultrasound Common Femoral Artery Size Results

	Celt ACD (N=25)[$]	**Manual Compression (N=10)[$]**	**p-value**
Pre-procedure CFA diameter at puncture site (cm)	8.45 (7.85,9.45)	8.90 (8.7, 9.7)	
Post-procedure CFA diameter at puncture site (cm)	9.15 (7.2, 10.0)	9.63 (9.0, 9.85)	
Difference in diameter (cm; post- pre)	1.20 (0.35,1.70)	0.5 (-0.05,0.8)	0.134[$]

[&] - Mann-Whitney U test between groups
[$] - Data presented as – Median (Inter-quartile range)

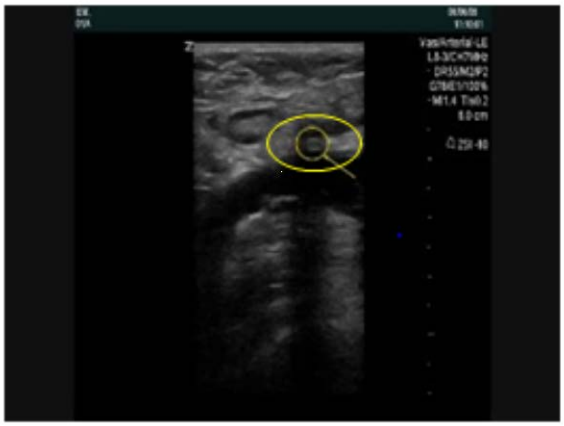
The mean velocity of blood in the vessel (and 95% Confidence Interval) at the puncture site pre- and post-procedure is shown in Table 8, along with the difference in pre- and post-procedure measures, between the manual compression and Celt ACD® randomized groups. There were 20 Celt ACD® group and 10 manual compression observations available for analysis. As the data were normally distributed, a Students t-test was applied and there was found to be no statistically significant difference between the randomized groups for change in velocity. In summary, the statistical analysis found no significant difference between the randomized groups in terms of the change in pre- and post-measurements of CFA diameter and PSV at the puncture site.

Table 8: Doppler Ultrasound Peak Systolic Velocity Results

	Celt ACD (N=25)[$&]	**Manual Compression (N=10)[$]**	**p-value**
Pre-procedure PSV at puncture site (cm/s)	109.25 (89.59, 128.91)	110.0 (91.84, 128.16)	
Post-procedure PSV at puncture site (cm/s)	99.25 (79.61, 118.89)	103.7 (84.30, 123.10)	
Difference (post-pre) in PSV (cm/s)	-10 (-38.75, 18.75)	-6.3 (-30.38, 17.78)	0.861#

[#] - t-test for difference between groups
[$] - Data presented as – Median (Inter-quartile range)
[&] - 5 Participants did not have velocity data both pre- and post-procedure

The qualitative assessment of the artery was made both before the procedure and 30 days after implantation of Celt ACD® or after use of manual compression to achieve hemostasis. There was no evidence of hematoma, pseudoaneurysm, or arteriovenous fistula observed in any patient in the ultrasound sub-study. No iatrogenic vascular injury was discovered in any patients in the study. All subjects in the sub-study demonstrated patency of the access site artery. There were no episodes of arterial thrombosis or clinically significant stenosis in this sub-study patient cohort. Peri-arterial inflammation was not identified in any of the images during the DUS study. Direct visualization of the Celt ACD® implant, while not a part of the protocol nor a focus of examination, was noted in many of the examinations, typically represented as a bright echogenic image in the CFA (common femoral artery) as shown below.



The DUS data reported concludes that arterial blood flow is not interrupted by successful Celt ACD® closure of a femoral access site and that luminal patency is preserved in patients undergoing percutaneous interventional procedures when compared to manual compression. Imaging also demonstrates a lack of soft tissue reaction to the implant.

2. Effectiveness Results

The analysis of effectiveness was based on the 207 evaluable patients at 30-day time point. Key effectiveness outcomes are presented below.

The primary effectiveness endpoint was time-to-hemostasis (TTH). Time-to-hemostasis was defined as the elapsed time between sheath removal and the time hemostasis is first observed. Hemostasis was defined as cessation of pulsatile bleeding in the absence of expanding or developing hematoma. Cutaneous or subcutaneous oozing that is readily treated by light compression methods sandbags, pressure dressing or light manual pressure was considered to comply with the definition of hemostasis.

The TTH data are shown in Table 9. Data on TTH were missing for seven (7) individuals from the manual compression group. The data were significantly skewed (non-normal), therefore, median and inter-quartile range (25^{th} to 75^{th} percentile) in addition to the mean and standard deviation (SD) are presented, and the non-parametric Wilcoxon rank sum test and parametric t-test were both applied to compare the two (2) randomized groups.

There was a considerably lower median TTH in the Celt ACD® group (0 mins) compared to manual compression (8.5 mins), which was highly statistically significant. There was also a statistically significant lower mean TTH in the Celt ACD® group (0.99 mins) compared to the manual compression arm (17.54 mins).

Table 9: Time-to-Hemostasis Results (mins)

	Celt ACD (N=148)	Manual Compression (N=52)[&]	All Patients (N=200)	p-value
Mean (SD)	0.99 (4.15)	17.54 (54.55)	5.29 (28.78)	0.034[#]
95% CI for Mean TTH	(0.32, 1.67)	(2.35, 32.73)	(1.28, 9.31)	
Median	0	8.5	0	<0.0001[$]
Inter-quartile range	(0, 0.33)	(0, 20)	(0, 2)	
Range (min, max)	(0, 44)	(0, 398)	(0, 398)	

[#] - Independent t-test with Satterthwaite method for unequal variances.
[$] - Data were non-normal therefore the Wilcoxon rank sum test was used to test the null hypothesis.
[&] - Seven subjects did not have TTH recorded in the manual compression group.

The TTH data were further analyzed by post-procedural time interval and these data are shown in Table 10. This analysis shows that 60% of patients in the Celt ACD® group had immediate hemostasis and that 95.9% had hemostasis in under 5 minutes and 98.6% under 10 min. The manual compression patients, unlike the Celt ACD® patients, did not have the sheath removed immediately at the end of the procedure. Analysis of information from patient notes (N=16) showed that the mean time between end of procedure and sheath removal was 2 hrs. 46 min. This was not factored into the statistical analysis of the data collected. In the manual compression group 28.8% had 'immediate' hemostasis and 65.3% achieved hemostasis in less than 10 minutes.

Table 10: Time-to-Hemostasis by post-procedural time interval (N (%))

Interval (mins)	0	0.1–5	5.1–10	10.1–15	15.1–30	30.1–60	> 60
Celt ACD (N-148)	89 (60.1)	53 (35.8)	4 (2.7)	0 (0)	1 (0.7)	1 (0.7)	0 (0)
Manual Compression (N=52)[&]	15 (28.8)	1 (1.9)	18 (34.6)	3 (5.8)	14 (26.9)	0 (0)	1 (1.9)

[&] - Seven subjects did not have TTH recorded in the manual compression group.

Time-to-ambulation was defined as the elapsed time between sheath removal and the time when the patient stands and walks 6 m or approximately 20 ft without re-bleeding. Patients were recommended to have their ambulatory status evaluated

at a range of times, however ambulation was not required if contrary to the clinical judgment of the physician.

The time-to-ambulation (TTA) data for those with data available (n=145, 70%) are shown in Table 11. Data on actual TTA were not available for 62 patients (30%) and most missing data were from the fourth center (n=58 missing TTA). There were no statistically significant differences in the mean or median TTA between the Celt ACD® and manual compression groups.

Table 11: Time-to-Ambulation results (mins)

	Celt ACD (n=101)[&]	Manual Compression (n= 44)[&]	All Patients (n=145)	p-value
Mean (SD)	360.0 (418.4)	406.4 (216.2)	374.0 (368.7)	0.38[#]
95% CI for mean	(274.4,442.5)	(340.7,472.1)	(313.5,434.6)	
Median	240	360	265.0	0.49[$]
Inter-quartile range	(170,360)	(252.5,512)	(180,447)	
Range (min, max)	(74,2644)	(30,895)	(30,2644)	

[#] - Independent t-test with unequal variances assumed.
[$] - Data were non-normal therefore the Wilcoxon rank sum test was used to test the null hypothesis.
[&] - Data not available on all subjects (only 68% of Celt ACD and 74.6% of manual compression group had data available for analysis).

Table 12 shows TTA categorised by post-procedural time interval. The data show that 73% of the Celt ACD® group and 48% of the manual compression group were ambulated within 6 hours.

Table 12: Time-to-Ambulation by post-procedural time interval (N (%))

Interval (hours)	< 2	2–3.9	4–5.9	6–7.9	8–9.9	10–11.9	≥ 12
Celt ACD (N=101)[$]	2 (2.0)	47 (46.5)	25 (24.8)	11 (10.9)	6 (5.9)	1 (1.0)	9 (8.9)
Manual Compression (N=44)[$]	2 (4.6)	6 (13.6)	13 (29.6)	6 (13.6)	8 (18.2)	3 (6.8)	6 (13.6)

[$] - Data not available on all subjects (only 68% of Celt ACD and 74.6% of manual compression group had data available for analysis).

Table 13 shows the results regarding whether the subject was fit for ambulation by < 6 hours or ≥ 6 hours, for which there were more complete data (n=197, 95.2%). For the Celt ACD® device group the majority of individuals (81%) were fit for ambulation within 6 hours, compared to 70.9% of the manual compression group. This difference was not statistically significant.

Table 13: Time-to-Ambulation within 6 hour time interval (N (%))

Interval (hours)	< 6	≥ 6	p-value
Celt ACD (N=142)[$]	115 (81.0)	27 (19.0)	0.12[&]
Manual Compression (N=55)[$]	39 (70.9)	16 (29.1)	

[$] - Data not available on all subjects (n=6 not recorded for CELT ACD and n=4 for manual compression (MC)); differences between actual time and data presented here (n=2 and n=6 in CELT ACD and MC group respectively had actual time ≥6

hours, but were considered fit for ambulation within 6 hrs; n=1 in MC group not recorded here but had TTA data; n=1 in CELT ACD group had TTA<6 hours but considered not fit for ambulation).

[&] - Chi-square test applied (statistic=2.36)

Time-to-Dischargeability (TTD) was defined as the elapsed time between sheath removal and 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 TTD was available for 100 (48.3%) patients, and the results for both randomized groups are shown in Table 14. There were no statistically significant differences in the mean or median TTD between the Celt ACD® and manual compression groups.

Table 14: Time-to-Dischargeability results (mins)

	Celt ACD (N=71)[&]	Manual Compression (N= 29)[&]	All Patients (N=100)	p-value
Mean (SD)	662.51 (511.7)	511.76 (350.2)	618.79 (473.8)	0.15[#]
95% CI for mean	(541.40, 783.61)	(378.55, 644.96)	(524, 712.81)	
Median	416	330	377	0.47[$]
Inter-quartile range	(179,1196)	(240, 796)	(184.5, 1074)	
Range (min, max)	(6, 1402)	(34, 1140)	(6, 1402)	

[#] - Independent t-test with unequal variances assumed.

[$] - Data were non-normal therefore the Wilcoxon rank sum test was used to test the null hypothesis.

[&] - Data not available on all subjects (only 48% of Celt ACD and 49% of manual compression group had data available for analysis).

Table 15 shows TTD categorized by post-procedural time interval. For the Celt ACD® group approximately 52% of subjects (n=37) were eligible for discharge within 12 hours. For the manual compression group 69% (n=20) were eligible for discharge within 12 hours.

Table 15: Time-to-Dischargeability by post-procedural time interval (N (%))

Interval (hours)	< 2	2–3.9	4–5.9	6–7.9	8–9.9	10–11.9	≥ 12
Celt ACD (N=101) [$]	4 (5.6)	27 (38.0)	4 (5.6)	1 (1.4)	1 (1.4)	0 (0)	34 (47.9)
Manual Compression (N=44) [$]	3 (10.3)	4 (13.8)	8 (27.6)	0 (0)	2 (6.9)	3 (10.3)	9 (31.0)

Procedure Success was defined as the attainment of hemostasis using any method with no major complications during the follow-up period. Device Success was defined as the successful deployment of the Celt ACD® device with the attainment of hemostasis. The procedure and device success rates for the Celt ACD® group and the manual compression group are shown in Table 16.

The rate of procedure success was similar in both groups at 99.3% (147/148) in the Celt ACD® group and 98.1% (51/52) in the manual compression group. The difference in procedure success rate between the two groups was not statistically significant.

The device success was 99.3% (147/148) due to one Celt ACD® device implant deploying correctly but not being properly positioned in the femoral artery puncture site, resulting in the embolization of the device. This was the sole major complication in the Celt ACD® group in the trial.

Table 16: Device and Procedural Success

	Celt ACD (N=148)	Manual Compression (N=52)[&]	All Patients (N=200)	Difference (95% CI)	p-value
Procedure Success	147 (99.32%)	51 (98.08%)	198 (99%)	1.24% (-2.71%, 5.21%)[$]	0.45[$]
Device Success	147 (99.32%)	N/A			

[&] - Seven subjects did not have time to hemostasis recorded in the manual compression group

[$] - Wald asymptotic confidence intervals and Fishers exact test applied.

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 four (4) investigators of which none were full-time or part-time employees of the sponsor and two (2) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. 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 effectiveness of the device was evaluated in the clinical study conducted to support PMA approval, as described above. In the clinical study the primary effectiveness endpoint was time-to-hemostasis. The secondary effectiveness endpoints included time to-ambulation and time-to- dischargeability. The clinical data show that the Celt ACD® VCD group had a lower mean time-to-hemostasis than the corresponding time for the manual compression group, and that the difference in this time was statistically and clinically significant. The data also show that the Celt ACD® VCD group had a mean time-to-ambulation and a mean time-to-dischargeability that were not statistically or clinically significantly different from the corresponding times for the manual compression group. Although the study involved only interventional patients, the effectiveness data apply to both interventional patients and diagnostic patients because interventional patients typically have longer times-to-hemostasis than do diagnostic patients due to the antiplatelet and anticoagulant medications that interventional patients receive before and during the catheterization procedures.

B. Safety Conclusions

The risks of the device were evaluated in the nonclinical laboratory and animal studies as well as in the clinical study conducted to support PMA approval, as described above. In the clinical study the primary safety endpoint was the rate of combined access site-related major complications within 30 ± 7 days following the catheterization procedure, and the secondary safety endpoint was the rate of combined access site-related minor complications within 30 ± 7 days following the catheterization procedure. The clinical data show that the rate of combined access site-related major complications for the Celt ACD® VCD group was lower than and statistically non-inferior to that for the manual compression group. The data also show that the rate of combined access site-related minor complications for the Celt ACD® VCD group was lower than and statistically non-inferior to that for the manual compression group. Although the study involved only interventional patients, the safety data apply to both interventional patients and diagnostic patients because interventional patients serve as a worst-case scenario for potential VCD-related complications.

C. Benefit-Risk Conclusion

The probable benefit of the device is based on data collected in the clinical study conducted to support PMA approval, as described above. The probable benefit is reduced time-to-hemostasis.

When assessing the risks and probable benefit of the Celt ACD® VCD, factors that were considered included risk mitigation actions and the generalizability of the clinical study results to diagnostic patients.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

For percutaneous closure of common femoral artery puncture sites in patients who have undergone diagnostic or interventional intra-arterial catheterization procedures, the data support the conclusion that the probable benefits of the Celt ACD® VCD outweighs the probable risks.

D. Overall Conclusion

The data provided in this PMA application support the reasonable assurance of safety and effectiveness of the Celt ACD® Vascular Closure Device when used in patients who have undergone diagnostic or interventional intra-arterial catheterization procedures where either 5F or 6F introducer sheaths have been used. The data support the claim of reduced time-to-hemostasis in diagnostic and interventional patients with a clinically acceptable rate of major and minor complications.

XIII. CDRH DECISION

CDRH issued an approval order on July 20, 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.