The CONFORM Pivotal Trial

An Evaluation of the Safety and Effectiveness of the Conformal CLAAS System for Left Atrial Appendage Occlusion

Clinical Investigation Plan

Protocol #21-101

Revision R

NCT: 05147792 (Pivotal Phase)

NCT: 06049615 (Conscious Sedation Sub-Study)

Sponsor: Conformal Medical, Inc.
15 Trafalgar Square, Ste. 101
Nashua, NH 03063

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4 Protocol Synopsis

Study Title	**The CONFORM Pivotal Trial**
Study Device	The Conformal CLAAS® Device is a permanent implant designed to occlude the left atrial appendage (LAA) to eliminate blood flow into and clot passage from the LAA. **Sizes**: Regular and Large to accommodate LAA Ostium Diameter size range of 10-40 mm **Delivery System**: CLAAS Delivery Catheter and Access Sheath available in either Single or Double Curves
Clinical Trial Intended Use	The CLAAS System is intended to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who: • Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for oral anticoagulation (OAC) (Coumadin or DOAC) therapy; AND • Are deemed by their physician to be suitable for OAC; AND • Have an appropriate rationale to seek a non-pharmacological alternative to OAC, taking into account the safety and effectiveness of the device compared to OAC
Objective	**Objective 1:** To evaluate the safety and effectiveness of the CLAAS System by demonstrating non-inferiority to currently marketed Left Atrial Appendage Occlusion (LAAO) systems in subjects with non-valvular atrial fibrillation. **Objective 2**: To demonstrate the safety of a post procedure pharmacologic antiplatelet regimen that consists of DAPT alone without concomitant oral anticoagulation therapy (OAC). **Objective 3:** To demonstrate the ability to safely deliver the CLAAS Device using a conscious sedation protocol without general anesthesia. To investigate this objective, a separate Sub-Study will be conducted after recruitment of the Randomized Clinical Trial (RCT) is complete at select, qualified sites based on the experience demonstrated in the RCT. **Objective 4:** Support regulatory approval(s) in territories outside the US.
Study Design	This is a pivotal clinical trial that includes three components: (1) Roll-In Phase using the CLAAS system alone

	(2) Randomized Clinical Trial (RCT) comparing CLAAS to commercially available LAAO systems. The RCT will be performed in a staged manner with no more than 250 subjects treated in the initial phase to support a safety summary on the first 50 CLAAS implants. Once approved by FDA, the RCT will advance to the second stage completing recruitment of the RCT cohort. (3) Conscious Sedation Single Arm Sub-study: A, single arm sub-study investigating the use of a conscious sedation protocol; conducted after enrollment in the RCT is complete and is listed under a separate NCT number within the clinicaltrials.gov website (NCT06049615). Appendix E provides a summary of the Sub-Study with statistical rationale.
Medicare Considerations	The study eligibility criteria include subjects that are largely identified in the Medicare population. As such, the randomized trial design is considered adequate to characterize the safety and effectiveness of the CLAAS System and will appropriately support the CMS criterion for coverage.
Sample Size	The sample size requirements for each of the study cohorts is listed below. **Roll-in Phase:** a maximum of 300 subjects can be enrolled as roll-in cases. **RCT Phase**: Up to one thousand six hundred (1600) subjects will be included in the randomized control trial.
Randomization	Randomization will be 1:1 to CLAAS Device (Investigational) versus currently marketed LAAO device (Control) using block randomization that is stratified by site.
Investigational Sites	Up to one hundred (100) investigational sites in North America, five (5) sites in Japan, and up to fifteen (15) sites in EU/EEA and Central Asia will be included in this study. The United States will account for ≥ 50% of the total subjects enrolled in the RCT cohort. Further, no more than 15% of the maximum sample size for the randomized trial will be enrolled by a single site. An ongoing list of all investigational sites shall be maintained in Sponsor files
Study Duration/ Follow-up Period	The trial is expected to take approximately 3 years to enroll, and each subject will be followed for a total of 5 years.

Primary Safety Endpoint	A composite of: • Major Procedure-Related Complications including (identified within 12 months of procedure and adjudicated as procedure related): a) cardiac perforation b) pericardial effusion requiring drainage c) ischemic stroke d) device embolization e) major vascular complications • Major bleeding through 12 months post procedure or • All-cause death 12 months post procedure All definitions are provided for all components in Appendix A. All events will be adjudicated by the independent Clinical Events Committee (CEC).
Primary Effectiveness Endpoint	A composite of ischemic stroke and systemic embolism through 18 months.
Secondary Endpoints	**Secondary Safety Endpoints** All elements of the Primary Safety Endpoint shall be reported descriptively at the time of PMA submission and at the time of PAS reports, for all subjects who have reached follow-up through 18-month, 2-year, 3-year, 4-year, 5-year timepoints, post-index procedure. **Secondary Performance and Efficacy Endpoints Including (all definitions provided in Appendix A):** 1. Device Success 2. Technical success 3. Procedure success 4. Embolic Events 5. Closure Success at 12 months based upon each of the following criteria: a. demonstration of peri-device leak ≤5 mm b. demonstration of peri-device leak ≤3 mm **Secondary Effectiveness Endpoints with Statistical Hypothesis Testing** The following endpoints will have formal statistical hypothesis tests with a gatekeeping approach to control the Type 1 error rate. Each endpoint will be based on a comparison of the treatment and control arms and is

	described in detail in the Statistical Analysis Plan and Section 14 of the protocol. 1. **Non-inferior closure success (≤5mm) at 45 days**, defined as peri-device residual leak ≤5mm by TEE as evaluated by an independent core lab. A 3% margin will be used. 2. **Non-inferior closure success (≤3mm) at 45-days**, defined as peri-device residual leak ≤3mm by TEE as evaluated by an independent core lab. A 5% margin will be used. 3. **Non-inferior complete closure success at 45 days,** defined as peri-device residual leak ≤1mm by TEE as evaluated by an independent core lab. A 5% margin will be used. 4. **Superior closure success (≤3mm) at 45 days,** defined as peri-device residual leak ≤3mm by TEE as evaluated by an independent core lab. 5. **Superior closure success (≤3mm) at 45 days, device subgroup test:** CLAAS vs. specific control device: defined as peri-device residual leak ≤3mm by TEE as evaluated by an independent core lab. Tests associated with this endpoint will be performed in descending order of use of specific control devices. Device testing will be performed only for control devices that are used in >20% of control cases. 6. **Superior complete closure success at 45 days,** defined as peri-device residual leak ≤1mm on TEE as evaluated by an independent core lab. 7. **Superior complete closure success at 45 days, device subgroup test:** CLAAS vs. specific control device: defined as peri-device residual leak ≤1mm on TEE as evaluated by an independent core lab. Tests associated with this endpoint will be performed in descending order of use of specific control devices. Device testing will be performed only for control devices that are used in >20% of control cases.
Antiplatelet and Anticoagulant Therapy	**Antiplatelet and oral anticoagulant therapy requirements (CLAAS):** **Pre-Procedure** Pre-procedure oral anticoagulation (Warfarin or DOAC) should be managed as per site protocol. Warfarin should be discontinued in accordance with site standard of care practices including the monitoring of INR levels on the day of the procedure. The following loading doses should be administered prior to the index procedure: • **Aspirin**

	○ ASA 81-100 mg (administered 1 day prior to procedure), or ○ ASA 325 mg (chewed 1 hour prior to procedure) • **Antibiotic Prophylaxis** ○ Pre-procedure antibiotic for endocarditis prophylaxis should be delivered prior to the procedure as per local standard of care. **Intra-Procedure** Intraprocedural anticoagulation with heparin should be administered per standard of care, maintaining an activated clotting time (ACT) of 250-350s throughout the procedure. **Post-Procedure (For Patient Assigned to Receive the CLAAS Implant)** • If the final procedural – post tether release TEE demonstrates adequate seal (residual leak ≤5mm) and there is no evidence of thrombus, subjects *shall* receive DAPT (ASA 81-100 mg QD and clopidogrel* 75 mg QD) until 45 days post-procedure imaging. • **If the 45-day TEE demonstrates adequate closure:** DAPT *should* be continued to 6 months, unless deemed unsafe by the subject's physician. • At 6 months, if adequate closure has been documented, DAPT should be replaced by monotherapy (ASA 81-100 mg or, P2Y12 inhibitors) until 12-month clinical assessment and is recommended for the duration of the Trial (Clopidogrel* may be substituted for ASA as the discretion of the subject's physician). • 12 months, if adequate closure has been documented, post-procedure, anti-platelet therapy should be administered as per standard of care. • Appropriate endocarditis prophylaxis is recommended for 6 months following device implantation. The decision to continue beyond 6 months is at the discretion of the site principal investigator. **NOTE: A substitute P2Y12 inhibitor (i.e., prasugrel, ticagrelor) may be used as per managing physician's judgement. For patients who are known clopidogrel non-responder an alternative P2Y12 inhibitor should be used.* **ADDITIONAL CONSIDERATIONS:** • **<u>Inadequate seal:</u>** Subjects with inadequate seal (residual leak >5mm) at the post-deployment (or any subsequent TEE) should be evaluated for treatment with DOAC and ASA for 4-6 weeks

	followed by TEE. If inadequate seal persists, antithrombotic therapy should be considered until seal is confirmed on follow up imaging. Antithrombotic therapy should be individualized to the patient based on anatomic (size of leak) and clinical (risk of anticoagulation) considerations. • **Device Related Thrombus:** Thrombus detected on the LA surface of the device, at the post-procedure TEE (or any subsequent TEE), should be evaluated for treatment with OAC and ASA for 4-6 weeks followed by repeat imaging. Antithrombotic therapy should be continued until thrombus has been confirmed to be resolved on the follow up imaging. Antithrombotic therapy should be individualized to the patient based on clinical (risk of anticoagulation) considerations. **Antiplatelet and oral anticoagulant therapy requirements, Control Group** Control subjects should be treated according to the marketed LAAO device manufacturer's Instructions for Use. *NOTE: A substitute P2Y12 inhibitor (i.e., prasugrel, ticagrelor) may be used as per managing physician's judgement. For patients who are known clopidogrel non-responder an alternative P2Y12 inhibitor should be used.* Subjects found to have Leak or Device Related Thrombus identified on Cardiac CT must have confirmation by TEE.
Subject Population	The subject population from which subjects for this trial will be recruited consists of adult subjects with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to long-term oral anticoagulation, and who have been deemed appropriate for LAA closure by the site investigator and a clinician not a part of the procedural team using a shared decision process in accordance with standard of care.
Inclusion Criteria	Potential subjects must meet **ALL** of the following criteria to be eligible for inclusion in the study: ***General Inclusion Criteria*** 1. Male or non-pregnant female aged ≥18 years. 2. Documented non-valvular AF (paroxysmal, persistent, or permanent). 3. High risk of stroke or systemic embolism, defined as CHA2DS2-VASc score of ≥3. 4. Has an appropriate rationale to seek a non-pharmacologic alternative to long-term oral anticoagulation.

	5. Deemed by the site investigator to be suitable for short term oral anticoagulation therapy but deemed less favorable for long-term oral anticoagulation therapy. 6. Deemed appropriate for LAA closure by the site investigator and a clinician not a part of the procedural team using a shared decision-making process in accordance with standard of care. 7. Able to comply with the protocol-specified medication regimen and follow-up evaluations. 8. The patient (or legally authorized representative, where allowed) has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent approved by the appropriate Institutional Review Board (IRB)/Regional Ethics Board (REB)/Ethics Committee (EC).
Exclusion Criteria	Potential subjects will be excluded if **ANY** of the following conditions apply: ***General Exclusion Criteria*** 1. Pregnant or nursing patients and those who plan pregnancy in the period up to one year following the index procedure. Female patients of childbearing potential must have a negative pregnancy test (per site standard test) **within 7 days** prior to index procedure. 2. Anatomic conditions that would prevent performance of an LAA occlusion (e.g., atrial septal defect (ASD) requiring closure, high-risk patent foramen ovale (PFO) requiring closure, a highly mobile inter-atrial septal aneurysm precluding a safe TSP, presence of a PFO/ASD closure device, history of surgical ASD repair or history of surgical LAAO closure). 3. Atrial fibrillation that is defined by a single occurrence or that is transient or reversible (e.g., secondary thyroid disorders, acute alcohol intoxication, trauma, recent major surgical procedures). 4. A medical condition (other than atrial fibrillation) that mandates long-term oral anticoagulation (e.g., history of unprovoked deep vein thrombosis or pulmonary embolism, or prosthetic mechanical heart valve). 5. History of bleeding diathesis or coagulopathy, or patients in whom antiplatelet and/or anticoagulant therapy is contraindicated. 6. Documented active systemic infection. 7. Symptomatic carotid artery disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject has a history of carotid stent or endarterectomy the subject is eligible if there is <50% stenosis noted at the site of prior treatment.

	8. Recent (**within 30 days** of index procedure) or planned (**within 60 days** post-procedure) cardiac or major non-cardiac interventional or surgical procedure. 9. Recent (**within 30 days** of index procedure) stroke or transient ischemic attack. 10. Recent **(within 30 days** of index procedure) myocardial infarction. 11. Vascular access precluding delivery of implant with catheter-based system. 12. Severe heart failure (New York Heart Association Class IV). 13. Prior cardiac transplant, history of mitral valve replacement or transcatheter mitral valve intervention, or any prosthetic mechanical valve implant. 14. Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 (by the Modification of Diet in Renal Disease equation). 15. Platelet count <75,000 cells/mm3 or >700,000 cells/mm3, or white blood cell count <3,000 cells/mm3. 16. Known allergy, hypersensitivity or contraindication to aspirin, heparin, or that would preclude any P2Y12 inhibitor therapy, or to device materials (e.g., nickel, titanium), or the subject has contrast sensitivity that cannot be adequately pre-medicated. 17. Actively enrolled or plans to enroll in a concurrent clinical study in which the active treatment arm may confound the results of this trial. 18. Unable to undergo general anesthesia. 19. Known other medical illness or known history of substance abuse that may cause non-compliance with the protocol or protocol-specified medication regimen, confound the data interpretation, or is associated with a life expectancy of less than 5 years. 20. A condition which precludes adequate transesophageal echocardiographic (TEE) assessment. ***Echocardiographic Exclusion Criteria*** 1. Left atrial appendage anatomy which cannot accommodate a commercially available control device or the CLAAS Implant per manufacturer IFU (e.g., the anatomy and sizing must be appropriate for both the investigational (CLAAS) and a commercially available device to be enrolled in the trial). 2. Intracardiac thrombus or dense spontaneous echo contrast consistent with thrombus, as visualized by TEE. 3. Left ventricular ejection fraction (LVEF) <30%. 4. Moderate or large pericardial effusion >10 mm or symptomatic pericardial effusion, signs or symptoms of acute or chronic pericarditis, or evidence of tamponade physiology 5. Atrial septal defect that warrants closure. 6. High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion >15 mm or length >15 mm) or large shunt

	(early [within 3 beats] and/or substantial passage of bubbles, e.g., ≥20). 7. Moderate or severe mitral valve stenosis (mitral valve area <1.5cm^2). 8. Complex atheroma with mobile plaque of the descending aorta and/or aortic arch. 9. Evidence of cardiac tumor.
Follow-up Requirements	Follow-up visits will occur prior to hospital discharge and at 7 days via telehealth assessment and at 45 days (imaging and telehealth), 6 months (telehealth visit), 12 months (imaging and telehealth) and 18 months (clinic visit), and 2, 3, 4 and 5 years (telehealth) post procedure. *NOTE: If the subject has not yet been discharged from the index procedure hospitalization at day 7 post-procedure, the 7-day follow-up may be conducted in-hospital.*
Statistical Summary	All endpoints will be reported using appropriate descriptive statistics. Statistics for continuous variables will include sample size, mean, standard deviation, median, interquartile range, minimum, and maximum. Binary variables will be summarized using sample size, frequencies, and percentages. Kaplan-Meier analysis will be used for time-to-event analyses. The primary effectiveness endpoint will be analyzed for non-inferiority based on a margin of 0.032. The primary safety endpoint will be analyzed for non-inferiority based on a margin of 0.058. The primary effectiveness and safety endpoints will also be reported using descriptive statistics and nominal confidence bounds.
Safety Oversight	The study will include subject safety protection measures that include safety committees that will assure patient safety. The study will include an independent Clinical Events Committee comprised of a multi-disciplinary team of physicians that will adjudicate all SAFETY ENDPOINT events and confirm causality and seriousness. An independent, multi-disciplinary Data Safety Monitoring Board will also be established and is tasked with reviewing all safety data at regular intervals to monitor for the incidence of serious adverse events that would warrant modification or termination of the trial.
Public Release of Study and Results	The CONFORM TRIAL (Roll-In and Pivotal Trial Phase) is listed on clinicaltrials.gov under NCT05147792. The CONFORM TRIAL (Conscious Sedation Sub-Study) is listed on clinicaltrials.gov under separate NCT06049615.

	In accordance with the requirements of ClinicalTrials.gov (as outlined Section 801 of the FDA Amendments Act) results will be posted when the complete data analysis is performed.

5 Study Schedule of Assessments

	Screening	Procedure[0]	Pre-Discharge	7-Day	45-Day	6 Month (180 days)	12 Month (365 days)	18 Month (545 days)	2, 3, 4, 5 Year (730, 1095, 1460, 1825 days)	Stroke/SE Assessment[1]
		Day 0		+2 Days	±7 Days	±30 Days	±30 Days	±30 Days	±60 Days	
	Clinic Visit			Telehealth[2]	Clinic Visit/ Telehealth[2]	Telehealth[2]	Clinic Visit/ Telehealth[2]	Clinic Visit	Telehealth[2]	
Informed Consent	X									
Medical and Surgical History	X									
Physical Exam/Assessment	X									
Vital Signs	X									
CHA_2DS_2-VASc	X									
HAS-BLED	X									
Serum Creatinine or GFR/eGFR	X[3]									
CBC, Platelet count and Hgb/Hct	X[3]	X[4]								
ECG 12 Lead	X[5]									
Pregnancy Test	X[6]									
Neuro Assessment	X[7]		X[7]					X		X[20]
QVSFS	X[8]			X	X	X	X	X	X	X
Cardiac CT	X[9]				X[11]		X[11]			X[18]
TTE	X[9]		X[10]							
TEE	X[9]	X[19]			X[12]		X[12]			X[18]
Brain Imaging	X[13]									X[14]
AE Assessment	X	X	X	X	X	X	X	X	X	
Medication Review[15]	X	X	X	X	X	X	X	X	X	
INR[16]	X	X								
Randomization	X[17]									
LAA Measurements		X								

TABLE FOOTNOTES

For more in-depth information regarding the Schedule of Assessments, see **Section 9 Study Procedures and Assessments**

[0] Procedure must occur within 14 days from the date of randomization.

[1] In the event of a suspected stroke or systemic embolism, an Adverse Event of Special Interest CRF should be completed.

[2] Tele-Health Visit: Clinical evaluation can be performed via phone call, video link or clinic visit.

[3] May be performed as part of standard of care up to 60 days prior to consent.

[4] Performed within 48 hours of index procedure.

[5] Performed within 30 days prior to the index procedure may be used as the baseline ECG, provided there have been no signs or symptoms of myocardial ischemia between the time of the ECG and the screening assessment (in which case the ECG should be performed within 24 hours prior to the index procedure).

[6] Required for females of childbearing potential within 7 days of index procedure (by site standard, either serum or urine).

[7] Neuro Assessment to include National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale for Neurologic Disability (MRS) within 30 days of index procedure. The pre-discharge stroke assessment must be done after the effects of anesthesia have resolved.

[8] QVSFS: Questionnaire for Verifying Stroke-Free Status within 30 days of index procedure.

[9] **Screening imaging (TEE or CT) must be performed prior to randomization.** Imaging is required to assess the anatomic screening criteria. Cardiac CT or TEE can be used to assess all Echocardiographic Eligibility Criteria. TTE and MRI studies are limited to the assessment of Left ventricular ejection fraction and for detection of pericardial effusions. TTE and MRI cannot be used to assess other Echocardiographic Eligibility Criteria.

[10] Implanted subjects only (does not include patients who did not receive a LAAO device). TTE is required to surveil for pericardial effusion. The study must be performed at a minimum of 4 hours from the end of the procedure (removal of the access sheath).

[11] Cardiac CT may be used in lieu of TEE to screen for end point findings, e.g., DRT or >3mm peri-device Leak.

- If a Device Related Thrombus is detected, a TEE is required to confirm the finding as soon as possible (recommended assessment within 2 weeks; at latest, 4-6 weeks from date of original study or at the patient's next follow up visit, whichever is first). If a thrombus can be classified as a large thrombus (defined as protruding and >10 mm), a confirmatory TEE is not mandated.
- If a non-trivial peri-device leak is noted on CT, a TEE is required to confirm the finding, as soon as possible (ideally within 2 weeks; at latest, 4-6 weeks from date of original study or at the patient's next follow up visit, whichever is first).

  Note: A non-trivial peri-device leak found on CT is one in which the site investigator determination indicates a likely finding of leak >3mm if measured by TEE.
- If a Pericardial Effusion measuring >10mm is detected on Cardiac CT, TTE evaluation is required for quantification.

[12] If TEE demonstrates a pericardial effusion measuring >10 mm, a TTE is required.

[13] Brain Imaging: For subjects with documented history of TIA/Stroke in the 24-month period prior to enrollment, the most recent brain imaging (CT/MRI) report is required at baseline. If there is no available imaging report or there has been a suspected neuro event, brain imaging may be requested by the Sponsor as a baseline reference.

[14] Brain Imaging is ONLY required for patients with Systemic Embolism (SE) if there are new findings suggestive of TIA/Stroke.

[15] Medication assessment data collection includes the use of antiplatelet, anticoagulation and prophylactic antibiotic medication only.

[16] INR levels required only for patients taking Warfarin, or in accordance with standard of care.

[17] **Randomization after all clinical assessments and eligibility criteria are confirmed** and shall be performed within 90 days of informed consent.

[18] For embolic stroke, imaging of LAA is required. TEE is preferred, however Cardiac CT is acceptable

[19] The procedure TEE can serve as both the screening and procedure TEE if done prior to randomization.

[20] NIHSS and mRS should be collected at time of event (or as soon as clinically feasible). For all stroke subjects a 90-day mRS is also required to assess disability status