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CIP: The CONFORMAL Prague Study

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The CONFORMAL Prague Study

An Evaluation of the Safety and Performance of the Conformal Left Atrial Appendage Seal for Left Atrial Appendage Occlusion

Clinical Investigation Plan

Protocol # 19-101

Revision A

March 22, 2019

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

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1.0 Document Control

1.1 Version History

Version (Date)	Description
A (March 22, 2019)	Initial submission to Prague

1.2 Protocol Approval Page

Study title:	The CONFORMAL Prague Study An evaluation of the safety and performance of the Conformal Left Atrial Appendage Seal for Left Atrial Appendage Occlusion
Protocol version:	A
Protocol date:	March 22, 2019

Principal Investigator
Vivek Reddy, M.D.

Date

Chris Cain
Vice President, Clinical & Regulatory Affairs
Conformal Medical, Inc.

Date

1.3 Investigator Signature Page

Study title: The CONFORMAL Prague Study

An evaluation of the safety and performance of the Conformal Left Atrial Appendage Seal Device for Left Atrial Appendage Occlusion

Protocol version: A

Protocol date: March 22, 2019

Investigator's Responsibility

As the site Principal Investigator, I understand that I must obtain written approval from my Institutional Review Board prior to participation in the trial. This approval must include my name and a copy must be provided to Conformal Medical (or designee), along with the approved Patient Information and Consent Form prior to the first enrollment at my study site.

As the site Principal Investigator, I must also:

1. Conduct the study in accordance with the study protocol, the signed Clinical Investigation Agreement, applicable laws, 21 CFR Part 812 and other applicable United States Food and Drug Administration (FDA) regulations, any conditions of approval imposed by the FDA or IRB, International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and the Declaration of Helsinki, and ensure that all study personnel are appropriately trained prior to any study activities.
2. Ensure that the study is not commenced until all approvals have been obtained.
3. Supervise all use of the Conformal Medical Left Atrial Appendage Seal (CLAAS) device at my institution.
4. Ensure that written informed consent is obtained from each subject prior to any data collection and any study-specific procedures or assessments, using the most recent Institutional Review Board approved Informed Consent Form.
5. Provide all required data and reports and agree to source document verification of study data with patient's medical records by Conformal Medical (or designee) and any regulatory authorities.
6. Allow Conformal Medical personnel or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to national data protection laws.

Investigator Signature

I have read and understand the contents of this Clinical Investigation Plan and agree to abide by the requirements set forth in this document.

_____ _____

Investigator Name (print) Investigative Site (print)

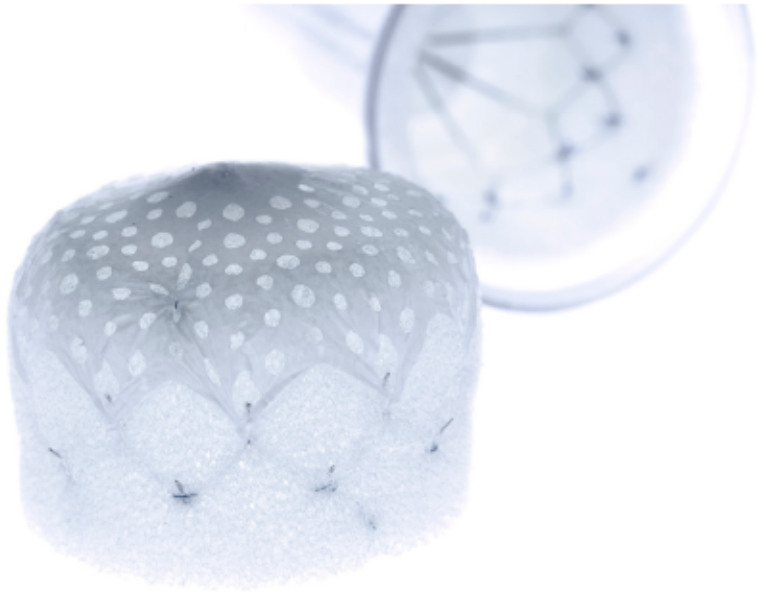
_____ _____

Investigator Signature Date

2.0 Study Contacts

Sponsor	**Conformal Medical, Inc.** 15 Trafalgar Square, Ste. 101 Nashua, NH 03063 USA **Conformal Contact:** Chris Cain Vice President, Clinical & Regulatory Affairs Tel: 408.439.5154 email: ccain@conformalmedical.com
Principal Investigator	Prof. Petr Neuzil, M.D., Ph.D., FESC. Head of cardiology and Director of EP Animal Lab Na Homolce Hospital Roentgenova 2 Prague 150 30 phone: 420 257272211 fax: 420 257272693
Monitoring	**Conformal Medical, Inc.** **Contact:** Chris Cain VP, Clinical & Regulatory Affairs Email: ccain@conformalmedical.com

3.0 Protocol Synopsis

Study Title	**The Conformal Prague Study** An evaluation of the safety and performance of the Conformal Left Atrial Appendage Seal for Left Atrial Appendage Occlusion
Study Device	The Conformal Left Atrial Appendage Seal (CLAAS™) is a permanent implant designed to occlude the left atrial appendage (LAA) to eliminate blood flow into and clot passage from the LAA. 
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 CHA_2DS_2-VASc scores and are recommended for oral anticoagulation (OAC) therapy; 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	The primary objective is to evaluate the safety and technical performance of the CLAAS system for closure of the left atrial appendage in patients with non-valvular atrial fibrillation at increased risk for stroke and systemic embolism who are recommended for oral anticoagulation (OAC) therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC.

Study Design	A prospective, single center, open-label, single arm, study to evaluate the safety and technical performance of the CLAAS system for closure of the left atrial appendage. Patients presenting with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, and who meet all eligibility criteria, will be enrolled in the study and undergo LAA closure with the CLAAS system.
Sample Size	Up to 20 subjects shall be enrolled in the study.
Investigational Sites	One (1) investigational site in Europe.
Study Duration / Follow-up Period	Subjects will have clinical follow-up prior to hospital discharge and at 7 days, 45 days and, 6 and 12 months. Transesophageal echocardiographic (TEE) follow-up will be performed at 45 days and, 6 and 12 months.
Primary Safety Endpoint	**Freedom from major adverse events,** evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of: • All-cause mortality • Ischemic stroke • Systemic thromboembolism • Device- or procedure-related adverse events requiring open cardiac surgery or major endovascular intervention* *NOTE: Major endovascular intervention includes pseudoaneurysm repair, AV fistula repair, and other major endovascular repair. Non-major interventions that are excluded from this endpoint include percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications.
Primary Performance Endpoint	**Closure success**, defined as device success followed by complete closure or peri-device residual leak ≤5 mm in width on TEE, at 45 days post-procedure.
Secondary Endpoints	Unless otherwise indicated, the following secondary endpoints will be evaluated in-hospital and at 45 days and, 6 and 12 months: **Secondary Safety Endpoints** 1. **Major procedure-related complications,** defined as the composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and major vascular complications, as related to the study device or procedure [evaluated in-hospital]

	2. **Major safety events,** defined as the composite of all-cause mortality, overt CNS injury (Neuro ARC defined), and major bleeding (BARC Type 3-5) 3. **Mortality**, classified as cardiovascular or non-cardiovascular and reported cumulatively and individually **Secondary Performance Endpoints** 1. **Device success**, defined as successful implantation of the CLAAS device in the LAA with acceptable position, and seal (peri-device residual leak ≤5 mm in width on ICE post procedure) 2. **Procedure success**, defined as device success without major in-hospital procedure-related complications during hospitalization or at 7 days whichever is longer 3. **Closure success**, defined as closure or peri-device residual leak ≤5 mm in width on TEE at 6 months post-procedure **Secondary Effectiveness Endpoint** 1. **Embolic events**, defined as the composite of ischemic stroke and systemic embolism
Other Measure	**Use of TEE** to confirm post-procedure ICE evaluation of device seal and position as a comparator for device success.
Antiplatelet and Anticoagulant Therapy	Antiplatelet and oral anticoagulant therapy requirements are as follows: **Pre-Procedure** The following loading doses should be administered prior to the index procedure: • ASA 81-100 mg (administered 1 day prior to procedure and continued daily) **Intra-Procedure** Intraprocedural medication should be administered per standard of care, maintaining an activated clotting time (ACT) of 250-350s throughout the procedure. **Post-Procedure** If the post-procedure TEE demonstrates adequate seal (residual leak ≤5 mm) and there is no evidence of thrombus, subjects should receive DAPT (ASA 75-100 mg QD and clopidogrel 75 mg QD) until 45 days post-procedure. If the 45-day TEE demonstrates adequate closure, DAPT should be continued to 6 months. For high bleeding risk (HBR) subjects, monotherapy (ASA preferred, P2Y12 permitted) may be initiated per physician judgement. If the 6-month TEE demonstrates adequate closure, DAPT should be replaced by monotherapy (ASA preferred, P2Y12 permitted). • **Inadequate seal:** Subjects with inadequate seal (residual leak >5 mm) at the post-procedure TEE (or any subsequent TEE) should be evaluated for

	treatment with NOAC and ASA for 4-6 weeks followed by TEE. If inadequate seal persist, anti-thrombotic therapy should be individualized for the patient balancing bleeding risk with the associated persistent inadequate seal (seen on TEE). • **Thrombus:** For thrombus detected on 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 TEE. Anti-thrombotic therapy should be individualized for the patient, balancing bleeding risk and the assumed thrombo-embolic risk associated with the TEE findings.
Patient Population	Patients presenting with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation.
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 a CHA_2DS_2-VASc score of ≥ 2 4. The patient is recommended for oral anticoagulation therapy (OAC), but has an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation 5. The patient is willing and able to comply with the protocol-specified medication regimen and follow-up evaluations 6. The patient (or legally authorized representative) has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent approved by the appropriate 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 1 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 procedure (e.g., prior atrial septal defect [ASD] or patent foramen ovale

	[PFO], surgical repair or implanted closure device, or obliterated or ligated left atrial appendage) 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. Patients with a medical condition (other than atrial fibrillation) that mandates chronic oral anticoagulation (e.g., history of unprovoked deep vein thrombosis or pulmonary embolism, or mechanical heart valve) 5. History of bleeding diathesis or coagulopathy, or patients in whom antiplatelet and/or anticoagulant therapy is contraindicated 6. Active infection with bacteremia 7. Documented symptomatic carotid artery disease (>50% diameter stenosis with prior ipsilateral stroke or TIA) or known asymptomatic carotid artery disease (diameter stenosis of >70%) 8. Recent (within 30 days of index procedure) or planned (within 60 days post-procedure) cardiac or non-cardiac interventional or surgical procedure 9. Recent (within 90 days of index procedure) stroke, transient ischemic attack 10. Recent myocardial infarction within 60 days of index procedure 11. Vascular access precluding delivery of implant with catheter-based system 12. Severe heart failure (New York Heart Association Class III or IV) 13. Prior cardiac transplant, history of mitral valve replacement or transcatheter mitral valve intervention, or any mechanical valve implant 14. Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the Modification of Diet in Renal Disease equation), or dialysis at the time of screening 15. Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <3,000 cells/mm^3 16. Patient has a known allergy, hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, or device materials (e.g., nickel, titanium, gold), or the patient has contrast sensitivity that cannot be adequately pre-medicated 17. Current participation in another investigational drug or device study that interferes with this study 18. Patient is a prisoner 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 1 year 20. Patient has a condition which precludes adequate transesophageal echocardiographic (TEE) assessment ***Echocardiographic Exclusion Criteria*** 1. Left atrial appendage anatomy cannot accommodate the CLAAS device per manufacturer IFU (e.g., ostium width <13 mm or >30 mm) 2. Intracardiac thrombus or dense spontaneous echo contrast, as visualized by TEE within 2 days prior to implant 3. Left ventricular ejection fraction (LVEF) <30% 4. Circumferential 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 (exclusion >15 mm or length > 15 mm) or large shunt (early [within 3 beats] or substantial passage of bubbles) 7. Moderate or severe mitral valve stenosis (mitral valve area <1.5 cm^2) 8. Complex atheroma with mobile plaque of the aorta 9. Patient has evidence of cardiac tumor

4.0 Background

4.1 Clinical Background

4.1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common clinically significant cardiac tachyarrhythmia, affecting more than 33 million patients worldwide, with a projected incidence of 5 million patients per year.[4] In the United States alone, approximately 6 million individuals suffer from AF and over one million new cases are diagnosed annually; due the aging population, the number is expected to double by the year 2030.[5, 6]

AF is associated with a substantially increased risk of stroke and thromboembolic events,[7] primarily due to the Left Atrial Appendage (LAA) serving as a site for thrombus formation. Untreated patients with AF have a 2-5% annual incidence of stroke, with a history of stroke or thromboembolic events conferring an even higher risk.[8, 9] Strokes that occur with AF are large and can be quite debilitating, leading to death or costly and painful rehabilitation and adding significant financial burden to the medical system.

4.1.2 Current Standard of Care to Treat Atrial Fibrillation

The standard treatment for stroke prevention in subjects with AF is oral anticoagulant (OAC) therapy to reduce the likelihood of clot formation, which is recommended regardless of the management strategy of the underlying rhythm disorder.[10] Options include warfarin and the Novel oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban).[11-14] While pharmacotherapy can reduce stroke incidence in AF by approximately 60%,[15] OAC therapy is associated with an increased risk of bleeding complications,[16] an issue of significant concern due to the high bleeding risk of many AF patients. In addition, management of OAC therapy is burdensome and long-term compliance is poor even in the closely monitored setting of clinical trials, putting patients at risk for embolic events.

Echocardiographic evidence that the LAA is the source of thrombi in more than 90% of patients with AF has prompted the development of novel transcatheter therapies to occlude the LAA, thereby excluding it from the circulation in AF patients with non-valvular AF.[17-21] Randomized clinical trials have demonstrated acceptable benefit to risk ratios for LAA closure in patients with non-valvular AF and a high risk for stroke or systemic embolism and an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation.[10, 22] The WATCHMAN Left Atrial Appendage Closure Device (Boston Scientific Corporation, Marlborough, MA, US) received FDA approval in March 2015 on the basis of data from the . PROTECT-AF and PREVAIL randomized clinical trials and associated continued access registries that demonstrated that the device was non-inferior to warfarin for the primary composite endpoint of stroke, systemic embolism, or cardiovascular death. In addition, device implantation was associated with an approximately 80% reduction in hemorrhagic strokes and a >50% reduction in cardiovascular death.[10, 22]

While LAA closure with the WATCHMAN device represents an important advance in stroke prevention for patients with AF, important limitations and opportunities for improvement exist, including a technically challenging implantation process, restrictions of the LAA anatomies that can be effectively sealed, and low but persistent rates of residual leaks and device-related thrombus.

Conformal Medical has developed an alternative LAA closure technology that maintains the stroke prevention efficacy of the WATCHMAN device while offering a simplified implantation procedure; conformability to diverse LAA anatomies that reduces the opportunity for leakage; and a thromboresistant left atrial surface.

4.2 Investigational Device

4.2.1 Name of the Investigational Device

The Conformal Left Atrial Appendage Seal (CLAAS™)

4.2.2 Manufacturer

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

4.2.3 Proposed Indication for 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 CHA_2DS_2-VASc scores and are recommended for oral anticoagulation (OAC) therapy; 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.

4.2.4 Device Description

The following is a summary description of the Investigational Device. For additional information, please refer to the Instructions for Use.

4.2.4.1 Overview

The Conformal Left Atrial Appendage Seal (CLAAS™) system consists of a permanent implant and a delivery system and is designed to occlude the left atrial appendage (LAA) to eliminate blood flow into and clot passage from the LAA.

4.2.4.2 CLAAS Implant

The CLAAS implant is a self-expanding occluder consisting of a cylindrical nitinol endoskeleton (with low-profile anchor barbs around the midpoint) covered with a porous foam cup (Figure 4-1). The implant is designed to permanently close off the LAA from the LA with an endothelial layer that grows across the LA face of the implant. The proximal face of the porous foam cup has an ePTFE fabric cover to provide a thromboresistant outer surface, and the distal portion of the cup extends beyond the endoskeleton to serve as an atraumatic leading edge. The flexible implant is designed to conform to irregular LAA anatomy while maintaining secure fixation with less dependency on coaxial orientation. The CLAAS device is recapturable and redeployable prior to final release from the delivery system via a flexible tether (which attaches to a tether pin on the endoskeleton). The implant is currently available in a single size (regular) that is 27 mm in diameter (and 10 mm in depth). A 35 mm device will be available at a later date.

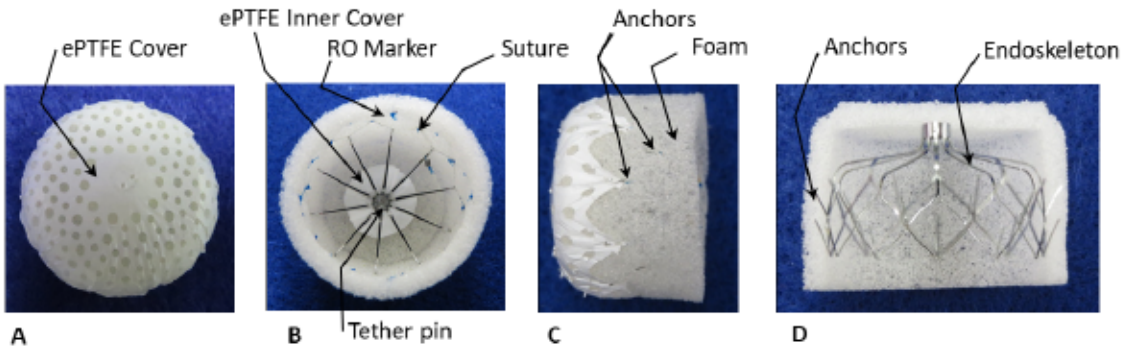


Figure 4-1. CLAAS implant. (A) Left atrial face with ePTFE cover; (B) Inside view showing the endoskeleton, foam, ePTFE inner cover, and tether pin; (C) Side view showing anchors and ePTFE attachment and (D) Cross-section showing endoskeleton and distal foam bumper.

4.2.4.3 CLAAS Delivery System

In addition to the implant, the CLAAS system includes a Delivery System to allow percutaneous delivery of the implant to the LAA via standard femoral venous access and transseptal puncture. The CLAAS Delivery System consists of an Access Sheath with a Dilator, a coaxial Delivery Catheter, a removable tether used to attach the implant to the Delivery Catheter, and a loading tool to load the implant into the Delivery Catheter in the catheterization laboratory.

4.3 Rationale

The CLAAS system is designed to provide the benefits of left atrial appendage closure with a conventional device, while potentially simplifying the implantation procedure, improving procedural safety, and reducing the peri-device leakage. The study will evaluate the feasibility of LAA closure with the CLAAS system and gather preliminary safety and effectiveness data to inform the design of a pivotal trial.

5.0 Study Design

5.1 Study Design Overview

This prospective, single center, open-label, single arm, study will enroll up to 20 subjects aimed at examining the safety and technical performance of the CLAAS device for LAA closure. Patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, and who meet all eligibility criteria, will be enrolled in the study and undergo LAA closure with the CLAAS system.

Subjects will have clinical follow-up prior to hospital discharge and at 7 days, 45 days, and 6- and 12-months post procedure. Transesophageal echocardiographic (TEE) follow-up will be performed at 45 days and, 6 and 12 months in all subjects.

The primary safety endpoint is freedom from major adverse events, evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of all-cause mortality, ischemic stroke, systemic thromboembolism, and device- or procedure-related

adverse events requiring open cardiac surgery or major endovascular intervention. The primary performance endpoint is closure success, defined as device success followed by successful LAA closure (complete closure or peri-device residual leak ≤5 mm in width on TEE at 45 days post-procedure). The study will also report additional secondary safety, performance, and effectiveness endpoints, as well as using TEE to confirm post-procedure ICE evaluation of device seal and position as a comparator for device success.

All endpoints will be reported using appropriate descriptive statistics in the primary analysis population (the ITT population), and no hypothesis testing will be performed. As a secondary analysis, all endpoints will be evaluated in the Implanted Patient (IP) population.

5.2 Study Objective

The primary objective of the study is to evaluate feasibility of ICE as primary imaging modality for device success in patients with non-valvular atrial fibrillation at increased risk for stroke and systemic embolism who are recommended for oral anticoagulation (OAC) therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC. TEE will be used to confirm the ICE evaluation.

5.3 Endpoints

5.3.1 **Primary Safety Endpoint**

The primary safety endpoint is **freedom from major adverse events,** evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of:

- All-cause mortality
- Ischemic stroke
- Systemic thromboembolism
- Device- or procedure-related adverse events requiring open cardiac surgery or major endovascular intervention*

*NOTE: Major endovascular intervention includes pseudoaneurysm repair, arteriovenous fistula repair, and other major endovascular repair. Non-major interventions that are excluded from this endpoint include percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications.

5.3.2 **Primary Performance Endpoint**

The primary performance endpoint is **closure success**, defined as device success followed by complete closure or peri-device residual leak ≤5 mm in width on TEE at 45 days post procedure.

5.3.3 **Secondary Endpoints**

Unless otherwise indicated, the following secondary endpoints will be evaluated in-hospital and at 45 days, and 6 and 12 months.

5.3.3.1 Secondary Safety Endpoints

5.3.3.1.1 **Major procedure-related complications**, defined as the composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and major vascular complications as related to the study device or procedure [evaluated in-hospital]

5.3.3.1.2 **Major safety events**, defined as the composite of all-cause mortality, overt CNS injury (Neuro ARC defined), and major bleeding (BARC Type 3-5)

5.3.3.1.3 **Mortality**, classified as cardiovascular or non-cardiovascular reported cumulatively and individually

5.3.3.2 Secondary Performance Endpoints

5.3.3.2.1 **Device success**, defined as successful implantation of the CLAAS device in the LAA with acceptable position and seal (peri-device residual leak ≤5 mm in width on ICE post procedure)

5.3.3.2.2 **Procedure success**, defined as device success without major in-hospital procedure-related complications during hospitalization or at 7 days whichever is longer

5.3.3.2.3 **Closure success**, defined as closure or peri-device residual leak ≤5 mm in width on TEE at 6 months post-procedure

5.3.3.3 **Secondary Effectiveness Endpoint**

5.3.3.3.1 **Embolic events**, defined as the composite of ischemic stroke and systemic embolism

5.3.4 Other Measures

The following other imaging-related measures will also be evaluated:

5.3.4.1 Intra Cardiac Echocardiography (ICE)

5.3.4.1.1 Ability to accurately assess CLAAS device position and seal [evaluated prior to implant release during the index procedure]

5.3.4.1.2 Ability to adequately visualize pericardial space to rule out effusion [evaluated post-implant during the index procedure]

6.0 Subject Selection and Withdrawal

6.1 Patient Population

The patient 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 and are recommended for OAC therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC, and who have been deemed appropriate for LAA closure by the Site PI on oral anticoagulants consistent with the standard of care.

6.2 Eligibility Criteria

6.2.1 **Inclusion Criteria**

Potential subjects must meet ALL of the following criteria to be eligible for enrollment into the study:

6.2.1.1 General Inclusion Criteria

6.2.1.1.1 Male or non-pregnant female aged ≥18 years

6.2.1.1.2 Documented non-valvular AF (paroxysmal, persistent, or permanent)

6.2.1.1.3 High risk of stroke or systemic embolism, defined as a CHA_2DS_2-VASc score of ≥ 2

6.2.1.1.4 The patient is recommended for oral anticoagulation therapy (OAC), but has an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation

6.2.1.1.5 The patient is willing and able to comply with the protocol-specified medication regimen and follow-up evaluations

6.2.1.1.6 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 Ethics Committee (EC)

6.2.2 **Exclusion Criteria**

Potential subjects will be excluded if ANY of the following criteria apply:

6.2.2.1 General Exclusion Criteria

6.2.2.1.1 Pregnant or nursing patients and those who plan pregnancy in the period up to 1 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.

6.2.2.1.2 Anatomic conditions that would prevent performance of an LAA occlusion procedure (e.g., prior atrial septal defect [ASD] or patent foramen ovale [PFO] surgical repair or implanted closure device, or obliterated or ligated left atrial appendage)

6.2.2.1.3 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)

6.2.2.1.4 Patients with a medical condition (other than atrial fibrillation) that mandates chronic oral anticoagulation (e.g., history of unprovoked deep vein thrombosis or pulmonary embolism, or mechanical heart valve)

6.2.2.1.5 History of bleeding diathesis or coagulopathy, or patients in whom antiplatelet and/or anticoagulant therapy is contraindicated

6.2.2.1.6 Active infection with bacteremia

6.2.2.1.7 Documented symptomatic carotid artery disease (>50% diameter stenosis with prior ipsilateral stroke or TIA) or known asymptomatic carotid artery disease (diameter stenosis of >70%)

6.2.2.1.8 Recent (within 30 days pre-procedure) or planned (within 60 days post-procedure) cardiac or non-cardiac interventional or surgical procedure

6.2.2.1.9 Recent (within 90 days pre-procedure) stroke or transient ischemic attack

6.2.2.1.10 Recent (within 60 days pre-procedure) myocardial infarction

6.2.2.1.11 Vascular access precluding delivery of implant with catheter-based system

6.2.2.1.12 Severe heart failure (New York Heart Association Class III or IV)

6.2.2.1.13 Prior cardiac transplant, history of mitral valve replacement or transcatheter mitral valve intervention, or any mechanical valve implant

6.2.2.1.14 Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the Modification of Diet in Renal Disease equation), or dialysis at the time of screening

6.2.2.1.15 Platelet count <75,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <3,000 cells/mm^3

6.2.2.1.16 Patient has a known allergy, hypersensitivity or contraindication to aspirin, heparin, or device materials (e.g., nickel, titanium, gold) or that would preclude any P2Y12 inhibitor therapy, or the patient has contrast sensitivity that cannot be adequately pre-medicated

6.2.2.1.17 Current participation in another investigational drug or device study that interferes with this study

6.2.2.1.18 Patient is a prisoner

6.2.2.1.19 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 1 year

6.2.2.1.20 Patient has a condition which precludes adequate transesophageal echocardiographic (TEE) assessment

6.2.2.2 Echocardiographic Exclusion Criteria

6.2.2.2.1 Left atrial appendage anatomy cannot accommodate the CLAAS device per manufacturer IFU

6.2.2.2.2 Intracardiac thrombus or dense spontaneous echo contrast, as visualized by TEE within 2 days prior to implant

6.2.2.2.3 Left ventricular ejection fraction (LVEF) <30%

6.2.2.2.4 Circumferential pericardial effusion >10 mm or symptomatic pericardial effusion, signs or symptoms of acute or chronic pericarditis, or evidence of tamponade physiology

6.2.2.2.5 Atrial septal defect that warrants closure

6.2.2.2.6 High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (exclusion >15 mm or length > 15 mm) or large shunt (early [within 3 beats] or substantial passage of bubbles)

6.2.2.2.7 Moderate or severe mitral valve stenosis (mitral valve area <1.5 cm^2)

6.2.2.2.8 Complex atheroma with mobile plaque of the aorta

6.2.2.2.9 Patient has evidence of cardiac tumor

6.3 Subject Screening

The study site will maintain a log of all screened and consented subjects. Reasons for meeting study criteria but failing to be enrolled will be captured on the screening log and entered into the database.

Potentially eligible subjects will undergo the process of informed consent (§6.4) prior to the performance of any study-specific assessments.

Potentially eligible subjects will be enrolled in the study only when the CLAAS Access Sheath has been introduced into the patient's body. Patients who do not meet general or echocardiographic eligibility criteria, or in whom the CLAAS Access Sheath is not introduced, will not be enrolled in the study.

Screen failures may be re-enrolled at a future date if it is determined that the eligibility criteria that initially excluded them from participation are no longer applicable (e.g., a thrombus identified on the initial TEE has resolved, a prior stroke is now outside of the exclusion window) or larger device is available.

6.4 Informed Consent

Relevant study information will be summarized on a Patient Information and Consent Form ("Informed Consent Form [ICF]") that has been approved by the CA. This document, or a modification based on local EC recommendations, must be approved by the applicable EC and signed by each subject or his/her legal representative (where allowed) prior to the performance of any study-specific procedures or assessments.

The subject or his/her legal representative (where allowed) must be provided with a copy of the signed and dated informed consent form.

The Investigator shall inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required, that may be relevant to the subject and his/her willingness to continue participation in the study. The consent form should be updated or amended whenever such new information becomes available and updated consent shall be recorded.

6.5 Subject Enrollment

Potentially eligible subjects who meet all general inclusion criteria, and no general exclusion criteria and who have consented to participate in the trial will undergo the protocol-specified screening assessments to confirm eligibility. At the time of the index procedure, Echo will be evaluated to confirm that adequate echocardiographic images can be acquired and that no echocardiographic exclusion criteria (§6.2.2.2) are met.

Subjects meeting all inclusion and no exclusion criteria, and in whom the CLAAS Access Sheath is introduced into the patient's body, will be enrolled in the trial.Subjects who meet all eligibility criteria, but in whom the CLAAS Access Sheath is not introduced, are classified as screen failures, which must be documented in accordance with §6.3.

6.6 Withdrawal, Loss to Follow-up, and Study Completion

6.6.1 **Voluntary Withdrawal**

Subjects can withdraw from the study at any time; the reason(s) for withdrawal (if given) will be documented. All data available at the time of withdrawal (if any) will be used for analysis, unless the subject has explicitly forbidden the use of such data and has documented this preference in accordance with local regulatory requirements. There will be no further follow-up (per this study protocol) on a subject who has withdrawn. Subjects who withdraw from the study will not be replaced. The withdrawal of a subject can be initiated by the Investigator if he/she determines it is in the best interest of the patient.

6.6.2 **Loss to Follow-up**

When a subject does not return for a clinic visit or is not reachable for a telephone contact, this event is considered a missed visit. Subjects with a missed visit may return for subsequent follow-up visits.

If a subject has a missed visit and has not voluntarily withdrawn from the trial, site personnel should make all reasonable efforts to locate and communicate with the subject, including the following, at each contact time point:

- A minimum of (3) three telephone calls to contact the subject should be recorded in the source documentation, including date, time, and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter should be sent to the subject.

Subjects with three consecutive missed visits, despite the above-mentioned communication attempts, will be considered lost to follow-up and administratively withdrawn from the study.

6.6.3 **Study Completion**

A study completion form must be completed for all subjects:

- In whom mortality has been documented
- Who voluntarily withdraw from the study or are withdrawn by the investigator to protect subject rights, welfare, or well-being (§6.6.1)
- Who are lost to follow-up and administratively withdrawn from the study (§6.6.2)
- Who have completed the final protocol-specified follow-up assessment:
    - The final protocol-specified assessment for patients who leave the index procedure catheterization laboratory with an implanted CLAAS device is the 12-month visit (§7.8).

6.7 Protocol Deviations

All deviations from the requirements of this Clinical Investigation Plan will be considered protocol deviations. In the event that a subject-level protocol deviation is identified by the site, a Protocol Deviation form should be completed in the eCRF and submitted to the Sponsor. Protocol deviations that will be collected include:

- Failure to obtain informed consent, or failure to obtain informed consent prior to the performance of study-specific procedures or assessments
- Enrollment of a subject who did not meet all study inclusion criteria, or who met one or more study exclusion criteria
- Failure to complete protocol-specified assessments, or completion of protocol-specified assessments outside of the protocol-defined time frame

It is the Site Principal Investigator's responsibility to ensure that there are no deviations from the protocol and to maintain compliance with all established procedures of the applicable EC. If a deviation from the protocol is deemed necessary by the Investigator to protect the safety or physical well-being of a subject, the Investigator is requested to notify the Sponsor as soon as practicable (if possible, before the deviation has occurred).

7.0 Study Procedures and Assessments

7.1 Schedule of Procedures and Assessments

Table 3. Study Schedule of Procedures and Assessments

	Screening	Pre-Procedure (day prior)	Index Procedure (day 0)	Pre-discharge[1]	7 Days (+2 days)[2]	45 days (45 ± 7 days)	6 months (± 30 days)	12 months (± 30 days)
	Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact / Optional Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
Demographics and Medical History	•							
Review of General Eligibility Criteria	•							
Informed consent	•							
Physical Examination	•			•		•		•
Stroke Assessment[3]	•			•	•	•	•	•
CHA_2DS_2-VASc; HAS-BLED scores	•							
Pregnancy Test[4]	•							
Laboratory tests[5]	•							
12-lead ECG[6]	•							
Brain Imaging[7]	•			•				
TTE				•				
TEE	•[8, 9]	•[10]	•[12]			•	•	•
ICE			•					
Angiography			•					
LAA occluder implantation			•					
Concomitant Medications	•		•	•	•	•	•	•
Adverse events	•[11]		•	•	•	•	•	•

[1] The pre-discharge visit must be conducted prior to hospital discharge from the index procedure; patients discharged on day 6 or earlier must also be followed up via telephone contact at 7 (+2) days post-procedure. For subjects who have not been discharged before day 7, the 7-day assessment may be performed in the clinic and no separate telephone contact is necessary.
[2] In patients who have been discharged from the index procedure hospitalization on day 6 or earlier, a telephone contact must be conducted at 7 (+2) days post procedure, and must include ascertainment of survival status, QVSFS, concomitant medication documentation, and reporting of any adverse events that may have occurred since the pre-discharge assessment.

	[3]The Questionnaire for Verifying Stroke-Free Status (QVSFS) and NIHSS must be completed at baseline and during each clinic visit to screen for interceding signs and symptoms of stroke or TIA. The modified Rankin Scale (mRS) must also be completed at baseline to establish the pre-stroke baseline value. For telephone contacts, stroke screening will consist of the QVSFS only. If a neurologic event is suspected at any time point, a formal neurologic examination and evaluation (to include the mRS) must be performed by a neurologist. [4] Female subjects of childbearing potential must have a pregnancy test (by site standard method) within 7 days prior to the index procedure to confirm study eligibility criteria. [5] Laboratory testing should be performed per site standard practice and should include CBC and serum creatinine. [6] A 12-lead ECG should be performed at baseline and pre-discharge and repeated with any signs or symptoms of myocardial ischemia. [7] Patients with a history of stroke are required to have a baseline MRI (or CT, if MRI is contraindicated) performed within 90 days prior to the scheduled index procedure. Brain imaging need not be repeated if an MRI or CT performed within 90 days pre-procedure as part of the standard of care is available. Patients with history of significant brain trauma or intra-cranial surgery should have a post procedure/event CT or MRI available for review. [8] An initial evaluation of echocardiographic eligibility based on review of the pre-procedure TTE and/or TEE (or cardiac CT, if that modality is the site standard of care for pre-procedure anatomic assessment) should be performed prior to the index procedure. [9] TEE (or CT) performed within 90 days prior to consent will be accepted, otherwise TEE must be conducted after consent. [10] Echocardiographic eligibility criteria must be confirmed by TEE at the time of the index procedure prior to the point of enrollment. [11]TTE performed within 6 months prior to consent will be accepted, otherwise TTE must be conducted after consent. [12]TEE performed after implant delivered.

7.2 Screening

The following tests and examinations must be performed prior to the procedure to verify eligibility and to collect baseline study data. Assessments performed as part of standard medical care prior to study enrollment are valid sources of data for verifying study eligibility and collecting baseline study data, provided that the previously performed assessments comply with applicable protocol requirements.

- Relevant medical history and patient demographic information
- Review of general inclusion, echo criteria and exclusion criteria
- Physical examination, to include NYHA functional class
- Stroke assessment (within 14 days pre-procedure), to include:
    - Questionnaire for Verifying Stroke-Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Modified Rankin Scale (mRS) to establish the pre-stroke baseline value; the mRS must be performed by a neurologist or research staff who have completed mRS training
    - Patients with documented history of stroke, TIA, or in whom an incident neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms,

will require a neurologic examination and evaluation be performed by a neurologist or clinical designee (e.g., neurology fellow)

- Atrial fibrillation stroke risk assessment with the CHA_2DS_2-VASc scores
- Major bleeding risk assessment with the HAS-BLED score
- Female patients of childbearing potential must have a pregnancy test (by site standard) performed within 7 days prior to the procedure
- Laboratory testing per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded. The results of any additional laboratory tests performed per site standard practice should also be collected.
- A 12-lead electrocardiogram (ECG). An ECG performed within 30 days prior to the 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 date of the index procedure).
- Brain imaging. Patients with a history of stroke are required to have a baseline MRI (or CT, if MRI is contraindicated) performed within 90 days prior to the scheduled index procedure. NOTE: Brain imaging need not be repeated if an MRI or CT performed within 90 days pre-procedure as part of the standard of care is available.
- Transthoracic echocardiogram (TTE) or TEE per site standard practice; if TTE and/or TEE (or cardiac CT) is performed as part of the standard of care, it should be reviewed by the investigating physician to evaluate echocardiographic eligibility. Note that echocardiographic eligibility must be confirmed by TEE at the time of the index procedure prior to subject enrollment.
- Documentation of all concomitant medications

7.3 Index Procedure

7.3.1 **Pre-Procedure Medical Therapy**

Pre-procedure anticoagulation therapy should be managed in accordance with standard institutional practice.

The following loading dose should be administered prior to the index procedure:

- ASA 81-100 mg (administered 1 day prior to procedure and continued daily)

7.3.2 **Intraprocedural Medical Therapy**

Intraprocedural anticoagulation should be maintained according to physician standard practice in accordance with published guidelines and local standards of care, with a goal of maintaining an activated clotting time (ACT) of 250-350 sec throughout the procedure. The highest and lowest intraprocedural ACT measurements must be recorded in the CRF for all subjects.

All medications administered, including the dose and timing, should be recorded in the patient's medical record and the CRF.

7.3.3 **Transseptal Puncture**

Percutaneous femoral vein access and transseptal puncture should be performed per physician standard practice using a standard commercially-available transseptal access system.

7.3.4 **Eligibility Confirmation**

The day prior to the index the investigator should confirm via TEE imaging that the patient is eligible for participation in the study:

1) Confirm that that the patient does not meet any echocardiographic exclusion criteria (§6.2.2.2)
2) Confirm that LAA anatomy is appropriate for implantation of the CLAAS implant per the device Instructions for Use

7.3.5 **Procedural Imaging**

ICE is the primary imaging source before, during, and after CLAAS Implant deployment.

At any time during the study, echocardiographic imaging obtained during a repeat procedure or for diagnostic purposes should also be forwarded to Conformal.

7.3.6 **CLAAS Implant Deployment**

After eligibility has been confirmed and the CLAAS Access Sheath has been introduced into the patient's body, the patient is enrolled in the study and should undergo implantation of the CLAAS Implant per the device Instructions for Use.

Procedural details should be entered into the eCRF. ACT should be measured at the onset of the procedure and at regular intervals throughout the procedure per routine hospital practice.

The procedure is considered complete once the last venous access sheath is removed or the patient has been discharged from the cath lab, whichever is first.

7.3.7 **Immediate Post-Procedure Medical Therapy**

Post-procedure loading with clopidogrel is suggested.

Protamine sulfate should be given for anticoagulation reversal only when clinically indicated (e.g., femoral oozing).

Prescribe appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

7.3.8 **Anticoagulation/antiplatelet Therapy**

If the post-procedure TEE demonstrates adequate seal (residual leak ≤5 mm) and there is no evidence of thrombus, subjects should receive DAPT (ASA 75-100 mg QD and clopidogrel 75 mg QD) until 45 days post-procedure. NOTE: A substitute P2Y12 inhibitor (i.e., prasugrel, ticagrelor) may be used in known non-responders to clopidogrel.

If the 45-day TEE demonstrates adequate closure, DAPT should be continued to 6 months. For high bleeding risk (HBR) subjects, monotherapy (ASA preferred, P2Y12 inhibitor permitted) may be initiated per physician judgment.

If a 6-month TEE demonstrates adequate closure, DAPT should be replaced by monotherapy (ASA preferred, P2Y12 inhibitor permitted) to 12 months post-procedure.

Beginning 12 months post-procedure, medical therapy should be administered per standard of care.

- **Inadequate seal:** Subjects with inadequate seal (residual leak >5 mm) at the post-procedure TEE (or any subsequent TEE) should be evaluated for treatment with OAC and ASA for 4-6 weeks followed by TEE. If inadequate seal persists, anti-thrombotic therapy should be individualized for the patient, balancing bleeding risk with the associated persistent inadequate seal (seen on TEE).
- **Thrombus:** Subjects with thrombus detected on 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 TEE. Anti-thrombotic therapy should be individualized for the patient, balancing bleeding risk and the assumed thrombo-embolic risk associated with the TEE findings.

7.4 TEE Post Implant

A confirmatory TEE will be conducted after the implant is delivered. The investigator will confirm the findings of the ICE imaging: position and seal.

7.5 Pre-discharge Follow-up

Post-procedure assessment must occur during the index procedure hospitalization prior to hospital discharge, and must include:

- Physical examination
- TTE
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke-Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, mRS must be documented, and repeated 90 ± 14 days post-event to assess disability.
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.

Prior to hospital discharge, research staff should review the follow-up requirements with the subject to ensure compliance with the subsequent follow-up assessment:

- For subjects discharged from the index procedure hospitalization on or before day 6 post-procedure, telephone numbers should be obtained from the subject to ensure the ability to reach him or her for the required 7 + 2-day telephone contact. These phone numbers should

include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

- For subjects discharged from the index procedure hospitalization on day 7 or later post-procedure, telephone numbers should be obtained from the subject to ensure that the subject returns to the clinic for the 45-day follow-up assessment.

7.6 7-day Follow-up (Telephone Contact / Optional Clinic Visit)

All subjects must undergo a follow-up assessment on day 7 to 9 post-procedure to enable timely documentation of safety endpoint events.

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, and no separate telephone contact is necessary.

For subjects who have already been discharged from the index procedure hospitalization, the 7-day follow-up will be conducted via telephone contact.

The 7-day follow-up assessment must include:

- Questionnaire for Verifying Stroke Free Status (QVSFS). If any question is answered "Yes", a formal neurologic examination and evaluation must be performed by a board-certified neurologist or clinical designee (e.g., neurology fellow).
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- Documentation of any adverse events occurring since the previous evaluation.

Note: for subjects discharged from the index procedure hospitalization prior to day 7, but who return to the clinic as part of their regular medical care during the specified follow-up window (7 to 9 days post procedure), the 7-day follow-up assessment may be conducted during the clinic visit, and no separate telephone contact is necessary.

7.7 45-day Follow-up (Clinic Visit)

All subjects will return to the clinic at 45 days (±7 days) post-procedure for a clinical evaluation. The 45-day follow up visit will include the following assessments:

- Physical examination
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, NIHSS and mRS must be documented, and repeated 90 ± 14 days post-event.

- A transesophageal echocardiogram (TEE) must be performed in all subjects who left the index procedure with an implanted CLAAS device.
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- Documentation of any adverse events occurring since the previous evaluation.

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient returns to the clinic for the 6-month follow-up visit.

7.8 Six-month Follow-up (Clinic Visit)

All subjects who received a CLAAS implant will return to the clinic at 6 months (± 30 days) to include the following assessments:

- Physical examination
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, NIHSS and mRS must be documented, and repeated 90 ± 14 days post-event.
- A transesophageal echocardiogram (TEE).
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded. If monotherapy has been initiated due to high bleeding risk, the factors contributing to the high bleeding risk assessment should be documented.
- Documentation of any adverse events occurring since the previous evaluation.

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient returns to the clinic for the 12-month follow-up visit

7.9 Twelve-month Follow-up (Clinic Visit)

All subjects who received a CLAAS implant will return to the clinic at 12 months (± 30 days) post-procedure for additional follow-up, to include the following assessments:

- Physical examination
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke Free Status (QVSFS)

  - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
  - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, NIHSS and mRS must be documented, and repeated 90 ± 14 days post-event.
- A transesophageal echocardiogram (TEE)
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded. If monotherapy has been initiated due to high bleeding risk, the factors contributing to the high bleeding risk assessment should be documented.
- Documentation of any adverse events occurring since the previous evaluation.

8.0 Adverse Events and Serious Adverse Events

In this study, patients should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning. Any time during the study, the patient may volunteer information that resembles an adverse event (AE). If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE CRFs.

8.1 Adverse Events (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in a study subject, whether or not related to the study device.

NOTES:

- The definition of AE includes events related to the study device or to the procedures involved but does not imply that there is a relationship between the adverse event and the study device.
- Pre-existing medical conditions or a repeat of symptoms reported prior to the procedure will **not** be reported as an AE. Pre-existing conditions that worsen during a study are to be considered adverse events.
- Planned procedures (scheduled prior to the index procedure) that occur after the index procedure are not considered reportable AEs. Complications from such procedures, however, must be reported.
- Abnormal non-cardiac laboratory findings are not considered a reportable AE unless:
  - The investigator determined that the finding is clinically significant; OR
  - The abnormal laboratory finding required intervention; OR
  - The abnormal laboratory finding required termination of the subject's participation in the study.

8.2 Serious Adverse Events (SAE)

A serious adverse event is an adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolongation of existing hospitalization
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

8.3 Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the Instructions for Use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

8.4 Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.5 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan.

8.6 Device Deficiencies, Malfunctions, and Use Error

Investigators are instructed to report all possible device deficiencies, malfunctions, misuse or use error observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

- **Device deficiency**: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.

- **Device malfunction**: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol. NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use but does not perform as described in the Instructions for Use.
- **Use error:** Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
    - **Device misuse:** Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

8.7 Documentation

Adverse events must be listed on the appropriate CRF. All AEs will be characterized by the following criteria which are detailed in the definition section:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

8.8 Reporting

8.8.1 General Adverse Event Reporting Procedures

Investigators are required to keep records on "all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)" according to 21 CFR 812.140. Adverse event collection will occur from the point of study enrollment to study closure. All new or worsening (from baseline) cardiovascular adverse events will be captured on the AE CRF through the 5-year follow-up telephone contact. Independent monitoring will be conducted (§12.1) to review source documentation and verify the complete and accurate capturing of adverse events.

The general procedure for investigators reporting any adverse event is as follows:

- If an adverse event occurs, complete all sections of the Adverse Event CRF. Note:
    - Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition
    - Planned procedures (scheduled prior to the index procedure) that occur after the index procedure are not considered reportable AEs. Complications from such procedures, however, must be reported.
    - Abnormal non-cardiac laboratory findings are not considered a reportable AE unless:
        - The investigator determined that the finding is clinically significant; OR
        - The abnormal laboratory finding required intervention; OR

  - The abnormal laboratory finding required termination of the subject's participation in the study.

- Each unique event/diagnosis must be documented separately
- The AE CRF must be reviewed by the investigator

For adverse events not meeting the criteria for an SAE or (potential) UADE, the Sponsor recommends that the Investigator notify the Sponsor within 10 working days of first learning of the AE using the electronic data capture (EDC) CRF. If necessary, the Investigator may be requested to provide de-identified copies of source documentation (e.g., physician/nurse notes or summaries) regarding the event.

The Investigator must also notify the responsible EC regarding new and significant safety information and any events identified by Conformal Medical that require expedited FDA or other regulatory authority reporting as serious, unexpected, and related to the investigational device. It is the responsibility of the investigator to ensure site-specific IRB/EC reporting requirement are met.

The Sponsor is responsible for reporting SAEs and device deficiencies to regulatory authorities in line with applicable regulatory requirements and for reviewing the risk analysis, determining the need for corrective or preventative action, and informing investigators and regulatory authorities accordingly.

8.8.2 **Serious Adverse Events**

The Sponsor recommends that the Investigator notify Conformal Medical Clinical Lead, within 2 working days of first learning of any SAE using the eCRF.

It is the responsibility of each Investigator to report all serious adverse events and/or serious adverse device effects and device deficiencies that could have led to a serious adverse device effect to the IRB/EC, according to national regulations and EC requirements. If required by national regulations, the Investigator may also be required to report SAEs to the applicable regulatory authority.

8.8.3 **Unanticipated Adverse Device Effects**

As defined in 21 CFR §812.3, an unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Investigators must report any (potential) unanticipated adverse device effects to the Sponsor and their EC as soon as possible but no later than within 5 working days after the investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately on the eCRF and via telephone to the Sponsor Clinical Project Lead; contact details are provided in §2.0.

If an event is determined by Conformal Medical to be a UADE, the Sponsor will report the event to the FDA and other applicable regulatory authorities. The Sponsor will take the necessary steps to investigate the event and will be responsible for notifying FDA and all other participating ECs (or other, as required) and all investigators.

8.9 Expected Adverse Events

The device and procedure are both associated with risks. Below is a summary of the expected risks that may occur. They are divided between those events associated with the procedure versus those associated with the CLAAS system. There may be additional risks that are unknown at this time.

Procedural Risks: The risks of delivery of the CLAAS device are similar to those of other procedures that require a transseptal puncture and transcatheter delivery of an implant through the venous system, across the interatrial septum, and into the left atrium using a large bore catheter (e.g., EP procedures and/or other LAA devices such as WATCHMAN). These risks are well recognized and experienced clinicians that are well versed in the use of large bore catheters have mitigated these risks to the extent possible in their standard of care. The recognized procedural risks include (in alphabetical order):

- Acute Kidney Injury potentially requiring need for dialysis
- Air embolus
- Allergic reaction to contrast media necessary for imaging during procedure
- Anesthesia risks (e.g., nausea/vomiting, aspiration pneumonia)
- Arrhythmia
- Bleeding/anemia requiring transfusion
- Cardiac Perforation, Puncture, Tamponade, and/or Effusion requiring draingage and/or "open heart" surgery
- Chest pain/angina
- Damage to cardiac structure (eg. valve, chordae)
- Death
- Deep Vein Thrombosis or Pulmonary Embolism
- Fever
- Hematuria
- Hemodynamic Instability (hypotension/hypertension)
- Hemothorax
- Iatrogenic ASD requiring treatment
- MI including ST segment elevation
- Pericardial Effusion/tamponade
- Pleural Effusion
- Pulmonary Edema
- Respiratory failure

- Stroke/TIA or Systemic embolization
- Systemic Infection including pneumonia
- TEE/intubation risks including throat pain, trauma to airway or esophagus with or without bleeding
- Thrombocytopenia
- Thromboembolic event
- Venous access site complications including pain, AV fistula, pseudoaneurysm, infection, hematoma, bleeding requiring transfusion and/or the need for surgical repair

Device Risks: In addition to the risks of undergoing an interventional procedure, there should be consideration to the risks which are specific to the CLAAS implant and CLAAS Delivery System. Conformal Medical has identified a set of risks that the rates of which may be different due to the design of the CLAAS system as outlined below. A number of the risks have been determined to be present with other interventional (e.g., WATCHMAN) as well as surgical implants designed to occlude the LAA. These risks include but are not limited to:

- Arrhythmias
- Cardiac perforation, puncture, tamponade, and/or effusion caused by device
- Chest pain
- Deep Vein Thrombosis or Pulmonary Embolism
- Death
- Device embolization or thrombosis
- Device malfunction/breakage requiring intervention
- Device migration requiring intervention
- Infection
- Major bleed requiring transfusion
- Myocardial Erosion
- Prolonged procedure time risk
- Re-intervention due to incomplete seal
- Re-intervention to remove device
- Residual leak in LAA
- Stroke/TIA or Systemic embolization
- Thrombus formation

9.0 Benefit: Risk Analysis

9.1 Potential Benefits

The targeted patient population consists of patients presenting with non-valvular atrial fibrillation, and who are at increased risk for stroke and systemic embolism and are recommended for OAC therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC, and who have been deemed appropriate for LAA closure by the Site PI and a non-interventional physician using an evidence-based decision-making tool on oral anticoagulants consistent with the standard of care. Compared with LAA closure with a commercially available device, LAA closure with the CLAAS-device may offer a simpler, safer implantation procedure and an increased likelihood of achieving successful closure.

Subjects in the CONFORMAL Study may not derive any direct benefit from their participation in the trial; however, subjects may gain satisfaction from having made an altruistic contribution to medical science, and the results of the trial may contribute to improved treatments that could benefit future patients who require LAA closure for the prevention of stroke and systemic embolism.

9.2 Potential Risks and Discomforts

Enrollment in the trial involves exposure to some risks. The risks of trial participation are not expected to be materially different from those encountered by an individual undergoing LAA closure with a commercially available device outside the context of the trial (§0). However, as an early feasibility evaluation of a novel device, the use of the CLAAS device may pose additional potential risks of an unknown nature or frequency.

In addition to the study device, participation in the clinical study involves exposure to potential risks and discomforts related to the protocol-specified assessments, including TEE assessments at pre-specified time points. These procedures are not experimental but are being performed for research purposes. The potential risks and discomfort related to study-specific tests will be detailed in the Informed Consent Form and discussed with each patient prior to enrollment in the study.

9.3 Methods to Minimize Risks

Extensive risk management activities have been conducting during the development of the CLAAS device to identify and analyze known and foreseeable hazards and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and Instructions for Use of the product to reduce the residual risk of each hazard to levels that are as low as reasonably practicable.

The clinical investigation plan is specifically designed to manage and minimize risks through the selection of qualified and experience investigators, thorough training of investigators and the investigational team, careful subject selection, adherence to pre-determined time points to assess subject clinical status, and regular clinical monitoring visits by Sponsor-appointed monitoring personnel. In addition, an independent Data Safety Monitor will review accumulating safety data at regular intervals to monitor for the incidence of serious adverse events that would warrant modification or termination of the trial, an independent Clinical Events Committee will meet regularly

to adjudicate the relationship of site-reported adverse events to the investigational device and procedure.

9.4 Benefit-Risk Assessment

A risk analysis of the CLAAS device has been performed and concluded that the identified risks have been reduced to a level as low as reasonably practical. When combined with the risk management measures incorporated into the design of the clinical trial, the potential benefits of the clinical use of the CLAAS device in the CONFORMAL Study are judged to justify the potential risks to study participants. The potential benefits and risks of study participation will be evaluated on an individual basis and discussed with each patient prior to enrollment in the study.

10.0 Statistical Considerations and Analysis Plan

10.1 Sample Size Rationale

The trial will enroll subjects in a staged manner to ensure patient safety in the Early Feasibility Study construct. A total of 20 subjects at 1 center is targeted for this feasibility study.

10.2 Analysis Populations

10.2.1 **Intention to Treat (ITT) Analysis Population**

The Intention to Treat (ITT) analysis population is defined as all subjects enrolled in the study (the point of enrollment is introduction of the CLAAS Access Sheath into the patient's body), regardless of the treatment actually received.

The ITT population will be the primary analysis population for the primary safety endpoint, the primary performance endpoint, and all secondary endpoints and other measures.

10.2.2 **The Implanted Patient (IP) Analysis Population**

The Implanted Patient (IP) analysis population is defined as all subjects who leave the catheterization laboratory with an implanted CLAAS device.

The IP population will be the secondary analysis population for the primary safety endpoint, the primary performance endpoint, and all secondary endpoints and other measures.

10.3 Method of Analysis & Reporting

10.3.1 **General Approach**

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. No hypothesis testing will be performed.

Analysis will be conducted using SAS (version 9.3 or greater), unless otherwise noted. Additional details will be pre-specified in the formal Statistical Analysis Plan (SAP) prior to initiation of enrollment.

10.3.2 **Baseline Characteristics**

The following data will be summarized using descriptive statistics and presented for the ITT and IP populations:

- Baseline demographics
- Baseline comorbidities, risk factors, and medical history
- Cardiac risk factors and cardiac history
- Procedural characteristics
- Device details

10.3.3 **Endpoint Analysis**

All endpoints will be reported in the ITT population using appropriate descriptive statistics. No formal hypothesis testing will be performed. As an additional analysis, all endpoints will be evaluated in the IP population.

All efforts will be made to minimize the amount of missing data; where it occurs, the reasons and counts and percentages of subjects with loss to follow-up will be summarized. In the final analyses, no adjustment will be made for missing data.

10.3.4 **Additional Analyses**

The following data will be summarized using descriptive statistics presented by treatment group in the ITT and IP populations:

- Frequency (number and percentage of patients) with each type of concomitant medication
- Frequency (number and percentage of patients) with each site-reported Treatment Emergent AE overall and by MedDRA system organ class and preferred term (a treatment emergent AE is an AE that started or worsened during or after the index procedure)
- Frequency (number and percent of patients) with each site-reported Treatment Emergent Serious AE overall and by MedDRA system organ class and preferred term
- Protocol deviations (number and percentage of patients with each deviation type)
- Detailed listings on primary and secondary endpoints, site-reported AEs, and protocol deviations

11.0 Publication Policy

The data obtained from this study may be presented for publication and/or presentation as long as Conformal and all investigators and authors assure that no information, which would reveal a subject's identity, is used in any publication. Information, which could be used to establish a subject's identity, should not be provided to Conformal. Authors and Conformal will take every reasonable precaution to protect the identity of subjects enrolled in the study.

12.0 Data Collection and Monitoring

12.1 Data Collection and Monitoring

All required data for this study will be collected on standardized Case Report Forms (CRFs). The investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews.

Monitoring will be performed by the Sponsor and/or its designee(s) to ensure that the investigator and his/her study team conduct the clinical investigation in accordance with contract specifications, this protocol, the Declaration of Helsinki, ICH-GCP, ISO 14155, 21 CFR Part 812, and other applicable FDA and local regulations, and to ensure adequate protection of the rights and safety of subjects and the quality and integrity of the resulting data. All monitors will receive study-specific training on the Clinical Investigation Plan, the CRF, and the use of the investigational device in accordance with Sponsor SOPs.

Submitted trial data will be verified against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance with the pre-specified Monitoring Plan. The Investigator/institution will permit direct access to source data/documents in order for trial-related monitoring, audits, EC review and regulatory inspections to be performed.

Progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the Sponsor
- Telephone communications between site personnel (e.g., Site Investigator, Trial Coordinator) and trial monitors
- Review of CRFs and associated clinical records
- Review of regulatory documents

If a monitor becomes aware that an Investigator is not complying with the requirements mentioned above, the sponsor will be notified by the monitor. The Sponsor will evaluate the non-compliance and if necessary, immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator's participation in continued enrollment in the investigation. The Investigator will be required to return all unused devices to the Sponsor.

12.2 Source Documentation

Auditors, monitors, ECs, the Sponsor, and the FDA and other regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled patient (no source documentation will be recorded directly on the CRF). At a minimum, the following must be included in each patient's file:

- Sufficient medical history and current physical condition, including any medication(s) the patient is taking at the time of the procedure to assess the patient's eligibility;
- The medical file should reveal the patient's participation in this study, including documentation of written informed consent;

- Dated report of the index procedure including medication, material usage, and complications, if applicable;
- Dated reports of the post-procedure / pre-discharge and follow-up assessments;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and
- In the case of withdrawal of patient consent, the reason and patient status at time of withdrawal.

The Site Investigator will permit study-related monitoring, audits, EC review, and FDA and other applicable regulatory authority inspections by allowing direct access to the source data.

In case of electronic source data, periodic access will be allowed for full safety review. The review will be specific to study subjects and the records that would contain potential safety data. Dated print-outs are acceptable for preliminary review of safety information. Print-outs will not be limited to cardiac data only but should include all available data related to the identified patient(s).

12.3 Auditing

As a quality assurance measure, investigational sites may be audited during the trial or following trial completion. The purpose of an audit is to provide an independent evaluation of trial conduct and protocol and GCP compliance, separate from routine monitoring and quality control functions. The audit may be conducted by Conformal Medical personnel (or designee), the FDA, or another regulatory body.

Site Investigators are requested to notify the Sponsor if the FDA or other regulatory body requests an audit. The site investigator and/or institution shall permit Conformal Medical (or designee) personnel and regulatory body representatives direct access to source data and all other relevant documents.

13.0 Device Accountability

Information regarding opened, introduced, and implanted CLAAS devices will be recorded on the applicable CRF. Information regarding opened and introduced delivery systems will also be recorded on the applicable CRF.

Investigational devices will be shipped after documentation of site activation is sent to the site and shipping authorization is completed.

The principal investigator or an authorized designee must maintain a device accountability log documenting the date of receipt, the identification of each investigational device (i.e. serial number), the subject identification, the date of use, and final disposition. Devices must be stored in a locked location with access restricted only to investigators and authorized research personnel

14.0 Ethical and Regulatory Considerations

14.1 Applicable Regulations

This trial will be conducted in compliance with this protocol, the Sponsor's standard operating procedures and/or guidelines, FDA regulations concerning the protection of human subjects, e.g., 21 CFR parts 50, 56, and 812 and 45 CFR part 46, ICH GCP guidelines, the Declaration of Helsinki, and ISO 14155.

14.2 Ethics Committee

This trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The investigator will assure that an appropriately constituted Ethics Committee (EC) complies with the requirements of the International Conference on Harmonization Guideline. Prior to initiation of the study, the investigator will forward copies of the protocol, Investigators Brochure, informed consent form and all other appendices to be used for the study to the EC for its review and approval. A copy of the written EC approval must be provided to the Sponsor (or designee) and should include the following:

- A statement of EC approval for the proposed study at the institution;
- The date the study was approved and the duration of approval (if applicable);
- Identification of the approved documents including version dates and/or other references. At a minimum, the following documents should be listed:
    - Study protocol
    - Patient information and consent form
    - Any additional written information to be provided to the patient
- A listing of any conditions attached to the approval (if applicable);
- Identification of the approved primary investigator;
- The signature of the EC chairperson;
- Acknowledgement of the sub-Investigators.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the EC and written approval obtained prior to implementation. Substantive changes will be submitted to the EC for approval prior to implementation, and the EC will be notified of any changes not requiring approval according to applicable guidelines.

14.3 Regulatory Approval

The Sponsor is responsible for obtaining CA approval to conduct the study according to regulatory requirements. Investigators may not commence enrollment of subjects until they have met any local EC and hospital management requirements and have received confirmation from the Sponsor that the appropriate regulatory approvals have been obtained.

14.4 Records and Reports

Sponsor and investigator will maintain records related to this study for 5 years (or longer according to local requirements) after the end of this study.

Records maintained by the Sponsor will include:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- *Curriculum vitae* for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms prepared and signed by the Investigators and all received source documentation
- Clinical Investigation Plan (CIP) and any amendments
- Investigators Brochure / Report of Prior Investigations
- Site monitoring reports
- Financial disclosure information

Records maintained by each Site Investigator (the investigator may delegate responsibility for record maintenance to a member of his/her study team, but remains the ultimate responsible person) will include:

- All essential correspondence related to the clinical trial
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation).
- Signed Investigator Agreement
- *Curriculum vitae*
- Clinical Investigation Plan (CIP) and any amendments

The Sponsor and Site Investigators are each responsible for the preparation, review, and submission of all required reports in accordance with local laws and regulations, the requirements of the CA and other regulatory authorities as applicable, and the requirements of local ECs.

14.5 Protocol Amendments

Any protocol amendments will be approved by the Sponsor, the Principal Investigator, the EC and any necessary regulatory body before it can be implemented. Substantive changes will be submitted to the CA (and other regulatory authorities as applicable) for approval prior to implementation, and

the CA (and other regulatory authorities as applicable) will be notified of any changes not requiring approval in accordance with relevant guidelines.

14.6 Informed Consent

Informed consent will be obtained and documented as described in §6.4 prior to the performance of any study-specific procedures or assessments in accordance with 21 CFR Part 50, other applicable laws and regulations, and local EC requirements.

14.7 Termination of the Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Possible reasons for early trial termination include:

- Unanticipated Adverse Device Effects (UADEs) present an unreasonable risk to patients
- Sponsor decision to suspend or discontinue development of the device

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the ECs. The Sponsor will also inform the CA (and other regulatory authorities where required). In the case of early termination of trial enrollment, follow-up visits will continue for all enrolled subjects.

The Sponsor may terminate an investigator's or site's participation in the study if there is evidence of an investigator's failure to maintain adequate clinical standards or evidence of an investigator or staff's failure to comply with the protocol. Should investigator or site participation be considered for termination, the Sponsor (or designee) will ensure appropriate follow-up for any subjects enrolled, including transferal to the supervision of an approved investigator and approval of transfer of subject oversight and follow-up by the appropriate EC. Notification of study site suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. A suspended or terminated study site may not be reinitiated without approval of the reviewing EC. The investigator should notify the EC in writing as soon as possible but no later than within 10 days if the premature termination is related to safety or compliance issues. The same procedure will be applied to other applicable regulatory authorities where required.

14.8 Patient Privacy

The Sponsor affirms and upholds the principle of patient confidentiality. Throughout this study, all data provided to the Conformal Medical, Inc. or its designee(s) will only be identified by a study-specific subject identification number.

The investigator agrees that representatives of Conformal Medical, Inc., its designee(s), and regulatory authorities may inspect included patients' records to verify trial data, provide the data are treated as confidential and that the subject's privacy is maintained.

15.0 Site and Investigator Selection and Training

15.1 Selection of Study Sites and Investigators

The Sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based upon review of a recent site assessment questionnaire and the qualifications of the Primary Investigator at the site. Each site will have an interventional cardiologist and a cardiac electrophysiologist willing and able to participate in the study. All participating investigators will be trained to the protocol and study procedures prior to enrolling subjects.

15.2 Training of Investigators and Research Staff

15.2.1 General Training Requirements

All Investigators and trial research staff are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or another appropriate venue. Training by telephone may take place as required. Training of Investigators/trial personnel will include but is not limited to: the Clinical Investigation Plan (including imaging acquisition protocols), investigational device Instructions for Use, CRF completion, adverse event documentation and reporting requirements, and investigator and trial personnel responsibilities.

15.2.2 Investigator Training Requirements

Comprehensive Investigator training will be conducted to ensure that Investigators have a thorough knowledge of the investigational device Instructions for Use, the proper technique for implantation of the CLAAS device, and the Clinical Investigation Plan.

All participating investigators will receive formal training on the device at the site initiation visit. At a minimum, implanting investigators must receive the following training, unless otherwise noted in site-specific training records:

- CLAAS Device Training (including review of the Instructions for Use)
    - Device preparation, use and handling
    - Device positioning and deployment
    - Device removal and dislodgement
    - Implantation procedure steps and training
    - LAA anatomic measurements
- Clinical Investigation Plan Review
    - General procedural and data collection requirements

15.2.3 Training Documentation

A training log must be maintained at each site that documents the Investigators and research staff who have completed study-specific training, the training modules completed, and the date the training was completed. No trial-related activities (other than those considered standard of care at

the study site) may be performed by investigators or research staff who not completed study-specific training.

16.0 References

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17.0 Appendices

17.1 Appendix A: Definitions

Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

All adverse device effects will be assess using the following:

Intensity or Severity

Intensity of an adverse event to be used:

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

Relatedness

Relationship to the study device or procedure:

Not related	The cause of the AE is known, and the event is not related to the study device or procedure.
Unlikely to be related	There is little or no temporal relationship to the study device or procedure, and/or a more likely alternative etiology exists.
Possibly related	There is a reasonable possibility that the event may have been caused by the study device or procedure. The AE has a **timely relationship** to the study device or procedure(s); **however, follows no known pattern of response**, and an alternative

	cause seems more likely or there is significant uncertainty about the cause of the event.
Related	A **related** event has a **strong temporal relationship** and an alternative cause is unlikely.

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Outcome

The clinical outcome of the AE or SAE will be characterized as follows:

Death	The SAE CRF must be completed for this outcome
Recovered without sequelae	The patient returned to baseline status
Ongoing	Patient did not recover, and symptoms continue
Recovered with sequelae	The patient has recovered but with clinical sequelae from the event
Unknown	The patient outcome is unknown

Treatment or Action Taken

Action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment	Surgical, percutaneous or other procedure
Medical Treatment	Medication dose reduction/interruption or discontinuation, or medication initiated for event
None	No action is taken

Anticipated Serious Adverse Device Effect (ASADE)

An anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).

Bleeding complications

Defined according to the following BARC definitions[2], and classified as major bleeding (Type 3, 4, or 5) and minor bleeding (Type 2)

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Over bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)

Any transfusion with over bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed comprising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period (NOTE: cell saver products are not counted)

Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

NOTES:

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin)

Cardiac tamponade Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the LAA closure

CHA_2DS_2-VASc Score A clinical risk stratification scheme for predicting stroke and thromboembolism in patients with nonvalvular AF[27], updated from the earlier $CHADS_2$ score. Patients are assigned a score from 0 to 9 by adding the points for each applicable risk factor below to obtain a total score:

Risk Factors	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolic event in the past	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65 to 74 years	1
Sex **c**ategory (female gender)	1

Closure success	Device success (see definition) followed by successful LAA closure (complete closure or peri-device residual leak ≤5 mm in width on TEE at 45 days post-procedure). NOTE: The primary protocol definition of closure success is at the primary performance endpoint evaluation time point of 45 days; closure success at 6 and 12 months will also be evaluated.
CNS hemorrhage	NeuroARC defined[1] as any brain, spinal cord, or retinal hemorrhage on the basis of imaging or pathology, not caused by trauma (includes symptomatic intracerebral hemorrhage [Type 1.b], symptomatic subarachnoid hemorrhage [Type 1.c], and covert CNS hemorrhage [Type 2.b])
CNS infarction	NeuroARC defined[1] as any brain, spinal cord, or retinal infarction on the basis of imaging, pathology, *or* clinical symptoms persisting for ≥24 h (includes ischemic stroke [Type 1.a], ischemic stroke with hemorrhagic conversion [Type 1.a.H], stroke not otherwise specified [Type 1.d], symptomatic hypoxic-ischemic injury [Type 1.e], covert CNS infarction [Type 2.a], and covert CNS infarction with hemorrhagic conversion [Type 2.a.H])
Composite efficacy	Freedom from the composite of all-cause mortality, all stroke, TIA, and systemic thromboembolism
Covert CNS injury	Acutely asymptomatic brain or spinal cord injury detected by neuroimaging (NeuroARC Type 2)[1], including: <u>Type 2.a Covert CNS infarction</u> Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location <u>Subtype 2.a.H Covert CNS infarction with hemorrhagic conversion</u> Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 2.b Covert CNS hemorrhage

Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location

Death See "mortality"

Device deficiency Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.

Device malfunction Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol.

NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use but does not perform as described in the Instructions for Use.

Device misuse Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

Device success Successful implantation of the CLAAS device in the LAA with acceptable position and seal (peri-device residual leak ≤5 mm in width [evaluated post-procedure]

Embolic events A composite of ischemic stroke and systemic thromboembolism

HAS-BLED Score A scoring system to assess the risk of major bleeding in patients with atrial fibrillation receiving oral anticoagulation (OAC) therapy.[28] Patients are assigned a score from 0 to 9 by adding the points for each applicable clinical characteristic below to obtain a total score:

Clinical Characteristic	Score
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding history or predisposition	1
Labile INRs in patients taking warfarin	1

Elderly (> 65 years)	1
Drugs (concomitant antiplatelet agents or NSAIDs) or alcohol abuse (1 point each)	1 or 2

Implanted Patient (IP) Population

All subjects who leave the catheterization laboratory after the index procedure with an implanted CLAAS device

Intention to Treat (ITT) Population

All subjects enrolled in the study (the point of enrollment is introduction of the CLAAS delivery system into the patient's body), regardless of the treatment actually received.

Ischemic stroke

NeuroARC-defined[1] Type 1.a or 1.a.H overt CNS injury:

Type 1.a Ischemic stroke

Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:

1) Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either:
   a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or*
   b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected

   or

2) Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke.

Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H Ischemic stroke with hemorrhagic conversion

Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

	Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect
	Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect
Major endovascular intervention	Major endovascular intervention includes pseudoaneurysm repair, AV fistula repair, and other major endovascular repair. The following interventions are not considered major endovascular interventions: percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications.
Major procedure-related complications	A composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and major vascular complications, adjudicated by the independent Clinical Events Committee as related to the study device or procedure
Major safety events	A composite of all-cause mortality, overt CNS injury, and major bleeding
Mortality	Classified as cardiovascular (defined as cardiac or vascular) or noncardiovascular according to the following ARC definitions. All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (e.g., cancer, infection) should be classified as cardiac. • Cardiac death: Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death. • Vascular death: Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases. Noncardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.
Myocardial infarction	Defined according to VARC-2[3] as: Peri-procedural MI (≤72 h after the index procedure): • New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging

evidence of new loss of viable myocardium or new wall motion abnormality) AND

- Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure). Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
  - New pathological Q waves in at least two contiguous leads
  - Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

Neurologic dysfunction without CNS injury

Acutely symptomatic (NeuroARC Type 3[1]) without CNS injury, including:

Type 3.a TIA

Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)

Type 3.b Delirium without CNS injury

- Transient nonfocal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology

Neurologic events

See “ischemic stroke”, “Overt CNS Injury”, “Covert CNS Injury”, “Neurological dysfunction without CNS injury”, “CNS infarction”, and “CNS hemorrhage”

NYHA (New York Heart Association)

Classified as[29]:

functional capacity

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Overt CNS injury

Acutely symptomatic brain or spinal cord injury (NeuroARC Type 1)[1], including:

Type 1.a Ischemic stroke

Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:

3) Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either:
   a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or*
   b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected

   or

4) Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke.

Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H Ischemic stroke with hemorrhagic conversion

Ischemic stroke includes hemorrhagic conversions. These should be sub classified as Class A or B when ischemic stroke is the primary

mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechial or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 1.b Symptomatic intracerebral hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma

Type 1.c Symptomatic subarachnoid hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma

Type 1.d Stroke, not otherwise specified

An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified as either (i.e., no neuroimaging performed)

Type 1.e Symptomatic hypoxic-ischemic injury

Nonfocal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia

Pericardial effusion

Pericardial effusion will be classified for severity and time of occurrence according to the following definitions[30]:

Clinically non-relevant:

- Requiring no intervention
- Treated pharmacologically

Clinically relevant (sub-classified as with or without cardiac tamponade):

- Treated with therapeutic pericardiocentesis
- Treated with surgical intervention
- Requiring blood transfusion
- Resulting in shock and/or death

Time of occurrence:

	• Intraprocedural: during the index procedure • Acute: <48 hours after the index procedure Late: ≥48 hours after the index procedure
Procedure success	• Device success (see definition) without major in-hospital procedure-related complications (see definition)
Screen failure	Subjects who are deemed potentially eligible for participation in the study based on the results of pre-screening, and who undergo the process of informed consent, but do not reach the point of enrollment because they (1) are subsequently determined not to be eligible for enrollment in the study prior to the index procedure, or (2) are not exposed to the CLAAS Delivery System (introduction into the body).
Serious Adverse Device Effect (SADE)	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	A serious adverse event is an adverse event that: 1. Led to a death 2. Led to a serious deterioration in the health of the subject that: a. Resulted in a life-threatening illness or injury b. Resulted in a permanent impairment of a body structure or a body function c. Required in-patient hospitalization or prolongation of existing hospitalization d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function Led to fetal distress, fetal death or a congenital abnormality or birth defect. 3. Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g. trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.[30]
Systemic thromboembolism	
Transient ischemic attack (TIA)	NeuroARC defined[1] as transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging).
Unanticipated Adverse	An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or

Device Effect (UADE)	associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
Vascular complications	VARC-2 defined[3] as: <u>Major Vascular Complications</u>: • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury <u>Minor vascular complications</u>: • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR • Distal embolization treated with embolectomy and/or thrombectomy and

not resulting in amputation or irreversible end-organ damage OR

- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR

Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

-

17.2 Appendix B: Acronyms

AE	adverse event
ACT	activated clotting time
ADE	adverse device effect
AF	atrial fibrillation
ASA	acetylsalicylic acid (aspirin)
ASADE	anticipated serious adverse device effect
ASD	atrial septal defect
BARC	Bleeding Academic Research Consortium
CI	confidence interval
CIP	clinical investigation plan
CRF	case report form
CT	computed tomography
DAPT	dual antiplatelet therapy
DICOM	Digital Imaging and Communications in Medicine
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture (system)
EFS	early feasibility study
eGFR	estimated glomerular filtration rate
ePTFE	polytetrafluorotheylene
F	French (catheter scale system)
FDA	U.S. Food and Drug Administration

GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICE	intracardiac echocardiography
ICF	informed consent form
ICH	International Conference on Harmonization
IFU	instructions for use
INR	international normalized ratio
IP	implanted patient population
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intention to treat
LAA	left atrial appendage
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MRI	magnetic resonance imaging
NeuroARC	Neurologic Academic Research Consortium
NOAC	Novel oral anticoagulants
NYHA	New York Heart Association
OAC	oral anticoagulation
PI	principal investigator
PFO	patent foramen ovale
QD	quaque die (daily)
QVSFS	questionnaire for verifying stroke-free status
SADE	serious adverse device effect

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedures
TIA	transient ischemic attack
TBD	to be determined
TEE	transesophageal echocardiography
TTE	trans-thoracic echocardiography
UADE	unanticipated adverse device effect
VARC	Valve Academic Research Consortium
US	United States

17.3 Appendix C: Questionnaire for Verifying Stroke-Free Status (QVSFS)

Questionnaire for Verifying Stroke-Free Status (QVSFS) Form	
Exam Time Point:	❑ Screening ❑ Pre-discharge ❑ 7 days ❑ 45 days ❑ 6 months ❑ 1 year ❑ 2 years ❑ 3 years ❑ 4 years ❑ 5 years ❑ Other
Form Completed:	__ __ / __ __ / __ __ __ __ (mm/dd/yy) __ __ : __ __ (hour: min) (24 hr. format)
Instructions:	The QVSFS must be completed at screening, during each clinic visit, and during each telephone contact to screen for interceding signs and symptoms of stroke or TIA. If any question is answered "Yes", a formal neurologic examination and evaluation must be performed by a board-certified neurologist or clinical designee (e.g., neurology fellow).

1. Since the last routine study contact by phone or clinic, have you been told by a physician that you have had a stroke?

   ❑ YES ❑ NO ❑ Don't know/Not sure

2. Since the last routine study contact by phone or in the clinic, have you been told by a physician that you had a TIA, mini-stroke, or transient ischemic attack?

   ❑ YES ❑ NO ❑ Don't know/Not sure

3. Since the last routine study contact by phone or in the clinic, have you had sudden painless weakness on one side of your body?

   ❑ YES ❑ NO ❑ Don't know/Not sure

4. Since the last routine study contact by phone or in the clinic, have you had sudden numbness or a dead feeling on one side of your body?

   ❑ YES ❑ NO ❑ Don't know/Not sure

5. Since the last routine study contact by phone or in the clinic, have you had sudden painless loss of vision in one or both eyes?

   ❑ YES ❑ NO ❑ Don't know/Not sure

6. Since the last routine study contact by phone or in the clinic, have you suddenly lost one half of your vision?

   ❑ YES ❑ NO ❑ Don't know/Not sure

7. Since the last routine study contact by phone or in the clinic, have you suddenly lost the ability to understand what people were saying?

   ❑ YES ❑ NO ❑ Don't know/Not sure

8. Since the last routine study contact by phone or in the clinic, have you suddenly lost the ability to express yourself verbally or in writing?

   ❑ YES ❑ NO ❑ Don't know/Not sure

Source: Jones WJ, Williams LS and Meschia JF. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. *Stroke*. 2001;32:2232-6.

17.4 Appendix D: National Institutes of Health Stroke Scale (NIHSS)

National Institutes of Health Stroke Scale (NIHSS) Form	
Exam Time Point:	❑ Screening ❑ Pre-discharge ❑ 45 days ❑ 6 months ❑ 1 year ❑ Other
Form Completed:	__ __/__ __/__ __ __ __ (mm/dd/yy) __ __:__ __ (hour: min) (24 hr. format)
Instructions:	The NIHSS must be completed at screening and during each clinic visit. In the event of an increase from a patient's baseline NIHSS score, a formal neurologic examination and evaluation must be performed by a board-certified neurologist or clinical designee (e.g., neurology fellow). NOTE: Additional copies of the NIH Stroke Scale are available on the internet at https://stroke.nih.gov/resources/scale.htm.

NIHSS Assessment

1(a) Level of consciousness
O 0 = Alert, keenly responsive
O 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond
O 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)
O 3 Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid or areflexic

1(b) Level of consciousness questions
O 0 = Answers both questions correctly
O 1 = Answers one question correctly
O 2 = Answer neither question correctly

1(c) Level of consciousness commands
O 0 = Performs both tasks correctly
O 1 = Performs one task correctly
O 2 = Performs neither task correctly

2 Best gaze
O 0 = Normal
O 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.
O 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver

3 Visual
O 0 = No visual loss
O 1 = Partial hemianopia
O 2 = Complete hemianopia
O 3 = Bilateral hemianopia (blind including cortical blindness)

4 Facial palsy
O 0 = Normal symmetrical movements
O 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
O 2 = Partial paralysis (total or near-total paralysis of lower face)
O 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

5(a) Motor arm- left
O 0 = No drift, limb holds 90 (or 45) degrees for 10 full seconds
O 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support
O 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees; drifts down to bed, but has some effort against gravity
O 3 = No effort against gravity, limb falls

O 4 = No movement
O UN = Amputation or joint fusion Explain_____

5(b) Motor arm- right
O 0 = No drift, limb holds 90 (or 45) degrees for 10 full seconds
O 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support
O 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees; drifts down to bed, but has some effort against gravity
O 3 = No effort against gravity, limb falls
O 4 = No movement
O UN = Amputation or joint fusion Explain_____

6(a) Motor leg- left
O 0 = No drift; leg holds 30 degree position for full 5 seconds
O 1 = Drift; leg falls by the end of the 5-second period but does not hit bed
O 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity
O 3 = No effort against gravity; leg falls to bed immediately
O 4 = No movement
O UN = amputation or joint fusion Explain_____

6(b) Motor leg- right
O 0 = No drift; leg holds 30 degree position for full 5 seconds
O 1 = Drift; leg falls by the end of the 5 second period but does not hit bed
O 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity
O 3 = No effort against gravity; leg falls to bed immediately
O 4 = No movement
O UN = amputation or joint fusion Explain_____

7 Limb ataxia
O 0 = Absent
O 1 = Present in one limb
O 2 = Present in two limbs
O UN = Amputation or joint fusion Explain_____

8 Sensory
O 0 = Normal; no sensory loss
O 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched
O 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg

9 Best Language
O 0 = No aphasia; normal
O 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility or comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming

card content from patient's response.
O 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided form patient response.
0 3 = Mute, global aphasia; no usable speech or auditory comprehension

10 Dysarthria
O 0 = Normal
O 1 = Mild-to-moderate dysarthria; patient slurs at least some word and, at worst, can be understood with some difficulty.
O 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence or out of proportion to any dysphasia, or is mute/anarthric.
O UN = Intubated or other physical barrier Explain_____

11 Extinction and Inattention (formerly neglect)
O 0 = No abnormality
O 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.
O 2 = Profound hemi0inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Total Score: (format 99)
(Autocalculated)

17.5 Appendix E: Modified Rankin Scale (mRS)

Modified Rankin Scale (mRS) Form	
Exam Time Point:	❑ Screening ❑ Other
Form Completed:	__ __/ __ __/ __ __ __ __ (mm/dd/yy) __ __ : __ __ (hour: min) (24 hr. format)
Instructions:	The mRS must be completed at screening and whenever a suspected neurologic event triggers an evaluation by a board-certified neurologist or clinical designee (e.g., neurology fellow). In patients who experience a stroke, the mRS should be repeated 90 ± 14 days after the event.

Modified Rankin Scale	**Structured Interview for the Modified Rankin Scale**
5 = Severe disability bedridden, incontinent, and requiring constant nursing care and attention	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or untrained caregiver. Question: *Does the person require constant care?* ❑ YES ❑ NO
4 = Moderately severe disability unable to walk without assistance, and unable to attend to own bodily needs without assistance	4=Moderately severe disability; need for assistance with some basic activities of daily living (ADL), but not requiring constant care. Question: *Is assistance essential for eating, using the toilet, daily hygiene, or walking?* ❑ YES ❑ NO
3 = Moderate disability requiring some help, but able to walk without assistance	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: *Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?* ❑ YES ❑ NO
2 = Slight disability unable to carry out all previous activities but able to look after own affairs without assistance	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: *Has there been a change in the person's ability to work or look after others if these were roles before stroke?* *Has there been a change in the person's ability to participate in previous social and leisure activities?* *Has the person had problems with relationships or become isolated?* ❑ YES (to any question) ❑ NO (to all questions)

1 = No significant disability despite symptoms able to carry out all usual duties and activities	1=No significant disability; symptoms present but no physical or other limitations. Question: *Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?* ❑ YES ❑ NO
0=No symptoms at all	0=No symptoms at all; no limitations and no symptoms
mRS SCORE:	❑ 5 ❑ 4 ❑ 3 ❑ 2 ❑ 1 ❑ 0

Sources: Modified Rankin Scale: van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Inter-observer agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-607; Structured Interview: Wilson JRL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, Bone I. Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the Modified Rankin Scale. Stroke. 2002;33:2243-2246.

The CONFORMAL Prague Study

An Evaluation of the Safety and Performance of the Conformal Left Atrial Appendage Seal for Left Atrial Appendage Occlusion

Clinical Investigation Plan

Protocol # 19-101

Revision B

23 April 2021

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

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1.0 Document Control

1.1 Version History

Version (Date)	Description
A (March 22, 2019)	Initial submission to Prague
B (23 April 2021)	Added modified delivery system to Section 4.2. Modifications were made based on learnings from the US Early Feasibility Study and the European First in Human Trial.
	Echocardiographic eligibility is evaluated prior to implant delivery. This has been updated throughout.
	Added option of Cardiac CT scan at 12-M due to potential COVID restrictions.

1.2 Protocol Approval Page

Study title:	The CONFORMAL Prague Study An evaluation of the safety and performance of the Conformal Left Atrial Appendage Seal for Left Atrial Appendage Occlusion
Protocol version:	B
Protocol date:	23 April 2021

Principal Investigator
Petr Neuzil, M.D.

Date

Chris Cain
Vice President, Clinical & Regulatory Affairs
Conformal Medical, Inc.

Date

1.3 Investigator Signature Page

Study title: The CONFORMAL Prague Study

An evaluation of the safety and performance of the Conformal Left Atrial Appendage Seal Device for Left Atrial Appendage Occlusion

Protocol version: B

Protocol date: 23 April 2021

Investigator's Responsibility

As the site Principal Investigator, I understand that I must obtain written approval from my Institutional Review Board prior to participation in the trial. This approval must include my name and a copy must be provided to Conformal Medical (or designee), along with the approved Patient Information and Consent Form prior to the first enrollment at my study site.

As the site Principal Investigator, I must also:

1. Conduct the study in accordance with the study protocol, the signed Clinical Investigation Agreement, applicable laws, 21 CFR Part 812 and other applicable United States Food and Drug Administration (FDA) regulations, any conditions of approval imposed by the FDA or IRB, International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and the Declaration of Helsinki, and ensure that all study personnel are appropriately trained prior to any study activities.
2. Ensure that the study is not commenced until all approvals have been obtained.
3. Supervise all use of the Conformal Medical Left Atrial Appendage Seal (CLAAS) device at my institution.
4. Ensure that written informed consent is obtained from each subject prior to any data collection and any study-specific procedures or assessments, using the most recent Institutional Review Board approved Informed Consent Form.
5. Provide all required data and reports and agree to source document verification of study data with patient's medical records by Conformal Medical (or designee) and any regulatory authorities.
6. Allow Conformal Medical personnel or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to national data protection laws.

Investigator Signature

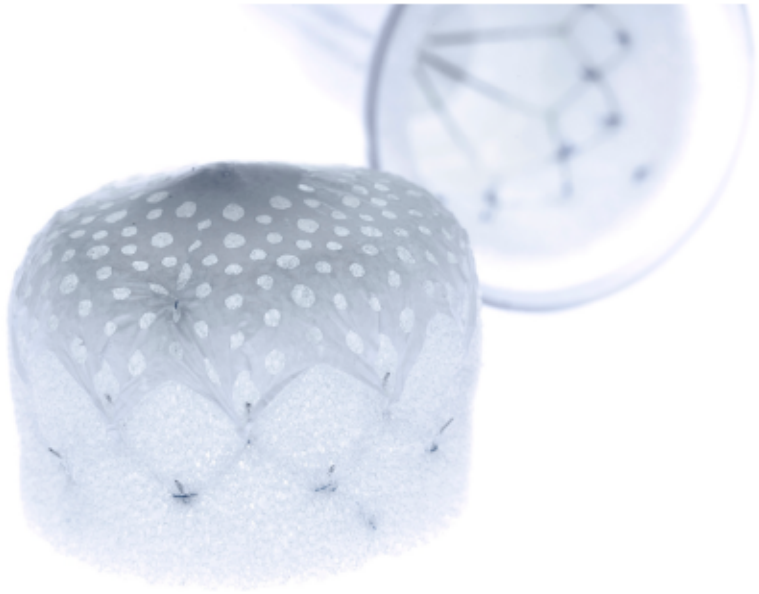
I have read and understand the contents of this Clinical Investigation Plan and agree to abide by the requirements set forth in this document.

_____	_____
Investigator Name (print)	Investigative Site (print)
_____	_____
Investigator Signature	Date

2.0 Study Contacts

Sponsor	**Conformal Medical, Inc.** 15 Trafalgar Square, Ste. 101 Nashua, NH 03063 USA **Conformal Contact:** Chris Cain Vice President, Clinical & Regulatory Affairs Tel: 408.439.5154 email: ccain@conformalmedical.com
Principal Investigator	Prof. Petr Neuzil, M.D., Ph.D., FESC. Head of cardiology and Director of EP Animal Lab Na Homolce Hospital Roentgenova 2 Prague 150 30 phone: 420 257272211 fax: 420 257272693
Monitoring	**Conformal Medical, Inc.** **Contact:** Chris Cain VP, Clinical & Regulatory Affairs Email: ccain@conformalmedical.com

3.0 Protocol Synopsis

Study Title	**The Conformal Prague Study** An evaluation of the safety and performance of the Conformal Left Atrial Appendage Seal for Left Atrial Appendage Occlusion
Study Device	The Conformal Left Atrial Appendage Seal (CLAAS®) is a permanent implant designed to occlude the left atrial appendage (LAA) to eliminate blood flow into and clot passage from the LAA. 
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 CHA_2DS_2-VASc scores and are recommended for oral anticoagulation (OAC) therapy; 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	The primary objective is to evaluate the safety and technical performance of the CLAAS system for closure of the left atrial appendage in patients with non-valvular atrial fibrillation at increased risk for stroke and systemic embolism who are recommended for oral anticoagulation (OAC) therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC.

Study Design	A prospective, single center, open-label, single arm, study to evaluate the safety and technical performance of the CLAAS system for closure of the left atrial appendage. Patients presenting with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, and who meet all eligibility criteria, will be enrolled in the study and undergo LAA closure with the CLAAS system.
Sample Size	Up to 20 subjects shall be enrolled in the study.
Investigational Sites	One (1) investigational site in Europe.
Study Duration / Follow-up Period	Subjects will have clinical follow-up prior to hospital discharge and at 7 days, 45 days and, 6 and 12 months. Transesophageal echocardiographic (TEE) follow-up will be performed at 45 days and, 6 and 12 months.
Primary Safety Endpoint	**Freedom from major adverse events,** evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of: • All-cause mortality • Ischemic stroke • Systemic thromboembolism • Device- or procedure-related adverse events requiring open cardiac surgery or major endovascular intervention* *NOTE: Major endovascular intervention includes pseudoaneurysm repair, AV fistula repair, and other major endovascular repair. Non-major interventions that are excluded from this endpoint include percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications.
Primary Performance Endpoint	**Closure success**, defined as device success followed by complete closure or peri-device residual leak ≤5 mm in width on TEE, at 45 days post-procedure.
Secondary Endpoints	Unless otherwise indicated, the following secondary endpoints will be evaluated in-hospital and at 45 days and, 6 and 12 months: **Secondary Safety Endpoints** 1. **Major procedure-related complications,** defined as the composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and major vascular complications, as related to the study device or procedure [evaluated in-hospital]

	2. **Major safety events,** defined as the composite of all-cause mortality, overt CNS injury (Neuro ARC defined), and major bleeding (BARC Type 3-5) 3. **Mortality**, classified as cardiovascular or non-cardiovascular and reported cumulatively and individually **Secondary Performance Endpoints** 1. **Device success**, defined as successful implantation of the CLAAS device in the LAA with acceptable position, and seal (peri-device residual leak ≤5 mm in width on ICE post procedure) 2. **Procedure success**, defined as device success without major in-hospital procedure-related complications during hospitalization or at 7 days whichever is longer 3. **Closure success**, defined as closure or peri-device residual leak ≤5 mm in width on TEE at 6 months post-procedure **Secondary Effectiveness Endpoint** 1. **Embolic events**, defined as the composite of ischemic stroke and systemic embolism
Other Measure	**Use of TEE** to confirm post-procedure ICE evaluation of device seal and position as a comparator for device success.
Antiplatelet and Anticoagulant Therapy	Antiplatelet and oral anticoagulant therapy requirements are as follows: **Pre-Procedure** The following should be administered prior to the index procedure: • ASA 81-100 mg (administered prior to procedure and continued daily) **Intra-Procedure** Intraprocedural medication should be administered per standard of care, maintaining an activated clotting time (ACT) of 250-350s throughout the procedure. **Post-Procedure** If the post-procedure TEE demonstrates adequate seal (residual leak ≤5 mm) and there is no evidence of thrombus, subjects should receive DAPT (ASA 75-100 mg QD and clopidogrel 75 mg QD) until 45 days post-procedure. If the 45-day TEE demonstrates adequate closure, DAPT should be continued to 6 months. For high bleeding risk (HBR) subjects, monotherapy (ASA preferred, P2Y12 permitted) may be initiated per physician judgement. If the 6-month TEE demonstrates adequate closure, DAPT should be replaced by monotherapy (ASA preferred, P2Y12 permitted). • **Inadequate seal:** Subjects with inadequate seal (residual leak >5 mm) at the post-procedure TEE (or any subsequent TEE) should be evaluated for

	treatment with NOAC and ASA for 4-6 weeks followed by TEE. If inadequate seal persist, anti-thrombotic therapy should be individualized for the patient balancing bleeding risk with the associated persistent inadequate seal (seen on TEE). • **Thrombus:** For thrombus detected on 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 TEE. Anti-thrombotic therapy should be individualized for the patient, balancing bleeding risk and the assumed thrombo-embolic risk associated with the TEE findings.
Patient Population	Patients presenting with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation.
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 a CHA_2DS_2-VASc score of ≥ 2 4. The patient is recommended for oral anticoagulation therapy (OAC), but has an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation 5. The patient is willing and able to comply with the protocol-specified medication regimen and follow-up evaluations 6. The patient (or legally authorized representative) has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent approved by the appropriate 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 1 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 procedure (e.g., prior atrial septal defect [ASD] or patent foramen ovale

	[PFO], surgical repair or implanted closure device, or obliterated or ligated left atrial appendage) 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. Patients with a medical condition (other than atrial fibrillation) that mandates chronic oral anticoagulation (e.g., history of unprovoked deep vein thrombosis or pulmonary embolism, or mechanical heart valve) 5. History of bleeding diathesis or coagulopathy, or patients in whom antiplatelet and/or anticoagulant therapy is contraindicated 6. Active infection with bacteremia 7. Documented symptomatic carotid artery disease (>50% diameter stenosis with prior ipsilateral stroke or TIA) or known asymptomatic carotid artery disease (diameter stenosis of >70%) 8. Recent (within 30 days of index procedure) or planned (within 60 days post-procedure) cardiac or non-cardiac interventional or surgical procedure 9. Recent (within 90 days of index procedure) stroke, transient ischemic attack 10. Recent myocardial infarction within 60 days of index procedure 11. Vascular access precluding delivery of implant with catheter-based system 12. Severe heart failure (New York Heart Association Class III or IV) 13. Prior cardiac transplant, history of mitral valve replacement or transcatheter mitral valve intervention, or any mechanical valve implant 14. Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the Modification of Diet in Renal Disease equation), or dialysis at the time of screening 15. Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <3,000 cells/mm^3 16. Patient has a known allergy, hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, or device materials (e.g., nickel, titanium, gold), or the patient has contrast sensitivity that cannot be adequately pre-medicated 17. Current participation in another investigational drug or device study that interferes with this study 18. Patient is a prisoner 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 1 year 20. Patient has a condition which precludes adequate transesophageal echocardiographic (TEE) assessment ***Echocardiographic Exclusion Criteria*** 1. Left atrial appendage anatomy cannot accommodate the CLAAS device per manufacturer IFU (e.g., ostium width <13 mm or >30 mm) 2. Intracardiac thrombus or dense spontaneous echo contrast, as visualized by echocardiography prior to implant 3. Left ventricular ejection fraction (LVEF) <30% 4. Circumferential 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 (exclusion >15 mm or length > 15 mm) or large shunt (early [within 3 beats] or substantial passage of bubbles) 7. Moderate or severe mitral valve stenosis (mitral valve area <1.5 cm^2) 8. Complex atheroma with mobile plaque of the aorta 9. Patient has evidence of cardiac tumor

4.0 Background

4.1 Clinical Background

4.1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common clinically significant cardiac tachyarrhythmia, affecting more than 33 million patients worldwide, with a projected incidence of 5 million patients per year.[4] In the United States alone, approximately 6 million individuals suffer from AF and over one million new cases are diagnosed annually; due the aging population, the number is expected to double by the year 2030.[5, 6]

AF is associated with a substantially increased risk of stroke and thromboembolic events,[7] primarily due to the Left Atrial Appendage (LAA) serving as a site for thrombus formation. Untreated patients with AF have a 2-5% annual incidence of stroke, with a history of stroke or thromboembolic events conferring an even higher risk.[8, 9] Strokes that occur with AF are large and can be quite debilitating, leading to death or costly and painful rehabilitation and adding significant financial burden to the medical system.

4.1.2 Current Standard of Care to Treat Atrial Fibrillation

The standard treatment for stroke prevention in subjects with AF is oral anticoagulant (OAC) therapy to reduce the likelihood of clot formation, which is recommended regardless of the management strategy of the underlying rhythm disorder.[10] Options include warfarin and the Novel oral anticoagulants (NOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban).[11-14] While pharmacotherapy can reduce stroke incidence in AF by approximately 60%,[15] OAC therapy is associated with an increased risk of bleeding complications,[16] an issue of significant concern due to the high bleeding risk of many AF patients. In addition, management of OAC therapy is burdensome and long-term compliance is poor even in the closely monitored setting of clinical trials, putting patients at risk for embolic events.

Echocardiographic evidence that the LAA is the source of thrombi in more than 90% of patients with AF has prompted the development of novel transcatheter therapies to occlude the LAA, thereby excluding it from the circulation in AF patients with non-valvular AF.[17-21] Randomized clinical trials have demonstrated acceptable benefit to risk ratios for LAA closure in patients with non-valvular AF and a high risk for stroke or systemic embolism and an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation.[10, 22] The WATCHMAN Left Atrial Appendage Closure Device (Boston Scientific Corporation, Marlborough, MA, US) received FDA approval in March 2015 on the basis of data from the . PROTECT-AF and PREVAIL randomized clinical trials and associated continued access registries that demonstrated that the device was non-inferior to warfarin for the primary composite endpoint of stroke, systemic embolism, or cardiovascular death. In addition, device implantation was associated with an approximately 80% reduction in hemorrhagic strokes and a >50% reduction in cardiovascular death.[10, 22]

While LAA closure with the WATCHMAN device represents an important advance in stroke prevention for patients with AF, important limitations and opportunities for improvement exist, including a technically challenging implantation process, restrictions of the LAA anatomies that can be effectively sealed, and low but persistent rates of residual leaks and device-related thrombus.

Conformal Medical has developed an alternative LAA closure technology that maintains the stroke prevention efficacy of the WATCHMAN device while offering a simplified implantation procedure; conformability to diverse LAA anatomies that reduces the opportunity for leakage; and a thromboresistant left atrial surface.

4.2 Investigational Device

4.2.1 **Name of the Investigational Device**

The Conformal Left Atrial Appendage Seal (CLAAS)

4.2.2 **Manufacturer**

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

4.2.3 **Proposed Indication for 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 CHA_2DS_2-VASc scores and are recommended for oral anticoagulation (OAC) therapy; 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.

4.2.4 **Device Description**

The following is a summary description of the Investigational Device. For additional information, please refer to the Instructions for Use.

4.2.4.1 Overview

The Conformal Left Atrial Appendage Seal (CLAAS®) System delivers a plug to the ostia of the Left Atrial Appendage (LAA) with a percutaneous delivery system (Figure 1). The implantable portion of the CLAAS System has been designed to occlude the LAA to eliminate blood flow into, and clot passage from, the LAA. The implant is provided on the Conformal custom-designed Delivery Catheter that is used to deliver the CLAAS implant through the CLAAS Access Sheath using a standard right femoral vein approach to the right atrium, across the atrial septum, and into the LAA. Echocardiography and fluoroscopy are used during the procedure to verify sizing and to aid in deployment of the implant to the target location.

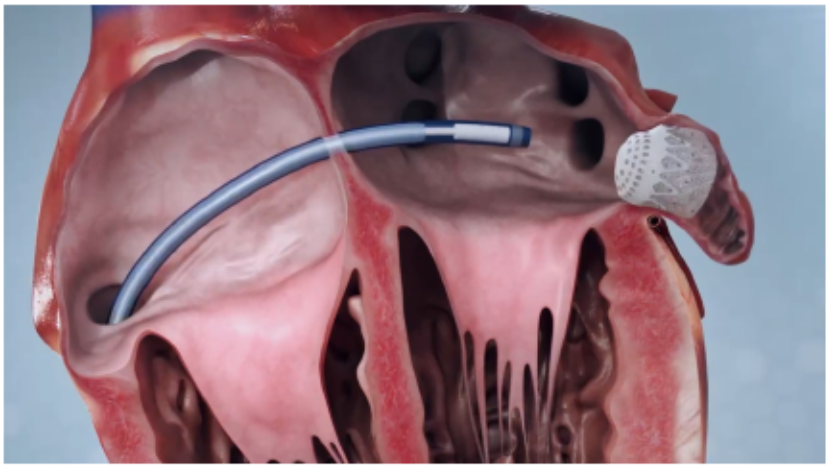


Figure 1: CLAAS Delivery System and Implant in LAA anatomy.

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4.2.4.1 CLAAS Implant

The implant is designed to permanently seal off the LAA from the LA with an endothelial layer that forms across the LA face of the implant. The implant has an inner, cylindrical, Nitinol endoskeleton (frame) that provides the mechanical base structure (#5 in Figure 2). The Nitinol endoskeleton contains 10 face struts and 20 anchors (Regular size) and 12 struts and 24 anchors (Large size) facing proximally to engage the tissue to resist movement. The endoskeleton also provides the conformable structure to enable the foam cylinder (#2 in Figure 2) to compress against the LAA tissue to facilitate sealing.

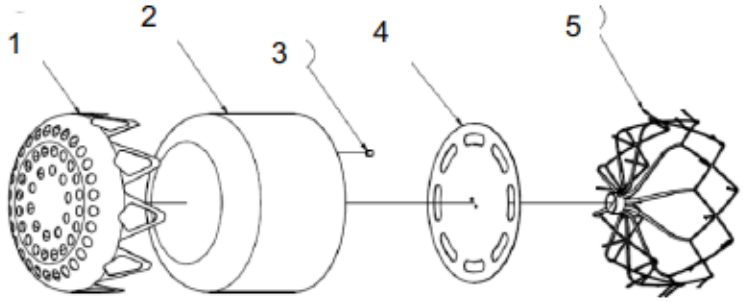

Figure 2: Implant components: (1) ePTFE cover, (2) Foam cup, (3) RO markers. (4) ePTFE inner cover, (5) Endoskeleton.

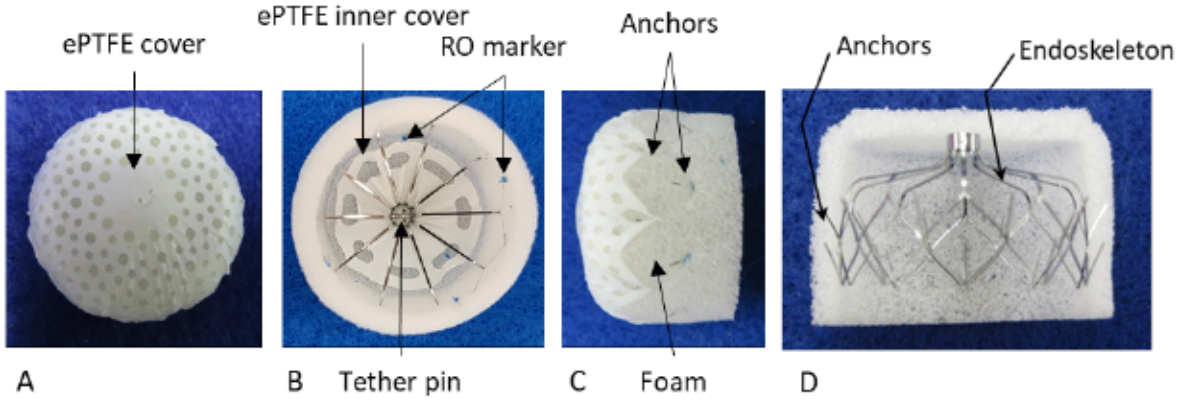

Figure 3: Regular CLAAS implant showing the left atrial face (A) ePTFE cover; inside (B) showing the endoskeleton, foam with ePTFE inner cover, sutures, RO marker and tether pin; side (C) showing anchors; and cross section (D) showing anchors and endoskeleton structure.

The implant is available in 2 sizes; Regular (27mm) and Large (35mm) diameters, which will accommodate the majority of patient LAA dimensions (Table 4). Both implant sizes require a minimum landing zone of approximately 10 mm to ensure engagement of the anchors with tissue distal to the LAA ostium. This short landing zone is an important aspect of the design and is only possible because the frame is shorter than the foam. Even though the implants are approximately 20mm deep (Figures 3 and 4), only 10mm of the anchor frame needs to engage tissue. There are 5mm of foam distal to the frame that act as a soft bumper during implant delivery and may fold into the frame as needed. The key nominal dimensions are shown in **Table 4**.

Table 4: CLAAS implant sizing.

Implant Size	Mean LAA Ostium Dia (D_{max} + D_{min}) / 2	LAA Ostium Diameter Range	Min Landing Zone
Regular	≤ 25 mm	10 – 33 mm	10 mm
Large	≤ 32 mm	20 – 40 mm	10 mm

4.2.4.2 CLAAS Delivery System

Delivery of the implant is achieved with two coaxial catheters. An access sheath that contains a metal braid, PTFE liner, Pebax, and polyurethane materials is initially placed into the proper position within the LAA. The pre-attached implant is loaded into the distal end of the braided, PTFE lined, polyurethane delivery catheter either by hand or with the assistance of the supplied hydraulic loader.

The delivery catheter is advanced through the access sheath to the LAA for implant delivery. The catheters are sufficiently long to access the LAA from a right femoral vein puncture. The delivery catheter working length is designed such that when the delivery catheter is locked to the access sheath, its distal tip is about 3cm short of the access sheath tip. This allows the user to advance the implant from the delivery catheter into the access sheath prior to deploying it into the patient.

Each catheter has a hemostatic valve at its proximal end that can be closed to prevent blood loss or opened to pass catheters (Figure 5 and 6).

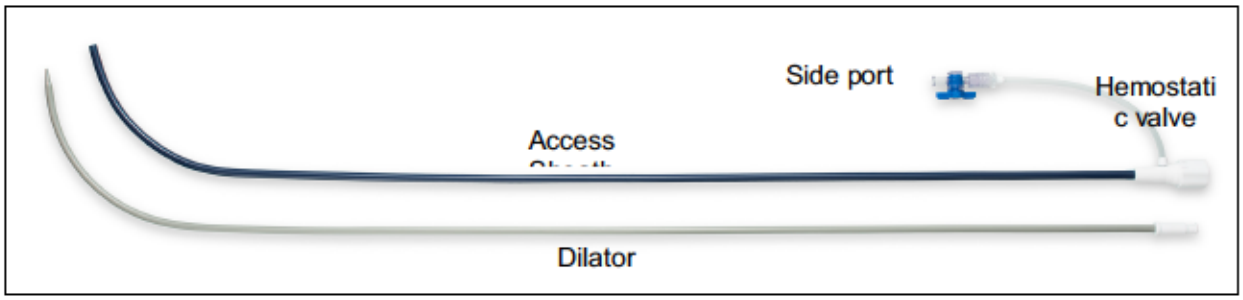

Figure 5: Single curve Access Sheath.

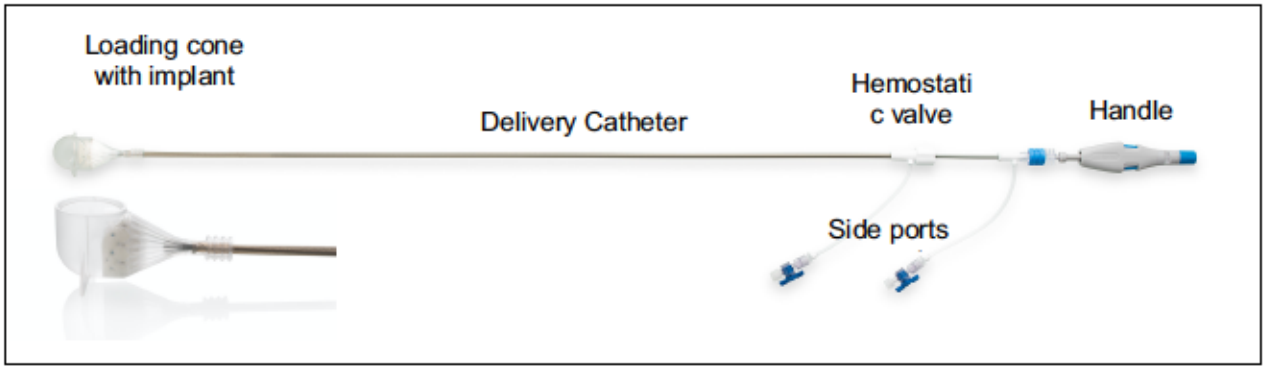

Figure 6: Delivery catheter assembly with deployment handle, hemostatic valve, injection ports, and implant loading cone.

4.3 Rationale

The CLAAS system is designed to provide the benefits of left atrial appendage closure with a conventional device, while potentially simplifying the implantation procedure, improving procedural safety, and reducing the peri-device leakage. The study will evaluate the feasibility of LAA closure with the CLAAS system and gather preliminary safety and effectiveness data to inform the design of a pivotal trial.

5.0 Study Design

5.1 Study Design Overview

This prospective, single center, open-label, single arm, study will enroll up to 20 subjects aimed at examining the safety and technical performance of the CLAAS device for LAA closure. Patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHA_2DS_2-VASc scores, and who are recommended for oral anticoagulation therapy but have an appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, and who meet all eligibility criteria, will be enrolled in the study and undergo LAA closure with the CLAAS system.

Subjects will have clinical follow-up prior to hospital discharge and at 7 days, 45 days, and 6- and 12-months post procedure. Transesophageal echocardiographic (TEE) follow-up will be performed at 45 days and, 6 and 12 months in all subjects.

The primary safety endpoint is freedom from major adverse events, evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of all-cause mortality, ischemic stroke, systemic thromboembolism, and device- or procedure-related adverse events requiring open cardiac surgery or major endovascular intervention. The primary performance endpoint is closure success, defined as device success followed by successful LAA closure (complete closure or peri-device residual leak ≤5 mm in width on TEE at 45 days post-procedure). The study will also report additional secondary safety, performance, and effectiveness endpoints, as well as using TEE to confirm post-procedure ICE evaluation of device seal and position as a comparator for device success.

All endpoints will be reported using appropriate descriptive statistics in the primary analysis population (the ITT population), and no hypothesis testing will be performed. As a secondary analysis, all endpoints will be evaluated in the Implanted Patient (IP) population.

5.2 Study Objective

The primary objective of the study is to evaluate feasibility of ICE as primary imaging modality for device success in patients with non-valvular atrial fibrillation at increased risk for stroke and systemic embolism who are recommended for oral anticoagulation (OAC) therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC. TEE will be used to confirm the ICE evaluation.

5.3 Endpoints

5.3.1 **Primary Safety Endpoint**

The primary safety endpoint is **freedom from major adverse events,** evaluated at hospital discharge or at 7 days post-procedure (whichever occurs later), and defined as absence of the composite of:

- All-cause mortality
- Ischemic stroke
- Systemic thromboembolism

- Device- or procedure-related adverse events requiring open cardiac surgery or major endovascular intervention*

*NOTE: Major endovascular intervention includes pseudoaneurysm repair, arteriovenous fistula repair, and other major endovascular repair. Non-major interventions that are excluded from this endpoint include percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications.

5.3.2 **Primary Performance Endpoint**

The primary performance endpoint is **closure success**, defined as device success followed by complete closure or peri-device residual leak ≤5 mm in width on TEE at 45 days post procedure.

5.3.3 **Secondary Endpoints**

Unless otherwise indicated, the following secondary endpoints will be evaluated in-hospital and at 45 days, and 6 and 12 months.

5.3.3.1 Secondary Safety Endpoints

5.3.3.1.1 **Major procedure-related complications**, defined as the composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and major vascular complications as related to the study device or procedure [evaluated in-hospital]

5.3.3.1.2 **Major safety events**, defined as the composite of all-cause mortality, overt CNS injury (Neuro ARC defined), and major bleeding (BARC Type 3-5)

5.3.3.1.3 **Mortality**, classified as cardiovascular or non-cardiovascular reported cumulatively and individually

5.3.3.2 Secondary Performance Endpoints

5.3.3.2.1 **Device success**, defined as successful implantation of the CLAAS device in the LAA with acceptable position and seal (peri-device residual leak ≤5 mm in width on ICE post procedure)

5.3.3.2.2 **Procedure success**, defined as device success without major in-hospital procedure-related complications during hospitalization or at 7 days whichever is longer

5.3.3.2.3 **Closure success**, defined as closure or peri-device residual leak ≤5 mm in width on TEE at 6 months post-procedure

5.3.3.3 **Secondary Effectiveness Endpoint**

5.3.3.3.1 **Embolic events**, defined as the composite of ischemic stroke and systemic embolism

5.3.4 **Other Measures**

The following other imaging-related measures will also be evaluated:

5.3.4.1 Intra Cardiac Echocardiography (ICE)

5.3.4.1.1 Ability to accurately assess CLAAS device position and seal [evaluated prior to implant release during the index procedure]

5.3.4.1.2 Ability to adequately visualize pericardial space to rule out effusion [evaluated post-implant during the index procedure]

6.0 Subject Selection and Withdrawal

6.1 Patient Population

The patient 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 and are recommended for OAC therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC, and who have been deemed appropriate for LAA closure by the Site PI on oral anticoagulants consistent with the standard of care.

6.2 Eligibility Criteria

6.2.1 **Inclusion Criteria**

Potential subjects must meet ALL of the following criteria to be eligible for enrollment into the study:

6.2.1.1 General Inclusion Criteria

6.2.1.1.1 Male or non-pregnant female aged ≥18 years

6.2.1.1.2 Documented non-valvular AF (paroxysmal, persistent, or permanent)

6.2.1.1.3 High risk of stroke or systemic embolism, defined as a CHA_2DS_2-VASc score of ≥ 2

6.2.1.1.4 The patient is recommended for oral anticoagulation therapy (OAC), but has an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation

6.2.1.1.5 The patient is willing and able to comply with the protocol-specified medication regimen and follow-up evaluations

6.2.1.1.6 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 Ethics Committee (EC)

6.2.2 **Exclusion Criteria**

Potential subjects will be excluded if ANY of the following criteria apply:

6.2.2.1 General Exclusion Criteria

6.2.2.1.1 Pregnant or nursing patients and those who plan pregnancy in the period up to 1 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.

6.2.2.1.2 Anatomic conditions that would prevent performance of an LAA occlusion procedure (e.g., prior atrial septal defect [ASD] or patent foramen ovale [PFO] surgical repair or implanted closure device, or obliterated or ligated left atrial appendage)

6.2.2.1.3 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)

6.2.2.1.4 Patients with a medical condition (other than atrial fibrillation) that mandates chronic oral anticoagulation (e.g., history of unprovoked deep vein thrombosis or pulmonary embolism, or mechanical heart valve)

6.2.2.1.5 History of bleeding diathesis or coagulopathy, or patients in whom antiplatelet and/or anticoagulant therapy is contraindicated

6.2.2.1.6 Active infection with bacteremia

6.2.2.1.7 Documented symptomatic carotid artery disease (>50% diameter stenosis with prior ipsilateral stroke or TIA) or known asymptomatic carotid artery disease (diameter stenosis of >70%)

6.2.2.1.8 Recent (within 30 days pre-procedure) or planned (within 60 days post-procedure) cardiac or non-cardiac interventional or surgical procedure

6.2.2.1.9 Recent (within 90 days pre-procedure) stroke or transient ischemic attack

6.2.2.1.10 Recent (within 60 days pre-procedure) myocardial infarction

6.2.2.1.11 Vascular access precluding delivery of implant with catheter-based system

6.2.2.1.12 Severe heart failure (New York Heart Association Class III or IV)

6.2.2.1.13 Prior cardiac transplant, history of mitral valve replacement or transcatheter mitral valve intervention, or any mechanical valve implant

6.2.2.1.14 Renal insufficiency, defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (by the Modification of Diet in Renal Disease equation), or dialysis at the time of screening

6.2.2.1.15 Platelet count <75,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <3,000 cells/mm^3

6.2.2.1.16 Patient has a known allergy, hypersensitivity or contraindication to aspirin, heparin, or device materials (e.g., nickel, titanium, gold) or that would preclude any P2Y12 inhibitor therapy, or the patient has contrast sensitivity that cannot be adequately pre-medicated

6.2.2.1.17 Current participation in another investigational drug or device study that interferes with this study

6.2.2.1.18 Patient is a prisoner

6.2.2.1.19 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 1 year

6.2.2.1.20 Patient has a condition which precludes adequate transesophageal echocardiographic (TEE) assessment

6.2.2.2 Echocardiographic Exclusion Criteria

6.2.2.2.1 Left atrial appendage anatomy cannot accommodate the CLAAS device per manufacturer IFU

6.2.2.2.2 Intracardiac thrombus or dense spontaneous echo contrast, as visualized by echocardiography prior to implant

6.2.2.2.3 Left ventricular ejection fraction (LVEF) <30%

6.2.2.2.4 Circumferential pericardial effusion >10 mm or symptomatic pericardial effusion, signs or symptoms of acute or chronic pericarditis, or evidence of tamponade physiology

6.2.2.2.5 Atrial septal defect that warrants closure

6.2.2.2.6 High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (exclusion >15 mm or length > 15 mm) or large shunt (early [within 3 beats] or substantial passage of bubbles)

6.2.2.2.7 Moderate or severe mitral valve stenosis (mitral valve area <1.5 cm^2)

6.2.2.2.8 Complex atheroma with mobile plaque of the aorta

6.2.2.2.9 Patient has evidence of cardiac tumor

6.3 Subject Screening

The study site will maintain a log of all screened and consented subjects. Reasons for meeting study criteria but failing to be enrolled will be captured on the screening log and entered into the database.

Potentially eligible subjects will undergo the process of informed consent (§6.4) prior to the performance of any study-specific assessments.

Potentially eligible subjects will be enrolled in the study only when the CLAAS Access Sheath has been introduced into the patient's body. Patients who do not meet general or echocardiographic eligibility criteria, or in whom the CLAAS Access Sheath is not introduced, will not be enrolled in the study.

Screen failures may be re-enrolled at a future date if it is determined that the eligibility criteria that initially excluded them from participation are no longer applicable (e.g., a thrombus identified on the initial TEE has resolved, a prior stroke is now outside of the exclusion window) or larger device is available.

6.4 Informed Consent

Relevant study information will be summarized on a Patient Information and Consent Form ("Informed Consent Form [ICF]") that has been approved by the CA. This document, or a modification based on local EC recommendations, must be approved by the applicable EC and signed by each

subject or his/her legal representative (where allowed) prior to the performance of any study-specific procedures or assessments.

The subject or his/her legal representative (where allowed) must be provided with a copy of the signed and dated informed consent form.

The Investigator shall inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required, that may be relevant to the subject and his/her willingness to continue participation in the study. The consent form should be updated or amended whenever such new information becomes available and updated consent shall be recorded.

6.5 Subject Enrollment

Potentially eligible subjects who meet all general inclusion criteria, and no general exclusion criteria and who have consented to participate in the trial will undergo the protocol-specified screening assessments to confirm eligibility. At the time of the index procedure, Echo will be evaluated to confirm that adequate echocardiographic images can be acquired and that no echocardiographic exclusion criteria (§6.2.2.2) are met.

Subjects meeting all inclusion and no exclusion criteria, and in whom the CLAAS Access Sheath is introduced into the patient's body, will be enrolled in the trial. Subjects who meet all eligibility criteria, but in whom the CLAAS Access Sheath is not introduced, are classified as screen failures, which must be documented in accordance with §6.3.

6.6 Withdrawal, Loss to Follow-up, and Study Completion

6.6.1 **Voluntary Withdrawal**

Subjects can withdraw from the study at any time; the reason(s) for withdrawal (if given) will be documented. All data available at the time of withdrawal (if any) will be used for analysis, unless the subject has explicitly forbidden the use of such data and has documented this preference in accordance with local regulatory requirements. There will be no further follow-up (per this study protocol) on a subject who has withdrawn. Subjects who withdraw from the study will not be replaced. The withdrawal of a subject can be initiated by the Investigator if he/she determines it is in the best interest of the patient.

6.6.2 **Loss to Follow-up**

When a subject does not return for a clinic visit or is not reachable for a telephone contact, this event is considered a missed visit. Subjects with a missed visit may return for subsequent follow-up visits.

If a subject has a missed visit and has not voluntarily withdrawn from the trial, site personnel should make all reasonable efforts to locate and communicate with the subject, including the following, at each contact time point:

- A minimum of (3) three telephone calls to contact the subject should be recorded in the source documentation, including date, time, and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter should be sent to the subject.

Subjects with three consecutive missed visits, despite the above-mentioned communication attempts, will be considered lost to follow-up and administratively withdrawn from the study.

6.6.3 **Study Completion**

A study completion form must be completed for all subjects:

- In whom mortality has been documented
- Who voluntarily withdraw from the study or are withdrawn by the investigator to protect subject rights, welfare, or well-being (§6.6.1)
- Who are lost to follow-up and administratively withdrawn from the study (§6.6.2)
- Who have completed the final protocol-specified follow-up assessment:
    - The final protocol-specified assessment for patients who leave the index procedure catheterization laboratory with an implanted CLAAS device is the 12-month visit (§7.8).

6.7 Protocol Deviations

All deviations from the requirements of this Clinical Investigation Plan will be considered protocol deviations. In the event that a subject-level protocol deviation is identified by the site, a Protocol Deviation form should be completed in the eCRF and submitted to the Sponsor. Protocol deviations that will be collected include:

- Failure to obtain informed consent, or failure to obtain informed consent prior to the performance of study-specific procedures or assessments
- Enrollment of a subject who did not meet all study inclusion criteria, or who met one or more study exclusion criteria
- Failure to complete protocol-specified assessments, or completion of protocol-specified assessments outside of the protocol-defined time frame

It is the Site Principal Investigator's responsibility to ensure that there are no deviations from the protocol and to maintain compliance with all established procedures of the applicable EC. If a deviation from the protocol is deemed necessary by the Investigator to protect the safety or physical well-being of a subject, the Investigator is requested to notify the Sponsor as soon as practicable (if possible, before the deviation has occurred).

7.0 Study Procedures and Assessments

7.1 Schedule of Procedures and Assessments

Table 3. Study Schedule of Procedures and Assessments

	Screening	Index Procedure (day 0)	Pre-discharge[1]	7 Days (+2 days)[2]	45 days (45 ± 7 days)	6 months (± 30 days)	12 months (± 30 days)
	Clinic Visit	Clinic Visit	Clinic Visit	Telephone Contact / Optional Clinic Visit	Clinic Visit	Clinic Visit	Clinic Visit
Demographics and Medical History	●						
Review of General Eligibility Criteria	●						
Informed consent	●						
Physical Examination	●		●		●		●
Stroke Assessment[3]	●		●	●	●	●	●
CHA_2DS_2-VASc; HAS-BLED scores	●						
Pregnancy Test[4]	●						
Laboratory tests[5]	●						
12-lead ECG[6]	●						
Brain Imaging[7]	●		●				
TTE			●				
TEE	●[8, 9]	●[11]			●	●	●
ICE		●[12]					
Angiography		●					
LAA occluder implantation		●					
Concomitant Medications	●	●	●	●	●	●	●
Adverse events	●[10]	●	●	●	●	●	●

[1] The pre-discharge visit must be conducted prior to hospital discharge from the index procedure; patients discharged on day 6 or earlier must also be followed up via telephone contact at 7 (+2) days post-procedure. For subjects who have not been discharged before day 7, the 7-day assessment may be performed in the clinic and no separate telephone contact is necessary.

[2] In patients who have been discharged from the index procedure hospitalization on day 6 or earlier, a telephone contact must be conducted at 7 (+2) days post procedure, and must include ascertainment of

	survival status, QVSFS, concomitant medication documentation, and reporting of any adverse events that may have occurred since the pre-discharge assessment. [3]The Questionnaire for Verifying Stroke-Free Status (QVSFS) and NIHSS must be completed at baseline and during each clinic visit to screen for interceding signs and symptoms of stroke or TIA. The modified Rankin Scale (mRS) must also be completed at baseline to establish the pre-stroke baseline value. For telephone contacts, stroke screening will consist of the QVSFS only. If a neurologic event is suspected at any time point, a formal neurologic examination and evaluation (to include the mRS) must be performed by a neurologist. [4] Female subjects of childbearing potential must have a pregnancy test (by site standard method) within 7 days prior to the index procedure to confirm study eligibility criteria. [5] Laboratory testing should be performed per site standard practice and should include CBC and serum creatinine. [6] A 12-lead ECG should be performed at baseline and repeated with any signs or symptoms of myocardial ischemia. [7] Patients with a history of stroke are required to have a baseline MRI (or CT, if MRI is contraindicated) performed within 90 days prior to the scheduled index procedure. Brain imaging need not be repeated if an MRI or CT performed within 90 days pre-procedure as part of the standard of care is available. Patients with history of significant brain trauma or intra-cranial surgery should have a post procedure/event CT or MRI available for review. [8] An initial evaluation of echocardiographic eligibility based on review of the pre-procedure TTE and/or TEE (or cardiac CT, if that modality is the site standard of care for pre-procedure anatomic assessment) should be performed prior to the index procedure. [9] TEE (or CT) performed within 90 days prior to consent will be accepted, otherwise TEE must be conducted after consent. [10]TTE performed within 6 months prior to consent will be accepted, otherwise TTE must be conducted after consent. [11]TEE performed after implant delivered, prior to tether release. [12]At time of index procedure, ICE performed to confirm eligibility criteria prior to enrollment.

7.2 Screening

The following tests and examinations must be performed prior to the procedure to verify eligibility and to collect baseline study data. Assessments performed as part of standard medical care prior to study enrollment are valid sources of data for verifying study eligibility and collecting baseline study data, provided that the previously performed assessments comply with applicable protocol requirements.

- Relevant medical history and patient demographic information
- Review of general inclusion, echo criteria and exclusion criteria
- Physical examination, to include NYHA functional class
- Stroke assessment (within 14 days pre-procedure), to include:
    - Questionnaire for Verifying Stroke-Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Modified Rankin Scale (mRS) to establish the pre-stroke baseline value; the mRS must be performed by a neurologist or research staff who have completed mRS training
    - Patients with documented history of stroke, TIA, or in whom an incident neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms,

will require a neurologic examination and evaluation be performed by a neurologist or clinical designee (e.g., neurology fellow)

- Atrial fibrillation stroke risk assessment with the CHA_2DS_2-VASc scores
- Major bleeding risk assessment with the HAS-BLED score
- Female patients of childbearing potential must have a pregnancy test (by site standard) performed within 7 days prior to the procedure
- Laboratory testing per site standard practice; if laboratory testing is part of the standard of care and includes CBC and serum creatinine, these should be recorded. The results of any additional laboratory tests performed per site standard practice should also be collected.
- A 12-lead electrocardiogram (ECG). An ECG performed within 30 days prior to the 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 date of the index procedure).
- Brain imaging. Patients with a history of stroke are required to have a baseline MRI (or CT, if MRI is contraindicated) performed within 90 days prior to the scheduled index procedure. NOTE: Brain imaging need not be repeated if an MRI or CT performed within 90 days pre-procedure as part of the standard of care is available.
- Transthoracic echocardiogram (TTE) or TEE per site standard practice; if TTE and/or TEE (or cardiac CT) is performed as part of the standard of care, it should be reviewed by the investigating physician to evaluate echocardiographic eligibility. Note that echocardiographic eligibility must be confirmed by echocardiography prior to subject enrollment.
- Documentation of all concomitant medications

7.3 Index Procedure

7.3.1 **Pre-Procedure Medical Therapy**

Pre-procedure anticoagulation therapy should be managed in accordance with standard institutional practice.

The following should be administered prior to the index procedure:

- ASA 81-100 mg (administered prior to procedure and continued daily)

7.3.2 **Intraprocedural Medical Therapy**

Intraprocedural anticoagulation should be maintained according to physician standard practice in accordance with published guidelines and local standards of care, with a goal of maintaining an activated clotting time (ACT) of 250-350 sec throughout the procedure. The highest and lowest intraprocedural ACT measurements must be recorded in the CRF for all subjects.

All medications administered, including the dose and timing, should be recorded in the patient's medical record and the CRF.

7.3.3 **Transseptal Puncture**

Percutaneous femoral vein access and transseptal puncture should be performed per physician standard practice using a standard commercially-available transseptal access system.

7.3.4 **Eligibility Confirmation**

Prior to implant, the investigator should confirm via echocardiographic imaging that the patient is eligible for participation in the study:

1) Confirm that that the patient does not meet any echocardiographic exclusion criteria (§6.2.2.2)
2) Confirm that LAA anatomy is appropriate for implantation of the CLAAS implant per the device Instructions for Use

7.3.5 **Procedural Imaging**

ICE is the primary imaging source before, during, and after CLAAS Implant deployment.

At any time during the study, echocardiographic imaging obtained during a repeat procedure or for diagnostic purposes should also be forwarded to Conformal.

7.3.6 **CLAAS Implant Deployment**

After eligibility has been confirmed and the CLAAS Access Sheath has been introduced into the patient's body, the patient is enrolled in the study and should undergo implantation of the CLAAS Implant per the device Instructions for Use.

Procedural details should be entered into the eCRF. ACT should be measured at the onset of the procedure and at regular intervals throughout the procedure per routine hospital practice.

The procedure is considered complete once the last venous access sheath is removed or the patient has been discharged from the cath lab, whichever is first.

7.3.7 **Immediate Post-Procedure Medical Therapy**

Post-procedure loading with clopidogrel is suggested.

Protamine sulfate should be given for anticoagulation reversal only when clinically indicated (e.g., femoral oozing).

Prescribe appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

7.3.8 **Anticoagulation/antiplatelet Therapy**

If the post-procedure TEE demonstrates adequate seal (residual leak ≤5 mm) and there is no evidence of thrombus, subjects should receive DAPT (ASA 75-100 mg QD and clopidogrel 75 mg QD) until 45 days post-procedure. NOTE: A substitute P2Y12 inhibitor (i.e., prasugrel, ticagrelor) may be used in known non-responders to clopidogrel.

If the 45-day TEE demonstrates adequate closure, DAPT should be continued to 6 months. For high bleeding risk (HBR) subjects, monotherapy (ASA preferred, P2Y12 inhibitor permitted) may be initiated per physician judgment.

If a 6-month TEE demonstrates adequate closure, DAPT should be replaced by monotherapy (ASA preferred, P2Y12 inhibitor permitted) to 12 months post-procedure.

Beginning 12 months post-procedure, medical therapy should be administered per standard of care.

- **Inadequate seal:** Subjects with inadequate seal (residual leak >5 mm) at the post-procedure TEE (or any subsequent TEE) should be evaluated for treatment with OAC and ASA for 4-6 weeks followed by TEE. If inadequate seal persists, anti-thrombotic therapy should be individualized for the patient, balancing bleeding risk with the associated persistent inadequate seal (seen on TEE).
- **Thrombus:** Subjects with thrombus detected on 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 TEE. Anti-thrombotic therapy should be individualized for the patient, balancing bleeding risk and the assumed thrombo-embolic risk associated with the TEE findings.

7.4 TEE Post Implant

A confirmatory TEE will be conducted after the implant is delivered, prior to tether release. The investigator will confirm the findings of the ICE imaging: position and seal.

7.5 Pre-discharge Follow-up

Post-procedure assessment must occur during the index procedure hospitalization prior to hospital discharge, and must include:

- Physical examination
- TTE
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke-Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, mRS must be documented, and repeated 90 ± 14 days post-event to assess disability.
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.

Prior to hospital discharge, research staff should review the follow-up requirements with the subject to ensure compliance with the subsequent follow-up assessment:

- For subjects discharged from the index procedure hospitalization on or before day 6 post-procedure, telephone numbers should be obtained from the subject to ensure the ability to reach him or her for the required 7 + 2-day telephone contact. These phone numbers should

include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

- For subjects discharged from the index procedure hospitalization on day 7 or later post-procedure, telephone numbers should be obtained from the subject to ensure that the subject returns to the clinic for the 45-day follow-up assessment.

7.6 7-day Follow-up (Telephone Contact / Optional Clinic Visit)

All subjects must undergo a follow-up assessment on day 7 to 9 post-procedure to enable timely documentation of safety endpoint events.

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, and no separate telephone contact is necessary.

For subjects who have already been discharged from the index procedure hospitalization, the 7-day follow-up will be conducted via telephone contact.

The 7-day follow-up assessment must include:

- Questionnaire for Verifying Stroke Free Status (QVSFS). If any question is answered "Yes", a formal neurologic examination and evaluation must be performed by a board-certified neurologist or clinical designee (e.g., neurology fellow).
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- Documentation of any adverse events occurring since the previous evaluation.

Note: for subjects discharged from the index procedure hospitalization prior to day 7, but who return to the clinic as part of their regular medical care during the specified follow-up window (7 to 9 days post procedure), the 7-day follow-up assessment may be conducted during the clinic visit, and no separate telephone contact is necessary.

7.7 45-day Follow-up (Clinic Visit)

All subjects will return to the clinic at 45 days (± 7 days) post-procedure for a clinical evaluation. The 45-day follow up visit will include the following assessments:

- Physical examination
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, NIHSS and mRS must be documented, and repeated 90 ± 14 days post-event.

- A transesophageal echocardiogram (TEE) must be performed in all subjects who left the index procedure with an implanted CLAAS device.
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded.
- Documentation of any adverse events occurring since the previous evaluation.

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient returns to the clinic for the 6-month follow-up visit.

7.8 Six-month Follow-up (Clinic Visit)

All subjects who received a CLAAS implant will return to the clinic at 6 months (± 30 days) to include the following assessments:

- Physical examination
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke Free Status (QVSFS)
    - NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
    - Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, NIHSS and mRS must be documented, and repeated 90 ± 14 days post-event.
- A transesophageal echocardiogram (TEE).
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded. If monotherapy has been initiated due to high bleeding risk, the factors contributing to the high bleeding risk assessment should be documented.
- Documentation of any adverse events occurring since the previous evaluation.

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient returns to the clinic for the 12-month follow-up visit

7.9 Twelve-month Follow-up (Clinic Visit)

All subjects who received a CLAAS implant will return to the clinic at 12 months (± 30 days) post-procedure for additional follow-up, to include the following assessments:

- Physical examination
- Stroke assessment, to include:
    - Questionnaire for Verifying Stroke Free Status (QVSFS)

- NIH Stroke Scale (NIHSS); the NIHSS must be performed by a neurologist or NIHSS-certified research staff
- Patients in whom a neurologic event is suspected on the basis of the QVSFS, NIHSS, or other signs or symptoms will require a neurologic examination and evaluation performed by a neurologist or clinical designee (e.g., neurology fellow). In patients with confirmed stroke, NIHSS and mRS must be documented, and repeated 90 ± 14 days post-event.

- A transesophageal echocardiogram (TEE) or Cardiac CT Scan*
- Current concomitant medications documentation. If DAPT has been interrupted or terminated the stop date (and resumption date, if applicable) and the reason for interruption/termination should be recorded. If monotherapy has been initiated due to high bleeding risk, the factors contributing to the high bleeding risk assessment should be documented.
- Documentation of any adverse events occurring since the previous evaluation.

*NOTE: Subjects evaluated by Cardiac CT which on review are found to have complete seal without thrombus will be considered as having closure success. If review indicates incomplete seal or thrombus, further evaluation by TEE will be required.

8.0 Adverse Events and Serious Adverse Events

In this study, patients should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning. Any time during the study, the patient may volunteer information that resembles an adverse event (AE). If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE CRFs.

8.1 Adverse Events (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in a study subject, whether or not related to the study device.

NOTES:

- The definition of AE includes events related to the study device or to the procedures involved but does not imply that there is a relationship between the adverse event and the study device.
- Pre-existing medical conditions or a repeat of symptoms reported prior to the procedure will **not** be reported as an AE. Pre-existing conditions that worsen during a study are to be considered adverse events.
- Planned procedures (scheduled prior to the index procedure) that occur after the index procedure are not considered reportable AEs. Complications from such procedures, however, must be reported.
- Abnormal non-cardiac laboratory findings are not considered a reportable AE unless:
  - The investigator determined that the finding is clinically significant; OR

- The abnormal laboratory finding required intervention; OR
- The abnormal laboratory finding required termination of the subject's participation in the study.

8.2 Serious Adverse Events (SAE)

A serious adverse event is an adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolongation of existing hospitalization
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

8.3 Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the Instructions for Use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

8.4 Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.5 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan.

8.6 Device Deficiencies, Malfunctions, and Use Error

Investigators are instructed to report all possible device deficiencies, malfunctions, misuse or use error observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

- **Device deficiency**: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.
    - **Device malfunction**: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol. NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use but does not perform as described in the Instructions for Use.
    - **Use error:** Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
        - **Device misuse:** Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

8.7 Documentation

Adverse events must be listed on the appropriate CRF. All AEs will be characterized by the following criteria which are detailed in the definition section:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

8.8 Reporting

8.8.1 General Adverse Event Reporting Procedures

Investigators are required to keep records on "all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)" according to 21 CFR 812.140. Adverse event collection will occur from the point of study enrollment to study closure. All new or worsening (from baseline) cardiovascular adverse events will be captured on the AE CRF through the 5-year follow-up telephone contact. Independent monitoring will be conducted (§12.1) to review source documentation and verify the complete and accurate capturing of adverse events.

The general procedure for investigators reporting any adverse event is as follows:

- If an adverse event occurs, complete all sections of the Adverse Event CRF. Note:
    - Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition
    - Planned procedures (scheduled prior to the index procedure) that occur after the index procedure are not considered reportable AEs. Complications from such procedures, however, must be reported.
    - Abnormal non-cardiac laboratory findings are not considered a reportable AE unless:

- The investigator determined that the finding is clinically significant; OR
- The abnormal laboratory finding required intervention; OR
- The abnormal laboratory finding required termination of the subject's participation in the study.

- Each unique event/diagnosis must be documented separately
- The AE CRF must be reviewed by the investigator

For adverse events not meeting the criteria for an SAE or (potential) UADE, the Sponsor recommends that the Investigator notify the Sponsor within 10 working days of first learning of the AE using the electronic data capture (EDC) CRF. If necessary, the Investigator may be requested to provide de-identified copies of source documentation (e.g., physician/nurse notes or summaries) regarding the event.

The Investigator must also notify the responsible EC regarding new and significant safety information and any events identified by Conformal Medical that require expedited FDA or other regulatory authority reporting as serious, unexpected, and related to the investigational device. It is the responsibility of the investigator to ensure site-specific IRB/EC reporting requirement are met.

The Sponsor is responsible for reporting SAEs and device deficiencies to regulatory authorities in line with applicable regulatory requirements and for reviewing the risk analysis, determining the need for corrective or preventative action, and informing investigators and regulatory authorities accordingly.

8.8.2 **Serious Adverse Events**

The Sponsor recommends that the Investigator notify Conformal Medical Clinical Lead, within 2 working days of first learning of any SAE using the eCRF.

It is the responsibility of each Investigator to report all serious adverse events and/or serious adverse device effects and device deficiencies that could have led to a serious adverse device effect to the IRB/EC, according to national regulations and EC requirements. If required by national regulations, the Investigator may also be required to report SAEs to the applicable regulatory authority.

8.8.3 **Unanticipated Adverse Device Effects**

As defined in 21 CFR §812.3, an unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Investigators must report any (potential) unanticipated adverse device effects to the Sponsor and their EC as soon as possible but no later than within 5 working days after the investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately on the eCRF and via telephone to the Sponsor Clinical Project Lead; contact details are provided in §2.0.

If an event is determined by Conformal Medical to be a UADE, the Sponsor will report the event to the FDA and other applicable regulatory authorities. The Sponsor will take the necessary steps to

investigate the event and will be responsible for notifying FDA and all other participating ECs (or other, as required) and all investigators.

8.9 Expected Adverse Events

The device and procedure are both associated with risks. Below is a summary of the expected risks that may occur. They are divided between those events associated with the procedure versus those associated with the CLAAS system. There may be additional risks that are unknown at this time.

Procedural Risks: The risks of delivery of the CLAAS device are similar to those of other procedures that require a transseptal puncture and transcatheter delivery of an implant through the venous system, across the interatrial septum, and into the left atrium using a large bore catheter (e.g., EP procedures and/or other LAA devices such as WATCHMAN). These risks are well recognized and experienced clinicians that are well versed in the use of large bore catheters have mitigated these risks to the extent possible in their standard of care. The recognized procedural risks include (in alphabetical order):

- Acute Kidney Injury potentially requiring need for dialysis
- Air embolus
- Allergic reaction to contrast media necessary for imaging during procedure
- Anesthesia risks (e.g., nausea/vomiting, aspiration pneumonia)
- Arrhythmia
- Bleeding/anemia requiring transfusion
- Cardiac Perforation, Puncture, Tamponade, and/or Effusion requiring draingage and/or “open heart” surgery
- Chest pain/angina
- Damage to cardiac structure (eg. valve, chordae)
- Death
- Deep Vein Thrombosis or Pulmonary Embolism
- Fever
- Hematuria
- Hemodynamic Instability (hypotension/hypertension)
- Hemothorax
- Iatrogenic ASD requiring treatment
- MI including ST segment elevation
- Pericardial Effusion/tamponade

- Pleural Effusion
- Pulmonary Edema
- Respiratory failure
- Stroke/TIA or Systemic embolization
- Systemic Infection including pneumonia
- TEE/intubation risks including throat pain, trauma to airway or esophagus with or without bleeding
- Thrombocytopenia
- Thromboembolic event
- Venous access site complications including pain, AV fistula, pseudoaneurysm, infection, hematoma, bleeding requiring transfusion and/or the need for surgical repair

Device Risks: In addition to the risks of undergoing an interventional procedure, there should be consideration to the risks which are specific to the CLAAS implant and CLAAS Delivery System. Conformal Medical has identified a set of risks that the rates of which may be different due to the design of the CLAAS system as outlined below. A number of the risks have been determined to be present with other interventional (e.g., WATCHMAN) as well as surgical implants designed to occlude the LAA. These risks include but are not limited to:

- Arrhythmias
- Cardiac perforation, puncture, tamponade, and/or effusion caused by device
- Chest pain
- Deep Vein Thrombosis or Pulmonary Embolism
- Death
- Device embolization or thrombosis
- Device malfunction/breakage requiring intervention
- Device migration requiring intervention
- Infection
- Major bleed requiring transfusion
- Myocardial Erosion
- Prolonged procedure time risk
- Re-intervention due to incomplete seal
- Re-intervention to remove device
- Residual leak in LAA

- Stroke/TIA or Systemic embolization
- Thrombus formation

9.0 Benefit: Risk Analysis

9.1 Potential Benefits

The targeted patient population consists of patients presenting with non-valvular atrial fibrillation, and who are at increased risk for stroke and systemic embolism and are recommended for OAC therapy but have an appropriate rationale to seek a non-pharmacological alternative to OAC, and who have been deemed appropriate for LAA closure by the Site PI and a non-interventional physician using an evidence-based decision-making tool on oral anticoagulants consistent with the standard of care. Compared with LAA closure with a commercially available device, LAA closure with the CLAAS-device may offer a simpler, safer implantation procedure and an increased likelihood of achieving successful closure.

Subjects in the CONFORMAL Study may not derive any direct benefit from their participation in the trial; however, subjects may gain satisfaction from having made an altruistic contribution to medical science, and the results of the trial may contribute to improved treatments that could benefit future patients who require LAA closure for the prevention of stroke and systemic embolism.

9.2 Potential Risks and Discomforts

Enrollment in the trial involves exposure to some risks. The risks of trial participation are not expected to be materially different from those encountered by an individual undergoing LAA closure with a commercially available device outside the context of the trial (§0). However, as an early feasibility evaluation of a novel device, the use of the CLAAS device may pose additional potential risks of an unknown nature or frequency.

In addition to the study device, participation in the clinical study involves exposure to potential risks and discomforts related to the protocol-specified assessments, including TEE assessments at pre-specified time points. These procedures are not experimental but are being performed for research purposes. The potential risks and discomfort related to study-specific tests will be detailed in the Informed Consent Form and discussed with each patient prior to enrollment in the study.

9.3 Methods to Minimize Risks

Extensive risk management activities have been conducting during the development of the CLAAS device to identify and analyze known and foreseeable hazards and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and Instructions for Use of the product to reduce the residual risk of each hazard to levels that are as low as reasonably practicable.

The clinical investigation plan is specifically designed to manage and minimize risks through the selection of qualified and experience investigators, thorough training of investigators and the investigational team, careful subject selection, adherence to pre-determined time points to assess

subject clinical status, and regular clinical monitoring visits by Sponsor-appointed monitoring personnel. In addition, an independent Data Safety Monitor will review accumulating safety data at regular intervals to monitor for the incidence of serious adverse events that would warrant modification or termination of the trial, an independent Clinical Events Committee will meet regularly to adjudicate the relationship of site-reported adverse events to the investigational device and procedure.

9.4 Benefit-Risk Assessment

A risk analysis of the CLAAS device has been performed and concluded that the identified risks have been reduced to a level as low as reasonably practical. When combined with the risk management measures incorporated into the design of the clinical trial, the potential benefits of the clinical use of the CLAAS device in the CONFORMAL Study are judged to justify the potential risks to study participants. The potential benefits and risks of study participation will be evaluated on an individual basis and discussed with each patient prior to enrollment in the study.

10.0 Statistical Considerations and Analysis Plan

10.1 Sample Size Rationale

The trial will enroll subjects in a staged manner to ensure patient safety in the Early Feasibility Study construct. A total of 20 subjects at 1 center is targeted for this feasibility study.

10.2 Analysis Populations

10.2.1 **Intention to Treat (ITT) Analysis Population**

The Intention to Treat (ITT) analysis population is defined as all subjects enrolled in the study (the point of enrollment is introduction of the CLAAS Access Sheath into the patient's body), regardless of the treatment actually received.

The ITT population will be the primary analysis population for the primary safety endpoint, the primary performance endpoint, and all secondary endpoints and other measures.

10.2.2 **The Implanted Patient (IP) Analysis Population**

The Implanted Patient (IP) analysis population is defined as all subjects who leave the catheterization laboratory with an implanted CLAAS device.

The IP population will be the secondary analysis population for the primary safety endpoint, the primary performance endpoint, and all secondary endpoints and other measures.

10.3 Method of Analysis & Reporting

10.3.1 **General Approach**

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. No hypothesis testing will be performed.

Analysis will be conducted using SAS (version 9.3 or greater), unless otherwise noted. Additional details will be pre-specified in the formal Statistical Analysis Plan (SAP) prior to initiation of enrollment.

10.3.2 **Baseline Characteristics**

The following data will be summarized using descriptive statistics and presented for the ITT and IP populations:

- Baseline demographics
- Baseline comorbidities, risk factors, and medical history
- Cardiac risk factors and cardiac history
- Procedural characteristics
- Device details

10.3.3 **Endpoint Analysis**

All endpoints will be reported in the ITT population using appropriate descriptive statistics. No formal hypothesis testing will be performed. As an additional analysis, all endpoints will be evaluated in the IP population.

All efforts will be made to minimize the amount of missing data; where it occurs, the reasons and counts and percentages of subjects with loss to follow-up will be summarized. In the final analyses, no adjustment will be made for missing data.

10.3.4 **Additional Analyses**

The following data will be summarized using descriptive statistics presented by treatment group in the ITT and IP populations:

- Frequency (number and percentage of patients) with each type of concomitant medication
- Frequency (number and percentage of patients) with each site-reported Treatment Emergent AE overall and by MedDRA system organ class and preferred term (a treatment emergent AE is an AE that started or worsened during or after the index procedure)
- Frequency (number and percent of patients) with each site-reported Treatment Emergent Serious AE overall and by MedDRA system organ class and preferred term
- Protocol deviations (number and percentage of patients with each deviation type)
- Detailed listings on primary and secondary endpoints, site-reported AEs, and protocol deviations

11.0 Publication Policy

The data obtained from this study may be presented for publication and/or presentation as long as Conformal and all investigators and authors assure that no information, which would reveal a subject's identity, is used in any publication. Information, which could be used to establish a subject's

identity, should not be provided to Conformal. Authors and Conformal will take every reasonable precaution to protect the identity of subjects enrolled in the study.

12.0 Data Collection and Monitoring

12.1 Data Collection and Monitoring

All required data for this study will be collected on standardized Case Report Forms (CRFs). The investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews.

Monitoring will be performed by the Sponsor and/or its designee(s) to ensure that the investigator and his/her study team conduct the clinical investigation in accordance with contract specifications, this protocol, the Declaration of Helsinki, ICH-GCP, ISO 14155, 21 CFR Part 812, and other applicable FDA and local regulations, and to ensure adequate protection of the rights and safety of subjects and the quality and integrity of the resulting data. All monitors will receive study-specific training on the Clinical Investigation Plan, the CRF, and the use of the investigational device in accordance with Sponsor SOPs.

Submitted trial data will be verified against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance with the pre-specified Monitoring Plan. The Investigator/institution will permit direct access to source data/documents in order for trial-related monitoring, audits, EC review and regulatory inspections to be performed.

Progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the Sponsor
- Telephone communications between site personnel (e.g., Site Investigator, Trial Coordinator) and trial monitors
- Review of CRFs and associated clinical records
- Review of regulatory documents

If a monitor becomes aware that an Investigator is not complying with the requirements mentioned above, the sponsor will be notified by the monitor. The Sponsor will evaluate the non-compliance and if necessary, immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator's participation in continued enrollment in the investigation. The Investigator will be required to return all unused devices to the Sponsor.

12.2 Source Documentation

Auditors, monitors, ECs, the Sponsor, and the FDA and other regulatory authorities may have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled patient (no source documentation will be recorded directly on the CRF). At a minimum, the following must be included in each patient's file:

- Sufficient medical history and current physical condition, including any medication(s) the patient is taking at the time of the procedure to assess the patient's eligibility;

- The medical file should reveal the patient's participation in this study, including documentation of written informed consent;
- Dated report of the index procedure including medication, material usage, and complications, if applicable;
- Dated reports of the post-procedure / pre-discharge and follow-up assessments;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and
- In the case of withdrawal of patient consent, the reason and patient status at time of withdrawal.

The Site Investigator will permit study-related monitoring, audits, EC review, and FDA and other applicable regulatory authority inspections by allowing direct access to the source data.

In case of electronic source data, periodic access will be allowed for full safety review. The review will be specific to study subjects and the records that would contain potential safety data. Dated print-outs are acceptable for preliminary review of safety information. Print-outs will not be limited to cardiac data only but should include all available data related to the identified patient(s).

12.3 Auditing

As a quality assurance measure, investigational sites may be audited during the trial or following trial completion. The purpose of an audit is to provide an independent evaluation of trial conduct and protocol and GCP compliance, separate from routine monitoring and quality control functions. The audit may be conducted by Conformal Medical personnel (or designee), the FDA, or another regulatory body.

Site Investigators are requested to notify the Sponsor if the FDA or other regulatory body requests an audit. The site investigator and/or institution shall permit Conformal Medical (or designee) personnel and regulatory body representatives direct access to source data and all other relevant documents.

13.0 Device Accountability

Information regarding opened, introduced, and implanted CLAAS devices will be recorded on the applicable CRF. Information regarding opened and introduced delivery systems will also be recorded on the applicable CRF.

Investigational devices will be shipped after documentation of site activation is sent to the site and shipping authorization is completed.

The principal investigator or an authorized designee must maintain a device accountability log documenting the date of receipt, the identification of each investigational device (i.e. serial number), the subject identification, the date of use, and final disposition. Devices must be stored in a locked location with access restricted only to investigators and authorized research personnel

14.0 Ethical and Regulatory Considerations

14.1 Applicable Regulations

This trial will be conducted in compliance with this protocol, the Sponsor's standard operating procedures and/or guidelines, FDA regulations concerning the protection of human subjects, e.g., 21 CFR parts 50, 56, and 812 and 45 CFR part 46, ICH GCP guidelines, the Declaration of Helsinki, and ISO 14155.

14.2 Ethics Committee

This trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The investigator will assure that an appropriately constituted Ethics Committee (EC) complies with the requirements of the International Conference on Harmonization Guideline. Prior to initiation of the study, the investigator will forward copies of the protocol, Investigators Brochure, informed consent form and all other appendices to be used for the study to the EC for its review and approval. A copy of the written EC approval must be provided to the Sponsor (or designee) and should include the following:

- A statement of EC approval for the proposed study at the institution;
- The date the study was approved and the duration of approval (if applicable);
- Identification of the approved documents including version dates and/or other references. At a minimum, the following documents should be listed:
    - Study protocol
    - Patient information and consent form
    - Any additional written information to be provided to the patient
- A listing of any conditions attached to the approval (if applicable);
- Identification of the approved primary investigator;
- The signature of the EC chairperson;
- Acknowledgement of the sub-Investigators.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the EC and written approval obtained prior to implementation. Substantive changes will be submitted to the EC for approval prior to implementation, and the EC will be notified of any changes not requiring approval according to applicable guidelines.

14.3 Regulatory Approval

The Sponsor is responsible for obtaining CA approval to conduct the study according to regulatory requirements. Investigators may not commence enrollment of subjects until they have met any local EC and hospital management requirements and have received confirmation from the Sponsor that the appropriate regulatory approvals have been obtained.

14.4 Records and Reports

Sponsor and investigator will maintain records related to this study for 5 years (or longer according to local requirements) after the end of this study.

Records maintained by the Sponsor will include:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- *Curriculum vitae* for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms prepared and signed by the Investigators and all received source documentation
- Clinical Investigation Plan (CIP) and any amendments
- Investigators Brochure / Report of Prior Investigations
- Site monitoring reports
- Financial disclosure information

Records maintained by each Site Investigator (the investigator may delegate responsibility for record maintenance to a member of his/her study team, but remains the ultimate responsible person) will include:

- All essential correspondence related to the clinical trial
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation).
- Signed Investigator Agreement
- *Curriculum vitae*
- Clinical Investigation Plan (CIP) and any amendments

The Sponsor and Site Investigators are each responsible for the preparation, review, and submission of all required reports in accordance with local laws and regulations, the requirements of the CA and other regulatory authorities as applicable, and the requirements of local ECs.

14.5 Protocol Amendments

Any protocol amendments will be approved by the Sponsor, the Principal Investigator, the EC and any necessary regulatory body before it can be implemented. Substantive changes will be submitted to the CA (and other regulatory authorities as applicable) for approval prior to implementation, and

the CA (and other regulatory authorities as applicable) will be notified of any changes not requiring approval in accordance with relevant guidelines.

14.6 Informed Consent

Informed consent will be obtained and documented as described in §6.4 prior to the performance of any study-specific procedures or assessments in accordance with 21 CFR Part 50, other applicable laws and regulations, and local EC requirements.

14.7 Termination of the Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Possible reasons for early trial termination include:

- Unanticipated Adverse Device Effects (UADEs) present an unreasonable risk to patients
- Sponsor decision to suspend or discontinue development of the device

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the ECs. The Sponsor will also inform the CA (and other regulatory authorities where required). In the case of early termination of trial enrollment, follow-up visits will continue for all enrolled subjects.

The Sponsor may terminate an investigator's or site's participation in the study if there is evidence of an investigator's failure to maintain adequate clinical standards or evidence of an investigator or staff's failure to comply with the protocol. Should investigator or site participation be considered for termination, the Sponsor (or designee) will ensure appropriate follow-up for any subjects enrolled, including transferal to the supervision of an approved investigator and approval of transfer of subject oversight and follow-up by the appropriate EC. Notification of study site suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. A suspended or terminated study site may not be reinitiated without approval of the reviewing EC. The investigator should notify the EC in writing as soon as possible but no later than within 10 days if the premature termination is related to safety or compliance issues. The same procedure will be applied to other applicable regulatory authorities where required.

14.8 Patient Privacy

The Sponsor affirms and upholds the principle of patient confidentiality. Throughout this study, all data provided to the Conformal Medical, Inc. or its designee(s) will only be identified by a study-specific subject identification number.

The investigator agrees that representatives of Conformal Medical, Inc., its designee(s), and regulatory authorities may inspect included patients' records to verify trial data, provide the data are treated as confidential and that the subject's privacy is maintained.

15.0 Site and Investigator Selection and Training

15.1 Selection of Study Sites and Investigators

The Sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based upon review of a recent site assessment questionnaire and the qualifications of the Primary Investigator at the site. Each site will have an interventional cardiologist and a cardiac electrophysiologist willing and able to participate in the study. All participating investigators will be trained to the protocol and study procedures prior to enrolling subjects.

15.2 Training of Investigators and Research Staff

15.2.1 General Training Requirements

All Investigators and trial research staff are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or another appropriate venue. Training by telephone may take place as required. Training of Investigators/trial personnel will include but is not limited to: the Clinical Investigation Plan (including imaging acquisition protocols), investigational device Instructions for Use, CRF completion, adverse event documentation and reporting requirements, and investigator and trial personnel responsibilities.

15.2.2 Investigator Training Requirements

Comprehensive Investigator training will be conducted to ensure that Investigators have a thorough knowledge of the investigational device Instructions for Use, the proper technique for implantation of the CLAAS device, and the Clinical Investigation Plan.

All participating investigators will receive formal training on the device at the site initiation visit. At a minimum, implanting investigators must receive the following training, unless otherwise noted in site-specific training records:

- CLAAS Device Training (including review of the Instructions for Use)
    - Device preparation, use and handling
    - Device positioning and deployment
    - Device removal and dislodgement
    - Implantation procedure steps and training
    - LAA anatomic measurements
- Clinical Investigation Plan Review
    - General procedural and data collection requirements

15.2.3 Training Documentation

A training log must be maintained at each site that documents the Investigators and research staff who have completed study-specific training, the training modules completed, and the date the training was completed. No trial-related activities (other than those considered standard of care at

the study site) may be performed by investigators or research staff who not completed study-specific training.

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17.0 Appendices

17.1 Appendix A: Definitions

Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

All adverse device effects will be assess using the following:

Intensity or Severity

Intensity of an adverse event to be used:

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

Relatedness

Relationship to the study device or procedure:

Not related	The cause of the AE is known, and the event is not related to the study device or procedure.
Unlikely to be related	There is little or no temporal relationship to the study device or procedure, and/or a more likely alternative etiology exists.
Possibly related	There is a reasonable possibility that the event may have been caused by the study device or procedure. The AE has a **timely relationship** to the study device or procedure(s); **however, follows no known pattern of response**, and an alternative

	cause seems more likely or there is significant uncertainty about the cause of the event.
Related	A **related** event has a **strong temporal relationship** and an alternative cause is unlikely.

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Outcome

The clinical outcome of the AE or SAE will be characterized as follows:

Death	The SAE CRF must be completed for this outcome
Recovered without sequelae	The patient returned to baseline status
Ongoing	Patient did not recover, and symptoms continue
Recovered with sequelae	The patient has recovered but with clinical sequelae from the event
Unknown	The patient outcome is unknown

Treatment or Action Taken

Action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment	Surgical, percutaneous or other procedure
Medical Treatment	Medication dose reduction/interruption or discontinuation, or medication initiated for event
None	No action is taken

Anticipated Serious Adverse Device Effect (ASADE)

An anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).

Bleeding complications Defined according to the following BARC definitions[2], and classified as major bleeding (Type 3, 4, or 5) and minor bleeding (Type 2)

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Over bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)

Any transfusion with over bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed comprising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period (NOTE: cell saver products are not counted)

Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Type 5a

Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

NOTES:

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin)

Cardiac tamponade

Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the LAA closure

CHA_2DS_2-VASc Score

A clinical risk stratification scheme for predicting stroke and thromboembolism in patients with nonvalvular AF[27], updated from the earlier $CHADS_2$ score. Patients are assigned a score from 0 to 9 by adding the points for each applicable risk factor below to obtain a total score:

Risk Factors	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolic event in the past	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65 to 74 years	1
Sex **c**ategory (female gender)	1

Closure success	Device success (see definition) followed by successful LAA closure (complete closure or peri-device residual leak ≤5 mm in width on TEE at 45 days post-procedure). NOTE: The primary protocol definition of closure success is at the primary performance endpoint evaluation time point of 45 days; closure success at 6 and 12 months will also be evaluated.
CNS hemorrhage	NeuroARC defined[1] as any brain, spinal cord, or retinal hemorrhage on the basis of imaging or pathology, not caused by trauma (includes symptomatic intracerebral hemorrhage [Type 1.b], symptomatic subarachnoid hemorrhage [Type 1.c], and covert CNS hemorrhage [Type 2.b])
CNS infarction	NeuroARC defined[1] as any brain, spinal cord, or retinal infarction on the basis of imaging, pathology, *or* clinical symptoms persisting for ≥24 h (includes ischemic stroke [Type 1.a], ischemic stroke with hemorrhagic conversion [Type 1.a.H], stroke not otherwise specified [Type 1.d], symptomatic hypoxic-ischemic injury [Type 1.e], covert CNS infarction [Type 2.a], and covert CNS infarction with hemorrhagic conversion [Type 2.a.H])
Composite efficacy	Freedom from the composite of all-cause mortality, all stroke, TIA, and systemic thromboembolism
Covert CNS injury	Acutely asymptomatic brain or spinal cord injury detected by neuroimaging (NeuroARC Type 2)[1], including: <u>Type 2.a Covert CNS infarction</u> Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location <u>Subtype 2.a.H Covert CNS infarction with hemorrhagic conversion</u> Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 2.b Covert CNS hemorrhage

Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location

Death See "mortality"

Device deficiency Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.

Device malfunction Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol.

NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use but does not perform as described in the Instructions for Use.

Device misuse Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

Device success Successful implantation of the CLAAS device in the LAA with acceptable position and seal (peri-device residual leak ≤5 mm in width [evaluated post-procedure]

Embolic events A composite of ischemic stroke and systemic thromboembolism

HAS-BLED Score A scoring system to assess the risk of major bleeding in patients with atrial fibrillation receiving oral anticoagulation (OAC) therapy.[28] Patients are assigned a score from 0 to 9 by adding the points for each applicable clinical characteristic below to obtain a total score:

Clinical Characteristic	Score
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding history or predisposition	1
Labile INRs in patients taking warfarin	1

Elderly (> 65 years)	1
Drugs (concomitant antiplatelet agents or NSAIDs) or alcohol abuse (1 point each)	1 or 2

Implanted Patient (IP) Population

All subjects who leave the catheterization laboratory after the index procedure with an implanted CLAAS device

Intention to Treat (ITT) Population

All subjects enrolled in the study (the point of enrollment is introduction of the CLAAS delivery system into the patient's body), regardless of the treatment actually received.

Ischemic stroke

NeuroARC-defined[1] Type 1.a or 1.a.H overt CNS injury:

Type 1.a Ischemic stroke

Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:

1) Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either:
   a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or*
   b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected

   or

2) Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke.

Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H Ischemic stroke with hemorrhagic conversion

Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Major endovascular intervention

Major endovascular intervention includes pseudoaneurysm repair, AV fistula repair, and other major endovascular repair. The following interventions are not considered major endovascular interventions: percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications.

Major procedure-related complications

A composite of cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and major vascular complications, adjudicated by the independent Clinical Events Committee as related to the study device or procedure

Major safety events

A composite of all-cause mortality, overt CNS injury, and major bleeding

Mortality

Classified as cardiovascular (defined as cardiac or vascular) or noncardiovascular according to the following ARC definitions. All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (e.g., cancer, infection) should be classified as cardiac.

- Cardiac death: Any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.
- Vascular death: Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Noncardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Myocardial infarction

Defined according to VARC-2[3] as:

Peri-procedural MI (≤72 h after the index procedure):

- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging

evidence of new loss of viable myocardium or new wall motion abnormality) AND

- Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure). Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
  - New pathological Q waves in at least two contiguous leads
  - Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

Neurologic dysfunction without CNS injury

Acutely symptomatic (NeuroARC Type 3[1]) without CNS injury, including:

Type 3.a TIA

Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)

Type 3.b Delirium without CNS injury

- Transient nonfocal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology

Neurologic events

See “ischemic stroke”, “Overt CNS Injury”, “Covert CNS Injury”, “Neurological dysfunction without CNS injury”, “CNS infarction”, and “CNS hemorrhage”

NYHA (New York Heart Association)

Classified as[29]:

functional capacity

Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Overt CNS injury

Acutely symptomatic brain or spinal cord injury (NeuroARC Type 1)[1], including:

Type 1.a Ischemic stroke

Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that:

3) Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either:
   a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or*
   b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected

   or

4) Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke.

Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H Ischemic stroke with hemorrhagic conversion

Ischemic stroke includes hemorrhagic conversions. These should be sub classified as Class A or B when ischemic stroke is the primary

mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechial or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 1.b Symptomatic intracerebral hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma

Type 1.c Symptomatic subarachnoid hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma

Type 1.d Stroke, not otherwise specified

An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified as either (i.e., no neuroimaging performed)

Type 1.e Symptomatic hypoxic-ischemic injury

Nonfocal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia

Pericardial effusion

Pericardial effusion will be classified for severity and time of occurrence according to the following definitions[30]:

Clinically non-relevant:

- Requiring no intervention
- Treated pharmacologically

Clinically relevant (sub-classified as with or without cardiac tamponade):

- Treated with therapeutic pericardiocentesis
- Treated with surgical intervention
- Requiring blood transfusion
- Resulting in shock and/or death

Time of occurrence:

- Intraprocedural: during the index procedure
- Acute: <48 hours after the index procedure

Late: ≥48 hours after the index procedure

Procedure success
- Device success (see definition) without major in-hospital procedure-related complications (see definition)

Screen failure
Subjects who are deemed potentially eligible for participation in the study based on the results of pre-screening, and who undergo the process of informed consent, but do not reach the point of enrollment because they (1) are subsequently determined not to be eligible for enrollment in the study prior to the index procedure, or (2) are not exposed to the CLAAS Delivery System (introduction into the body).

Serious Adverse Device Effect (SADE)
A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)
A serious adverse event is an adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolongation of existing hospitalization
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Systemic thromboembolism
3. Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g. trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion.[30]

Transient ischemic attack (TIA)
NeuroARC defined[1] as transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging).

Unanticipated Adverse
An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or

Device Effect (UADE)	associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
Vascular complications	VARC-2 defined[3] as: <u>Major Vascular Complications</u>: • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury <u>Minor vascular complications</u>: • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR • Distal embolization treated with embolectomy and/or thrombectomy and

not resulting in amputation or irreversible end-organ damage OR

- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR

Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

-

17.2 Appendix B: Acronyms

AE	adverse event
ACT	activated clotting time
ADE	adverse device effect
AF	atrial fibrillation
ASA	acetylsalicylic acid (aspirin)
ASADE	anticipated serious adverse device effect
ASD	atrial septal defect
BARC	Bleeding Academic Research Consortium
CI	confidence interval
CIP	clinical investigation plan
CRF	case report form
CT	computed tomography
DAPT	dual antiplatelet therapy
DICOM	Digital Imaging and Communications in Medicine
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture (system)
EFS	early feasibility study
eGFR	estimated glomerular filtration rate
ePTFE	polytetrafluorotheylene
F	French (catheter scale system)
FDA	U.S. Food and Drug Administration

GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICE	intracardiac echocardiography
ICF	informed consent form
ICH	International Conference on Harmonization
IFU	instructions for use
INR	international normalized ratio
IP	implanted patient population
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intention to treat
LAA	left atrial appendage
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MRI	magnetic resonance imaging
NeuroARC	Neurologic Academic Research Consortium
NOAC	Novel oral anticoagulants
NYHA	New York Heart Association
OAC	oral anticoagulation
PI	principal investigator
PFO	patent foramen ovale
QD	quaque die (daily)
QVSFS	questionnaire for verifying stroke-free status
SADE	serious adverse device effect

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedures
TIA	transient ischemic attack
TBD	to be determined
TEE	transesophageal echocardiography
TTE	trans-thoracic echocardiography
UADE	unanticipated adverse device effect
VARC	Valve Academic Research Consortium
US	United States

17.3 Appendix C: Questionnaire for Verifying Stroke-Free Status (QVSFS)

Questionnaire for Verifying Stroke-Free Status (QVSFS) Form	
Exam Time Point:	❑ Screening ❑ Pre-discharge ❑ 7 days ❑ 45 days ❑ 6 months ❑ 1 year ❑ 2 years ❑ 3 years ❑ 4 years ❑ 5 years ❑ Other
Form Completed:	__ __/ __ __/ __ __ __ __ (mm/dd/yy) __ __: __ __ (hour: min) (24 hr. format)
Instructions:	The QVSFS must be completed at screening, during each clinic visit, and during each telephone contact to screen for interceding signs and symptoms of stroke or TIA. If any question is answered "Yes", a formal neurologic examination and evaluation must be performed by a board-certified neurologist or clinical designee (e.g., neurology fellow).

1. Since the last routine study contact by phone or clinic, have you been told by a physician that you have had a stroke?

   ❑ YES ❑ NO ❑ Don't know/Not sure

2. Since the last routine study contact by phone or in the clinic, have you been told by a physician that you had a TIA, mini-stroke, or transient ischemic attack?

   ❑ YES ❑ NO ❑ Don't know/Not sure

3. Since the last routine study contact by phone or in the clinic, have you had sudden painless weakness on one side of your body?

   ❑ YES ❑ NO ❑ Don't know/Not sure

4. Since the last routine study contact by phone or in the clinic, have you had sudden numbness or a dead feeling on one side of your body?

   ❑ YES ❑ NO ❑ Don't know/Not sure

5. Since the last routine study contact by phone or in the clinic, have you had sudden painless loss of vision in one or both eyes?

   ❑ YES ❑ NO ❑ Don't know/Not sure

6. Since the last routine study contact by phone or in the clinic, have you suddenly lost one half of your vision?

   ❑ YES ❑ NO ❑ Don't know/Not sure

7. Since the last routine study contact by phone or in the clinic, have you suddenly lost the ability to understand what people were saying?

   ❑ YES ❑ NO ❑ Don't know/Not sure

8. Since the last routine study contact by phone or in the clinic, have you suddenly lost the ability to express yourself verbally or in writing?

   ❑ YES ❑ NO ❑ Don't know/Not sure

Source: Jones WJ, Williams LS and Meschia JF. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. *Stroke*. 2001;32:2232-6.

17.4 Appendix D: National Institutes of Health Stroke Scale (NIHSS)

National Institutes of Health Stroke Scale (NIHSS) Form	
Exam Time Point:	❑ Screening ❑ Pre-discharge ❑ 45 days ❑ 6 months ❑ 1 year ❑ Other
Form Completed:	__ __/ __ __/ __ __ __ __ (mm/dd/yy) __ __ : __ __ (hour: min) (24 hr. format)
Instructions:	The NIHSS must be completed at screening and during each clinic visit. In the event of an increase from a patient's baseline NIHSS score, a formal neurologic examination and evaluation must be performed by a board-certified neurologist or clinical designee (e.g., neurology fellow). NOTE: Additional copies of the NIH Stroke Scale are available on the internet at https://stroke.nih.gov/resources/scale.htm.

NIHSS Assessment

1(a) Level of consciousness
O 0 = Alert, keenly responsive
O 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond
O 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)
O 3 Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid or areflexic

1(b) Level of consciousness questions
O 0 = Answers both questions correctly
O 1 = Answers one question correctly
O 2 = Answer neither question correctly

1(c) Level of consciousness commands
O 0 = Performs both tasks correctly
O 1 = Performs one task correctly
O 2 = Performs neither task correctly

2 Best gaze
O 0 = Normal
O 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.
O 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver

3 Visual
O 0 = No visual loss
O 1 = Partial hemianopia
O 2 = Complete hemianopia
O 3 = Bilateral hemianopia (blind including cortical blindness)

4 Facial palsy
O 0 = Normal symmetrical movements
O 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
O 2 = Partial paralysis (total or near-total paralysis of lower face)
O 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

5(a) Motor arm- left
O 0 = No drift, limb holds 90 (or 45) degrees for 10 full seconds
O 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support
O 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees; drifts down to bed, but has some effort against gravity
O 3 = No effort against gravity, limb falls

O 4 = No movement
O UN = Amputation or joint fusion Explain_____

5(b) Motor arm- right
O 0 = No drift, limb holds 90 (or 45) degrees for 10 full seconds
O 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support
O 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees; drifts down to bed, but has some effort against gravity
O 3 = No effort against gravity, limb falls
O 4 = No movement
O UN = Amputation or joint fusion Explain_____

6(a) Motor leg- left
O 0 = No drift; leg holds 30 degree position for full 5 seconds
O 1 = Drift; leg falls by the end of the 5-second period but does not hit bed
O 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity
O 3 = No effort against gravity; leg falls to bed immediately
O 4 = No movement
O UN = amputation or joint fusion Explain_____

6(b) Motor leg- right
O 0 = No drift; leg holds 30 degree position for full 5 seconds
O 1 = Drift; leg falls by the end of the 5 second period but does not hit bed
O 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity
O 3 = No effort against gravity; leg falls to bed immediately
O 4 = No movement
O UN = amputation or joint fusion Explain_____

7 Limb ataxia
O 0 = Absent
O 1 = Present in one limb
O 2 = Present in two limbs
O UN = Amputation or joint fusion Explain_____

8 Sensory
O 0 = Normal; no sensory loss
O 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched
O 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg

9 Best Language
O 0 = No aphasia; normal
O 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility or comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming

card content from patient's response.
O 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided form patient response.
0 3 = Mute, global aphasia; no usable speech or auditory comprehension

10 Dysarthria
O 0 = Normal
O 1 = Mild-to-moderate dysarthria; patient slurs at least some word and, at worst, can be understood with some difficulty.
O 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence or out of proportion to any dysphasia, or is mute/anarthric.
O UN = Intubated or other physical barrier Explain_____

11 Extinction and Inattention (formerly neglect)
O 0 = No abnormality
O 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.
O 2 = Profound hemi0inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Total Score: (format 99)
(Autocalculated)

17.5 Appendix E: Modified Rankin Scale (mRS)

Modified Rankin Scale (mRS) Form	
Exam Time Point:	❑ Screening ❑ Other
Form Completed:	__ __ / __ __ / __ __ __ __ (mm/dd/yy) __ __ : __ __ (hour: min) (24 hr. format)
Instructions:	The mRS must be completed at screening and whenever a suspected neurologic event triggers an evaluation by a board-certified neurologist or clinical designee (e.g., neurology fellow). In patients who experience a stroke, the mRS should be repeated 90 ± 14 days after the event.

Modified Rankin Scale	**Structured Interview for the Modified Rankin Scale**
5 = Severe disability bedridden, incontinent, and requiring constant nursing care and attention	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or untrained caregiver. Question: *Does the person require constant care?* ❑ YES ❑ NO
4 = Moderately severe disability unable to walk without assistance, and unable to attend to own bodily needs without assistance	4=Moderately severe disability; need for assistance with some basic activities of daily living (ADL), but not requiring constant care. Question: *Is assistance essential for eating, using the toilet, daily hygiene, or walking?* ❑ YES ❑ NO
3 = Moderate disability requiring some help, but able to walk without assistance	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: *Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?* ❑ YES ❑ NO
2 = Slight disability unable to carry out all previous activities but able to look after own affairs without assistance	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: *Has there been a change in the person's ability to work or look after others if these were roles before stroke?* *Has there been a change in the person's ability to participate in previous social and leisure activities?* *Has the person had problems with relationships or become isolated?* ❑ YES (to any question) ❑ NO (to all questions)

1 = No significant disability despite symptoms able to carry out all usual duties and activities	1=No significant disability; symptoms present but no physical or other limitations. Question: *Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?* ❑ YES ❑ NO
0=No symptoms at all	0=No symptoms at all; no limitations and no symptoms
mRS SCORE:	❑ 5 ❑ 4 ❑ 3 ❑ 2 ❑ 1 ❑ 0

Sources: Modified Rankin Scale: van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Inter-observer agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-607; Structured Interview: Wilson JRL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, Bone I. Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the Modified Rankin Scale. Stroke. 2002;33:2243-2246.