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Appendage Occluder Randomized Controlled Trial

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Sponsor

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Appendage Occluder Randomized Controlled Trial

AMPLATZER™ Amulet™ Left Atrial Appendage Occluder

Randomized Controlled Trial

Clinical Investigational Plan

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1 SYNOPSIS

Name of Study	Amplatzer Amulet Left Atrial Appendage Occluder Randomized Controlled Trial
Study Sponsor	This investigational trial is being sponsored and conducted by St. Jude Medical (SJM)
Device	<p>Description: The transcatheter, self-expanding AMPLATZER™ Amulet™ LAA Occluder is made of nitinol mesh and a polyester patch. The lobe with stabilizing wires is placed within the left atrial appendage (LAA) and a disc (to cover the LAA orifice) is connected to the lobe by a central waist.</p> <p>Sizes: 16, 18, 20, 22, 25, 28, 31, and 34 mm (diameter)</p> <p>Delivery System: AMPLATZER TORQVUE 45x45 (sheath sizes 12 Fr or 14 Fr)</p>
Intended Purpose	<p>The AMPLATZER™ Amulet™ Left Atrial Appendage Occluder (Amulet) is intended to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation (AF) who:</p> <ul style="list-style-type: none"> • Are at increased risk for stroke and systemic embolism based on CHADS₂ or CHA₂DS₂-VASc scores and are recommended for anticoagulation therapy • Are deemed by their physician to be suitable for warfarin; and • Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin or other anticoagulation therapy, taking into account the safety and effectiveness of the device compared to warfarin and/or other anticoagulation therapy.
Study Design	<p>This IDE study includes:</p> <ul style="list-style-type: none"> • Randomized Controlled Trial: A prospective, randomized, multicenter, active control worldwide trial to evaluate safety and effectiveness of the Amulet device by demonstrating non-inferiority against the Control device • Roll-In Phase: At US sites or sites where the implanting physicians do not have Amulet implant experience, up to 3 subjects per sponsor-approved implanter may be implanted with Amulet prior to randomization as part of the roll-in phase, in order to provide initial experience to the site. Data from roll-in subjects will not be included in the primary or secondary endpoint analyses but these data will be summarized and reported separately. All roll-in

	<p>subjects will have the same data collection and follow-up schedule requirements as the randomized subjects.</p> <p>The randomized trial design was developed to adequately characterize the safety and effectiveness of the Amulet device and will include patients meeting inclusion criteria to include patients from the Medicare population. The study endpoints have been developed for appropriate characterization of health outcomes and the trial is powered under assumptions based on available scientific data (i.e. the sample size is adequate to answer the trial's objectives).</p> <p>Note: This trial is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals, as noted above and within the inclusion/exclusion criteria.</p>
Randomization	1:1 between Amulet LAA occlusion device (treatment) and Boston Scientific LAA closure device (Control)
Sample Size	<ul style="list-style-type: none"> • 1878 subjects will be randomized at up to 150 sites worldwide. Up to 100 sites in the US may participate. • Approximately 343 additional subjects may be enrolled in the Roll-in Phase. Since US implanting physicians have no experience with the Amulet device, up to 3 roll-in subjects per implanter will result in approximately 343 subjects enrolled in the Roll-in Phase (see Section 5.2.1 for additional details).
Study Objective/Principal Purpose and Rationale for the Trial	<p>To evaluate the safety and effectiveness of the Amulet device by demonstrating its performance is non-inferior to the commercially available Boston Scientific LAA closure (LAAC) device (Control) in subjects with non-valvular atrial fibrillation. The trial will test whether the device meaningfully improves health outcomes of all enrolled subjects through evaluation of the safety and effectiveness primary endpoints. The intended patient population for this trial are those already indicated for the Control device; therefore, a randomized device-to-device comparator trial is appropriate for evaluating the outcomes of those with non-valvular atrial fibrillation and an increased risk of stroke. Additionally, since there has been no prospective, randomized, device-to-device comparator trial to evaluate LAA closure, the results of this trial are not anticipated to duplicate existing knowledge or data.</p>
Primary Endpoints	<p>The trial has three primary endpoints to compare safety and effectiveness of the Amulet device against the Control device (see Appendix P for definitions):</p> <p><u>Safety</u></p>

	<ul style="list-style-type: none"> • A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months <p><u>Effectiveness</u></p> <ul style="list-style-type: none"> • A composite of ischemic stroke or systemic embolism through 18 months <p><u>Mechanism of Action</u></p> <ul style="list-style-type: none"> • Device closure (defined as residual jet around the device \leq 5 mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow
Secondary Endpoints	<p>The trial will also compare the Amulet device to the Control device for the following secondary endpoints:</p> <ul style="list-style-type: none"> • A composite of all stroke, systemic embolism, or cardiovascular/unexplained death through 18 months • Major bleeding rate through 18 months : defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC) definition • A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months (superiority analysis) • A composite of ischemic stroke or systemic embolism through 18 months (superiority analysis) • Device closure (defined as residual jet around the device \leq 5 mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow (superiority analysis)
Descriptive Endpoints/Outcomes Measures	<p>The randomized trial will descriptively summarize the following endpoints for each of the following measures:</p> <ul style="list-style-type: none"> • Technical success rate • Procedural success rate • Device success rate • Number of subjects on oral anticoagulant at each follow-up visit • Procedure duration • Procedural complications by operator • Device thrombosis • Transient ischemic attack • Hemorrhagic stroke • Systemic embolism

	<ul style="list-style-type: none"> • All-cause mortality • Cardiovascular mortality • Major bleeding, by site and severity (Major bleeding defined as Type 3 or greater per BARC) • Minor bleeding, by site and severity (Minor bleeding defined as Type 2 per BARC)
Operator Training/ Experience and Facility Requirements	<p>Intended users of both the Amulet and Control devices are interventional cardiologists and electrophysiologists trained in percutaneous and transseptal procedures, who have completed company-specified physician training programs.</p> <p>The following are required for the implanting facility to participate in this trial:</p> <ul style="list-style-type: none"> • Hospital with an established structural heart disease and/or electrophysiology program • Hospital with a cardiac catheterization lab or electrophysiology (EP) lab with fluoroscopy capability • Non-invasive imaging (i.e. transesophageal echocardiography) with echocardiography support • Anesthesiology support for administration of general anesthesia specific to this procedure (as necessary)
Inclusion Criteria	<p>To participate in the trial, subjects must meet the following inclusion criteria:</p> <ol style="list-style-type: none"> 1. 18 years of age or older 2. Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (AF) and the patient has not been diagnosed with rheumatic mitral valvular heart disease 3. At high risk of stroke or systemic embolism defined as CHADS₂ score ≥ 2 or a CHA₂DS₂-VASc score of ≥ 3 4. Has an appropriate rationale to seek an alternative to warfarin or other anticoagulation medication 5. Deemed by investigator to be suitable for short term warfarin therapy but deemed unable to take long term oral anticoagulation following the conclusion of shared decision making (see inclusion criteria #6) 6. Deemed suitable for LAA closure by a multidisciplinary team of medical professionals (including an independent non-interventional physician) involved in the formal and shared decision- making process, and by use of an evidence-based

	<p>decision tool on oral anticoagulation (final determination must be documented in the subject's medical record)</p> <ol style="list-style-type: none"> 7. Able to comply with the required medication regimen post-device implant 8. Able to understand and willing to provide written informed consent to participate in the trial 9. Able to and willing to return for required follow-up visits and examinations
Exclusion Criteria	<p>To participate in the trial, subjects must not meet any of the following exclusion criteria:</p> <ol style="list-style-type: none"> 1. Requires long-term oral anticoagulation therapy for a condition other than atrial fibrillation 2. Contraindicated for or allergic to aspirin, clopidogrel, or warfarin use 3. Indicated for chronic P₂Y₁₂ platelet therapy inhibitor 4. Is considered at high risk for general anesthesia, in the opinion of the investigator, and/or based on past adverse reaction(s) requiring medical intervention or which resulted in prolongation of hospital stay (criterion is only applicable where general anesthesia is planned for the study procedure) 5. Has undergone atrial septal defect (ASD) repair or has an ASD closure device implanted 6. Has undergone patent foramen ovale (PFO) repair or has a PFO closure device implanted 7. Implanted with a mechanical valve prosthesis 8. Has any of the customary contraindications for a percutaneous catheterization procedure (e.g. subject is too small to accommodate the transesophageal echocardiogram (TEE/TOE) probe or required catheters, or subject has active infection or bleeding disorder) 9. Stroke or transient ischemic attack (TIA) within 90 days prior to randomization or implant procedure (as applicable) 10. Underwent any cardiac or non-cardiac intervention or surgery within 30 days prior to randomization, or intervention or surgery is planned within 60 days after implant procedure (e.g. cardioversion, ablation, cataract surgery, etc.) 11. Myocardial infarction (MI) within 90 days prior to randomization

	<ol style="list-style-type: none"> 12. New York Heart Association Class IV Congestive Heart Failure 13. Left ventricular ejection Fraction (LVEF) $\leq 30\%$ 14. Symptomatic carotid artery disease (defined as $>50\%$ stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject has a history of carotid stent or endarterectomy the subject is eligible if there is $<50\%$ stenosis 15. Reversible cause of AF (i.e. secondary thyroid disorders, acute alcohol intoxication, trauma, recent major surgical procedures) 16. History of idiopathic or recurrent venous thromboembolism 17. Left atrial appendage is obliterated or surgically ligated 18. Thrombocytopenia or anemia requiring transfusions 19. Hypersensitivity to any portion of the device material or individual components of either the Amulet or Boston Scientific LAA closure device (e.g. nickel allergy) 20. Actively enrolled or plans to enroll in a concurrent clinical study in which the active treatment arm may confound the results of this trial 21. Subject is pregnant or pregnancy is planned during the course of the investigation 22. Active endocarditis or other infection producing bacteremia 23. Subject has had a transient case of AF (i.e. never previously detected, provoked/induced by surgical or catheter manipulations, etc.) 24. Subjects with severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73m²) 25. Subject whose life expectancy is less than 2 years 26. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical trial or to comply with follow up requirements, or impact the scientific soundness of the clinical trial results.
Echocardiographic Exclusion Criteria	<p>To participate in the trial, subjects must not meet any of the following echocardiographic exclusion criteria:</p> <ol style="list-style-type: none"> 1. Intracardiac thrombus visualized by echocardiographic imaging 2. Existing circumferential pericardial effusion >2mm

	<ol style="list-style-type: none"> 3. Significant mitral valve stenosis (i.e., mitral valve area <math><1.5\text{ cm}^2</math>) 4. High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion >15mm or length $\geq 15\text{mm}$; excursion defined as maximal protrusion of the ASA beyond the plane of the atrial septum) or large shunt (early, within 3 beats and/or substantial passage of bubbles i.e. ≥ 20) 5. Complex atheroma with mobile plaque of the descending aorta and/or aortic arch 6. Cardiac tumor 7. LAA anatomy cannot accommodate either a Boston Scientific LAAC or Amulet device, as per manufacturer's IFU. (i.e. the anatomy and sizing must be appropriate for both devices in order to be enrolled in the trial. This is applicable to all roll-in and randomized subjects). 8. Placement of the device would interfere with any intracardiac or intravascular structure
Requirements for Suspected Stroke / TIA Events During Follow-up	<p>Subjects suspected of having a TIA or stroke, or who experience any cognitive or behavioral changes at any time during trial participation must be seen by a stroke/TIA neurologist for evaluation and appropriate investigations must be done including neuro imaging, neurovascular imaging, and other tests as indicated. Every effort will be made to keep treating neurologists blinded to the subject's treatment assignment.</p> <ul style="list-style-type: none"> • If stroke is confirmed by neurologist: complete MRI (CT if MRI contraindicated) as soon as possible and within 10 days (if possible) of event, preferably using the following sequences: Fluid-Attenuated Inversion Recovery (FLAIR), Diffusion-Weighted Imaging (DWI), Susceptibility-Weighted Imaging (SWI), Gradient Recalled Echo (GRE) gradient, Apparent Diffusion Coefficient (ADC) maps • If ischemic stroke is confirmed through imaging, a TEE/TOE is required as soon as possible, but within 7 days of the neurological imaging • Neurological assessments to be performed and repeated 90 days after stroke/TIA
Follow-up Requirements	<p>Follow-up visits will occur at pre-hospital discharge, 45 days, 3 months (phone), 6 months, 9 months (phone), 12 months, 18 months, 24 months, and annually by phone until 5 years.</p>
Testing	<p><u>Baseline</u></p> <ul style="list-style-type: none"> • History and Physical

- Cardiovascular and medical exam
- Neurological exam (assessment by a neurologist for subjects with a history of TIA and/or stroke, per institutional standard of care)
- Neurologic assessments (instruments include Modified Rankin Scale (mRS), Barthel Index, and National Institute of Health Stroke Scale (NIHSS) (must be performed by NIHSS- Barthel- and mRS-certified personnel)
- Questionnaire for Verifying Stroke-Free Status (QVSFS)
- CT/MRI for subjects with documented history of TIA/stroke (previous imaging done post-neurological event is acceptable; otherwise must be repeated after consent)
- 12-lead ECG
- CHADS₂ and CHA₂DS₂-VASc Score
- HAS-BLED Score
- INR assessment (INR target range 2-3) if subject on warfarin (or other oral anticoagulants requiring INR assessments)
- Medication assessment including the use of antiplatelet, and any anticoagulation medication
- Pregnancy test (required for females of childbearing potential only)
- EQ-5D-5L (Health Questionnaire)
- TEE/TOE to confirm eligibility (echoes done up to 90 days prior to consent will be accepted as baseline)

Note: Once a subject is randomized, the LAA implant procedure must occur within 14 days.

Follow-up Testing:

- Transthoracic echocardiogram (TTE) before discharge to check for device embolization or pericardial effusion
- TEE/TOE at 45-day visit
 - Perform color Doppler assessment
 - If residual jet is present around the device, measure size of residual jet around the device
 - Confirm absence of intra-cardiac thrombus
 - If closure is **not** confirmed at 45-day visit, continue oral anticoagulation (OAC, including NOACS) (Amulet subjects) or warfarin* (Control subjects) until 6-month

TEE/TOE to assess LAA seal (closure is defined as ≤ 5 mm residual jet flow around margins of the device)

- TEE/TOE at 12-month visit
- Adverse event assessment, medication assessment, and stroke ascertainment at each follow-up
- Questionnaire for Verifying Stroke-Free Status (QVSFS) (all visits)
- INR assessment (if subject is still on warfarin or other oral anticoagulants requiring INR assessments)
- EQ-5D-5L health questionnaire at 45-day and 6-, 12-, and 18- month visits

*Subjects enrolled outside the US may take other anticoagulants/vitamin K antagonists in lieu of warfarin

Medication Requirements (All Subjects)

- Aspirin (81-100 mg) 1 day prior to implant

Amulet Subjects (Post-Procedure)

- Aspirin (81-100 mg) and clopidogrel OR aspirin (81-100 mg) and OAC daily until the 45-day TEE/TOE is performed. An alternative to clopidogrel may be used if a subject is a non-responder to clopidogrel, as documented in the subject's medical record/study chart.
- If the residual flow into the LAA is > 5 mm on post-procedure TEE/TOE, OAC therapy (if warfarin, INR of 2.0 - 3.0) and aspirin (81-100 mg) is required until the 45-day TEE/TOE is performed.
- If at the 45-day visit, the TEE/TOE shows adequate closure of the LAA (residual jet ≤ 5 mm) cessation of OAC is required. Subjects should then begin clopidogrel 75 mg daily until the 6-month visit and continue aspirin 81-100 mg daily. Cessation of clopidogrel is required at the 6-month visit (aspirin 81-100mg to be continued indefinitely).
- If at the 45-day visit, the TEE/TOE shows inadequate closure of the LAA (residual jet > 5 mm), the subject should remain on OAC and aspirin until the 6-month TEE/TOE is performed

Control Subjects (Post-Procedure)

- Aspirin (81-100 mg) + warfarin* (INR of 2.0 – 3.0) until TEE/TOE is performed at 45-day visit

	<ul style="list-style-type: none"> • If at the 45-day visit, the TEE/TOE shows adequate closure of the LAA (residual jet \leq 5mm) cessation of warfarin is required. Subject should then begin clopidogrel 75 mg daily until the 6-month visit and continue aspirin 81-100 mg daily. An alternative to clopidogrel may be used if a subject is a non-responder to clopidogrel, as documented in the subject's medical record/study chart. Cessation of clopidogrel is required at the 6-month visit (aspirin 81-100mg to be continued indefinitely). • If at 45-day visit, the TEE/TOE shows inadequate closure of the LAA (residual jet $>$ 5mm), the subject should remain on warfarin and aspirin until the 6-month TEE/TOE is performed <p>*Subjects enrolled outside the US may take other anticoagulants/vitamin K antagonists in lieu of warfarin</p> <p>Appropriate endocarditis prophylaxis is recommended for 6 months following device implantation for all subjects. The decision to continue endocarditis prophylaxis beyond 6 months is at physician's discretion.</p>
Estimated Enrollment Time	<p>The trial may continue for up to 8 years, depending on the rate of enrollment and the FDA approval timeline (as applicable). The trial is expected to take approximately 3 years to enroll, and each subject will be followed for 5 years. Follow-up visits may occur as part of a post-approval study, should the Amulet device gain approval for commercial distribution prior to the subject's 5-year visit.</p>
Subject Population/Protection /Compliance	<p>Subject screening will be conducted by trained study site personnel. Subjects that meet the inclusion criteria will be consented in compliance with all applicable US Federal regulations concerning the protection of human subjects (45 CFR Part 46, and 21 CFR Parts 50, 54, 56, and 812), and the Declaration of Helsinki. In addition, sites will comply with the study protocol and any additional requirements imposed by the IRB, EC, or HREC in Australia. This trial will provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data. All aspects of the trial will be conducted according to appropriate standards of scientific integrity and standards mandated by CMS. Protocol deviations will be collected and monitored by SJM for trending. Repeated and serious non-compliance of an investigational site can result in site visits, telephone discussions with the PI, or retraining by SJM. If compliance is not secured, the investigator and site participation may be terminated.</p>

Subject Enrollment	<p>Subjects will be considered enrolled once the informed consent has been signed and the subject is randomized. The trial is expected to include the Medicare population, based on demographic characteristics and cardiovascular risk factors, thereby representing this patient population as part of the overall cohort. These criteria are not expected to have a negative effect on the recruitment or retention of underrepresented populations. SJM intends to implement FDA’s guidance on sex-specific data in medical device clinical studies to ensure adequate representation of women and other traditionally underrepresented demographic subgroups. Additionally, SJM will approach sites that have experience implanting Control devices without consideration for racial or ethnic minorities, will provide training to participating sites to ensure adequate representation of these demographic subgroups, and will regularly review screening and enrollment logs. Informed consent material in alternative languages and recruitment materials may be provided. Withdrawal rates for underrepresented subgroups will also be regularly reviewed by SJM, and compared to rates in the overall study population.</p> <p>As this trial will enroll Medicare beneficiaries in the US, all standards of Medicare coverage requirements will be followed. Results of the trial are expected to be generalizable to the Medicare population based on age and cardiovascular risk factors.</p>
Risks and Benefits	<p>The anticipated clinical benefit of LAA closure is that subjects may not need to be on long-term warfarin therapy and thus will not be exposed to complications associated with long-term warfarin therapy, particularly bleeding complications.</p> <p>The potential benefit of participating in this clinical trial is close follow-up of the subject by their treating physicians. Potential benefits of the Amulet device (which are being assessed in this trial) are higher implant success rate, higher rate of device closure, lower rate of complications, and lower rate of stroke than the Control device. Future patients with non-valvular atrial fibrillation at high risk of stroke may benefit from the results of this clinical trial.</p> <p>Anticipated adverse events (AEs) associated with study participation and device implants are similar to those of other cardiac catheterization procedures. There are other possible risks associated with the use of the required medications and testing for the trial, but are also no different from those prescribed outside of this clinical trial. The trial requires FDA approval and IRB/EC/HREC approval per site, trained physicians specializing in cardiac catheterization procedures, and will utilize a Data and Safety Monitoring Board (DSMB) as an independent oversight committee in an effort to minimize potential risks to subjects. Subjects (preoperatively and postoperatively) will be</p>

	<p>under the care of a cohesive, multidisciplinary team of medical professionals, and procedures will be furnished in a hospital with an established structural heart disease and/or electrophysiology program.</p>
<p>Adverse Events/Complaints</p>	<p>Safety surveillance within this trial (and the safety reporting performed by the investigator) starts as soon as the subject is consented. Safety surveillance and safety reporting will continue until the last study visit has been performed, or the subject is deceased, or the subject concludes participation in the trial. The following types of adverse events will be collected for all subjects:</p> <ul style="list-style-type: none"> • Serious adverse events • Device and procedure-related adverse events • Unanticipated adverse device effects <p>In addition to reporting events to the sponsor, the investigator must also notify the IRB/EC/HREC, as appropriate, and in accordance with the national and local laws and regulations. Deaths are to be documented and reported to the sponsor within 10 days of becoming aware of the event.</p> <p>A complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, reliability, safety, effectiveness, or performance of a device after its release for distribution. All complaints for the Amulet device are to be submitted to SJM Postmarket Surveillance.</p>
<p>Committees/Core Lab</p>	<p>This clinical trial will utilize a Steering Committee who will advise SJM on trial design, trial conduct, and analysis and reporting of results. Additionally, the trial will have a Clinical Events Committee (CEC) and Data and Safety Monitoring Board (DSMB). The CEC will review and adjudicate AEs. The DSMB will advise SJM regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DSMB members will not be investigators in the trial.</p> <p>An independent echocardiography core lab will be utilized to analyze echo images.</p>
<p>Data Management/Monitoring</p>	<p>SJM will be responsible for data handling and analysis, and a secure, validated, electronic data capture system will be utilized. Site monitoring will be conducted by SJM personnel in order to ensure accurate and complete reporting of data is occurring. As part of our commitment, SJM is certified to the U.S.- European Union Framework Agreement regarding human resources and subject clinical trial personal information. SJM will make every effort to maintain the privacy of each subject; confidentiality of subject</p>

	information/data will be observed and secured against unauthorized access.
Public Release of Data and Outcomes/Publication Policy	Upon receiving IDE approval from the FDA, and prior to the first subject enrollment, this clinical trial will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes will be made public through the ClinicalTrials.gov website and according to the requirements of Section 801 of the FDA Amendments Act. Publications resulting from this clinical trial will follow the publication guidelines according to the International Committee of Medical Journal Editors (ICMJE).

2 STUDY CONTACTS

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St. Jude Medical
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[REDACTED]

3 INTRODUCTION

This document is a clinical investigational plan for the AMPLATZER™ Amulet™ Left Atrial Appendage Occluder randomized controlled trial. This trial is intended to evaluate the safety and effectiveness of St. Jude Medical's AMPLATZER™ Amulet™ device (Amulet) in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism. The trial will be conducted worldwide under an investigational device exemption (IDE) and is intended to support market approval of the Amulet device in the United States and other countries. The trial is sponsored by St. Jude Medical.

4 BACKGROUND

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder¹. During AF there are multiple simultaneous waves of contractions, which spread in a chaotic manner through both atria. This arrhythmia results in rapid, uncoordinated contractions, which decrease the blood pumped through the atria. The loss of mechanical efficiency during AF leads to insufficient contraction in the left atrium (LA)². Stagnation of blood flow in the LA leads to hypercoagulability and thus increases the risk for thrombus formation in the LA or left atrial appendage (LAA). Approximately 90% of all thrombi in subjects with non-valvular AF (NVAF) forming in the LA originate in the left atrial appendage³. The thrombus formation, in turn exposes the patient to thromboembolic events.

Echocardiographic risk factors for LAA thrombus formation include echocardiographic evidence of decreased LAA flow velocity and spontaneous echo contrast within the left atrium and left atrial appendage^{4, 5}. The normal flow pattern of the LAA is the ejection of blood from the appendage following atrial contraction at a velocity greater than 40 cm/s². Agmon et al. found that the relative risk of ischemic stroke was 2.6 times greater in patients with LAA flow velocities < 20 cm/s than those with higher LAA velocities⁶.

Non-valvular AF patients have been assessed to determine the risk of stroke based on the presence of independent risk factors. In a study by Gage et al. the CHADS₂ index was shown to be a tool to predict the risk of stroke in subjects with AF⁷. The CHADS₂ score assigns one point each for the presence of congestive heart failure, hypertension, age greater than 75, and diabetes mellitus and two points for history of stroke or transient ischemic attack (TIA). The study found that AF patients who were not treated with anti-thrombotic agents had an increased risk of stroke from 1.5% to 18.2% annually as CHADS₂ scores increased from 1 and 6.

A study by Go et al. reviewed outcome data (11,526 patients) in a large primary care setting and confirmed that thromboembolic risk increases progressively with CHADS₂ score⁸. The study also noted that oral anticoagulation with warfarin reduces the risk of stroke in most patients with the exception of those at lowest risk (CHADS₂ score of zero) and highest risk (CHADS₂ ≥ 5) for stroke. The more recently developed CHA₂DS₂-VASc risk assessment scheme⁹, which identifies truly low risk subjects, assigns two points to age ≥ 75 years and previous stroke, TIA or thromboembolism and one point each to congestive heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease, age between 65 and 74 years and female sex. A recent validation¹⁰ of these risk schemes in more than 90,000 patients without oral anticoagulation (OAC) but on aspirin showed annual ischemic stroke rates ranging from 0.6% in CHA₂DS₂-VASc = 1 to 4.8% in CHA₂DS₂-VASc = 4, and more than 12% for CHA₂DS₂-VASc = 9.

In a meta-analysis conducted by Andersen et al., warfarin was found to be superior to aspirin and placebo in reducing the risk of systemic embolism in subjects with NVAF¹¹. Hart et al. reported that adjusted dose warfarin reduces stroke by 64% (6 trials) and antiplatelet agents reduce stroke risk by 22%¹². The study also reported that risk of intracranial hemorrhage was doubled with adjusted-dose warfarin compared with aspirin.

Recently, new drugs (known as novel oral anticoagulant, or NOAC) have been developed with less dietary and pharmacological interactions than warfarin and no INR monitoring requirements. Major trials such as RE-LY and ROCKET AF demonstrated that dabigatran and rivaroxiban are non-inferior to warfarin in the prevention of stroke or systemic embolism^{13, 14}. The ARISTOTLE trial demonstrated apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in subjects with atrial fibrillation¹⁵. The ENGAGE AF-TIMI trial demonstrated both once-daily dose regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes¹⁶. A number of characteristics that increase a patient's risk for stroke also increase the patient's risk for bleeding, therefore an alternative to warfarin and NOAC drugs is needed.

Left atrial appendage occlusion (LAAO) is considered a viable alternative to oral anticoagulation (OAC) therapy for stroke prevention in patients with NVAF¹⁷⁻²⁷. Published evidence supporting LAAO is provided in large part by the major randomized controlled trials PROTECT AF and PREVAIL¹⁷⁻²⁰. Five-year results of PROTECT AF showed superiority of the WATCHMAN™ device in mortality and stroke compared to optimal medical treatment with warfarin²⁰.

This clinical trial will study the Amulet device, which is St. Jude Medical's second-generation LAA closure device. The first generation St. Jude Medical LAA closure device is the AMPLATZER Cardiac Plug (ACP) based on St. Jude Medical's AMPLATZER occluder technology. The ACP device received CE Mark approval in 2008. The ACP device demonstrated favorable feasibility and safety in observational studies in Europe²⁸⁻²⁹. Additionally, Park et al. reports the results of an investigator-initiated retrospective study to report on the initial European experience in patients treated with the ACP device between December 2008 and November 2009. SJM's ACP Registry results were also presented at EURO PCR in 2012 and 2014²⁸⁻²⁹. In addition, results from a multicenter study involving 22 sites, 1,047 consecutive patients undergoing implant of the ACP device showed a high procedural success rate and a favorable outcome for the prevention of AF-related thromboembolism³⁰.

The ACP device was also evaluated under an Investigational Device Exemption (IDE) in the United States. The trial was set up in two phases within a combined, single protocol: a small feasibility phase followed by a larger pivotal phase. Initial safety evaluation in the feasibility phase was based on device and/or procedure-related serious adverse events (SAEs) and the transesophageal echo (TEE) results measuring LAA closure at 45 days post implant. A total of 45 subjects were randomized (2: 1 device to control (warfarin)) between March 2010 and March 2011: 31 to the device group and 14 to the control group. There were no deaths or unanticipated adverse device effects in the device group reported through the 45-day follow up for this study population. Based on review of the feasibility data, FDA determined that sufficient data existed to support continuation into the pivotal phase of the IDE study. Enrollment in the pivotal phase began in February 2013 and 52 new subjects were enrolled (37 device and 15 control). SJM ceased enrollment in the trial on 20 December 2013 due to the anticipated FDA approval and subsequent market release of a competitive LAAO device. The decision to stop enrollment in the ACP trial was due to the expectation that once the competitive LAAO device was commercially available, patients would not consent to participate in a randomized trial including warfarin as a control group. The decision to stop enrollment was not due to safety or efficacy concerns.

In a comparative study between the ACP and the WATCHMAN devices (40 patients each), Chun et al.³¹ found the devices to perform similarly. The rate of successful implantation achieved with the ACP device was greater than with the WATCHMAN device (100% vs. 95%) although the difference was not statistically significant. TEE at follow-up revealed a significantly higher incidence of residual peri-device flow (jet > 5 mm) for the WATCHMAN device compared to the ACP device, although this was not associated with an increased incidence of thromboembolic events. This finding is consistent with other reports on the ACP device³²⁻³³.

The Amulet device is a second-generation ACP device. Early experiences with the Amulet device have been published^{34, 35, 36}. Freixa et al.³⁵ reported successful implantation of the Amulet device in 24 out of 25 patients. Patients who had a successful implant had varying LAA anatomies. The single unsuccessful case was in a patient with a bi-lobar, small and short LAA. No procedural device embolization, stroke or pericardial effusion occurred. At 2-3 months follow-up (21 patients) no stroke, peripheral embolism or bleeding had occurred and TEE showed no residual leak >3 mm in any of the patients. Lam et al.³⁷ implanted 17 patients with the Amulet device. All devices were successfully implanted. There was one procedure-related pericardial effusion successfully managed with pericardiocentesis. All patients were followed through 90 days. The authors concluded that the implantation of the Amulet device is associated with high success rate and good short-term outcome.

A comparative study Gloekler et al.³⁶ was conducted, which included 50 ACP devices and 50 Amulet devices. This study showed that the devices performed similarly with respect to safety (combined safety endpoint of surgical bailout, stroke, cardiac tamponade and peri-procedural death: 6% for ACP vs. 8% for the Amulet device). Procedural success was high for both devices (94% and 98% for the ACP and the Amulet device, respectively).

In conclusion, percutaneous LAAO devices have emerged as a feasible option for stroke reduction in AF patients who are at high risk for stroke, and early experience shows that the Amulet device can be safely implanted with good procedural outcomes. Refer to section 6 for a description of the device.

5 STUDY DESIGN

5.1 Purpose

The purpose of the trial is to demonstrate that safety and effectiveness of the Amulet device is non-inferior to that of the Boston Scientific LAAC device (Control) in subjects with non-valvular atrial fibrillation.

5.2 Study Design and Scope

The Amulet IDE trial is a prospective, randomized, multi-center active control worldwide trial, designed to evaluate the safety and effectiveness of the AMPLATZER Amulet Left Atrial Appendage Occluder. Subjects will be randomized in a 1:1 ratio between the Amulet LAA occlusion device (treatment) or a Boston Scientific LAA closure device (Control).

All enrolled subjects will follow the protocol-required tests and assessments at each scheduled follow-up visit. At US sites or sites where the implanting physicians do not have Amulet implant experience, up to 3 subjects per sponsor-approved implanter may be implanted with the Amulet device prior to randomization as part of the Roll-In Phase, in order to provide initial experience to the site. These data will not be included in the formal endpoint analyses, while data from roll-in subjects at each site will be included in the clinical investigation report and reported to regulatory authorities. All roll-in subjects will have the same data collection and follow-up schedule as randomized subjects.

The trial will be conducted at up to 150 sites worldwide, with up to 100 sites in the US. A majority of subjects will be enrolled in the US. Data collected during this trial will be used

to support approval of the Amulet device in the United States as well as other countries, as needed.

5.2.1 Number of Required Subjects

A total of 1878 subjects will be randomized to Amulet or Control at up to 150 sites worldwide.

Approximately 343 additional subjects are expected to be enrolled in the Roll-in Phase. Since US implanting physicians have no experience with the Amulet device, up to 3 roll-in subjects per US implanter will result in approximately 343 subjects enrolled in the Roll-in phase (assuming that 40 sites in the US will be initiated under protocol version C, with an average of 2 implanters per site, the total number of roll-in cases for the trial will be approximately 343 subjects: 103 under the previous criteria + 240 under protocol version C).

There is no minimum number of subjects to be enrolled at each site. To ensure enrollment balance across study sites, no investigational site will be permitted to enroll more than 20% of the maximum sample size for the randomized trial.

5.2.2 Estimated Enrollment Time

The trial may continue for up to 8 years, depending on the rate of enrollment and the FDA approval timeline (as applicable). The trial is expected to take approximately 3 years to enroll, and each subject will be followed for 5 years. Follow-up visits may occur as part of a post-approval study, should the Amulet device gain approval for commercial distribution prior to the subject's 5-year visit.

5.3 Study Endpoints

5.3.1 Primary Endpoints

The trial has three primary endpoints:

Safety:

- A composite of procedure-related complications, or all-cause death, or major bleeding (Type 3 or greater per Bleeding Academic Research Consortium) through 12 months. Complications are defined as adverse events requiring invasive surgical or percutaneous intervention..

Effectiveness:

- A composite of ischemic stroke or systemic embolism through 18 months

Mechanism of Action:

- Device closure (defined as residual jet around the device ≤ 5 mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow

5.3.2 Secondary Endpoints

The trial has the following secondary endpoints:

- A composite of all stroke, systemic embolism, or cardiovascular/unexplained death through 18 months
- Major bleeding rate through 18 months, defined as Type 3 or greater based on BARC definition
- A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months (superiority analysis)
- A composite of ischemic stroke or systemic embolism through 18 months (superiority analysis)
- Device closure (defined as residual jet around the device ≤ 5 mm) at the 45-day visit documented by TEE/TOE, defined by Doppler flow (superiority analysis)

5.3.3 Descriptive Endpoints/Outcome Measures

The following endpoints will be descriptively summarized in randomized subjects:

- Technical success rate
- Procedural success rate
- Device success rate
- Number of subjects on oral anticoagulant at each follow-up visit
- Procedure duration
- Procedural complications by operator
- Device thrombosis
- Transient ischemic attack
- Hemorrhagic stroke
- Systemic embolism
- All-cause mortality
- Cardiovascular mortality
- Major bleeding, by site and severity (defined as Type 3 based on BARC definition)
- Minor bleeding, by site and severity (Minor bleeding defined as Type 2 based on BARC)

5.4 Inclusion and Exclusion Criteria

All subjects enrolled in the clinical trial (including those withdrawn from the clinical study or lost to follow-up) will be documented and tracked by assigning an identification code

linked to name, alternative identification, or contact information. Refer to Section 5.5.3 for a description of when a subject will be considered enrolled in the trial.

5.4.1 Inclusion Criteria

To participate in this clinical trial, subjects must meet all of the following inclusion criteria:

1. 18 years of age or older
2. Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation and the patient has not been diagnosed with rheumatic mitral valvular heart disease
3. At high risk of stroke or systemic embolism defined as CHADS₂ score ≥ 2 or a CHA₂DS₂-VASc score of ≥ 3
4. Has an appropriate rationale to seek an alternative to warfarin or other anticoagulant medication
5. Deemed by investigator to be suitable for short term warfarin therapy but deemed unable to take long term anticoagulation, following the conclusion of shared decision making (see inclusion criteria #6)
6. Deemed suitable for LAA closure by a multidisciplinary team of medical professionals (including an independent non-interventional physician) involved in the formal and shared decision-making process, and by use of an evidence-based decision tool on oral anticoagulation (final determination must be documented in the subject's medical record)
7. Able to comply with the required medication regime post-device implant
8. Able to understand and is willing to provide written informed consent to participate in the trial
9. Able and willing to return for required follow-up visits and examinations

5.4.2 Exclusion Criteria

To participate in the trial, subjects must not meet any of the following exclusion criteria:

1. Requires long-term oral anticoagulation therapy for a condition other than atrial fibrillation
2. Contraindicated for or allergic to aspirin, clopidogrel, or warfarin use
3. Indicated for chronic P2Y₁₂ platelet therapy inhibitor
4. Is considered at high risk for general anesthesia, in the opinion of the investigator, and/or based on past adverse reaction(s) requiring medical intervention or which resulted in prolongation of hospital stay (criterion is only applicable where general anesthesia is planned for the study procedure).

5. Has undergone atrial septal defect (ASD) repair or has an ASD closure device present
6. Has undergone patent foramen ovale (PFO) repair or has a PFO closure device implanted
7. Implanted with a mechanical valve prosthesis
8. Has any of the customary contraindications for a percutaneous catheterization procedure (e.g. subject is too small to accommodate the TEE/TOE probe or required catheters, or subject has active infection or bleeding disorder)
9. Stroke or transient ischemic attack (TIA) within 90 days prior to randomization or implant procedure (as applicable)
10. Underwent any cardiac or non-cardiac intervention or surgery within 30 days prior to randomization, or intervention or surgery is planned within 60 days after implant procedure (e.g. cardioversion, ablation, cataract surgery, etc.)
11. Myocardial infarction (MI) within 90 days prior to randomization
12. New York Heart Association Class IV Congestive Heart Failure
13. Left ventricular ejection Fraction (LVEF) $\leq 30\%$
14. Symptomatic carotid disease (defined as $>50\%$ stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject has a history of carotid stent or endarterectomy the subject is eligible if there is $<50\%$ stenosis
15. Reversible cause of AF (i.e. secondary to thyroid disorders, acute alcohol intoxication, trauma, recent major surgical procedures)
16. History of idiopathic or recurrent venous thromboembolism
17. Left atrial appendage is obliterated or surgically ligated
18. Thrombocytopenia or anemia requiring transfusions
19. Hypersensitivity to any portion of the device material or individual components of either the Amulet or Boston Scientific LAA closure device (e.g. nickel allergy)
20. Actively enrolled or plans to enroll in a concurrent clinical study in which the active treatment arm may confound the results of this trial
21. Subject is pregnant or pregnancy is planned during the course of the investigation
22. Active endocarditis or other infection producing bacteremia
23. Subject has had a transient case of AF (i.e. never previously detected, provoked/induced by surgical or catheter manipulations, etc.)

24. Subjects with severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73m²)
25. Subject whose life expectancy is less than 2 years
26. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical trial or to comply with follow up requirements, or impact the scientific soundness of the clinical trial results.

To participate in the trial, subjects must not meet any of the following echocardiographic exclusion criteria:

1. Intracardiac thrombus visualized by echocardiographic imaging
2. Existing circumferential pericardial effusion >2mm
3. Significant mitral valve stenosis (i.e. mitral valve area <1.5 cm²)
4. High risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion > 15mm or length \geq 15mm; excursion defined as maximal protrusion of the ASA beyond the plane of the atrial septum) or large shunt (early, within 3 beats and/or substantial passage of bubbles i.e. \geq 20)
5. Complex atheroma with mobile plaque of the descending aorta and/or aortic arch
6. Cardiac tumor
7. LAA anatomy cannot accommodate either a Boston Scientific LAAC or Amulet device, as per manufacturer's IFU. (i.e. the LAA anatomy and sizing must be appropriate for both devices in order to be enrolled in the trial. This is applicable to all roll-in and randomized subjects).
8. Placement of the device would interfere with any intracardiac or intravascular structure

5.5 Subject Population

5.5.1 Subject Screening

Subjects presenting at the investigational site may be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be fully informed about the trial and requested to participate in the trial. If the subject agrees to participate in the trial, a duly signed and dated Patient Informed Consent will be obtained.

5.5.2 Screening Log

Study sites 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 may be requested and reviewed by SJM.

5.5.3 Point of Enrollment

Subjects will be considered enrolled in the randomized trial once the informed consent has been signed by the subject and the subject is randomized. Once a subject has been randomized, the LAA implant procedure must occur within 14 days.

Roll-in subjects will be considered enrolled once the informed consent has been signed by the subject, and when anesthesia and vascular access have been initiated.

5.5.4 Enrollment of Medicare Beneficiaries

This clinical trial will enroll Medicare beneficiaries in the US and therefore conforms to all standards of Medicare coverage requirements. Enrolled subjects are expected to be consistent with the Medicare population based on the demographic characteristics and cardiovascular risk factors, thereby representing this patient population as part of the overall cohort. These criteria are not expected to have a negative effect on the recruitment or retention of underrepresented populations.

As this trial will enroll Medicare beneficiaries in the US, all standards of Medicare coverage requirements will be followed. Results of the trial are expected to be generalizable to the Medicare population based on age and cardiovascular risk factors.

5.5.5 Enrollment/Representation of Traditionally Underrepresented Demographic Subgroups

Historically, specific demographic subgroups such as women and racial or ethnic minorities have been under-represented in or excluded from many clinical trials, leading to a lack of information on these subgroups for many medical treatments. Certain medical products elicit different responses in specific demographic subgroups. Therefore it is important to ensure there is an adequate representation of such demographic subgroups and to assess whether there is a different response between different demographic subgroups.

SJM intends to implement FDA's guidance on sex-specific data in medical device clinical studies³⁸ to ensure adequate representation of women and other traditionally under-represented demographic subgroups in the Amulet IDE clinical trial. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical trials have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the study population may unintentionally exclude specific subgroups



- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for study follow-up requirements

Additionally, for medical devices available in different sizes or configurations, smaller sizes or configurations intended primarily for women may not be available. Based on results reported on clinical studies of LAA occluders, between 30% and 40% of study participants were female^{39,40,41}, and between 5% and 10% of the study population was non-white. The Amulet IDE trial specifies an inclusion criterion of CHA₂DS₂-VASc score of 3 or greater. Since the CHA₂DS₂-VASc score assigns a score of 1 for female subjects, this inclusion criterion is expected to preferentially select female subjects. Furthermore, the population in this trial is expected to be older, therefore, some of the traditional reasons for low participation of women are unlikely to affect the Amulet trial (e.g., fear of fetal consequences, family responsibilities). SJM will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this trial:

- SJM will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups.
- SJM will regularly review enrollment logs and randomization forms to investigate whether there is under-representation of these demographic subgroups.
- SJM will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall study population.
- As appropriate and necessary, SJM will retrain sites on the importance of recruiting and retaining subjects in the trial.
- SJM will approach sites that have experience implanting Control devices without consideration for racial or ethnic minorities.
- SJM will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials.

The Statistical Analysis Plan pre-specifies analyses to assess heterogeneity of safety and effectiveness endpoints across demographic subgroups.

5.6 Informed Consent Process

5.6.1 General Process

The process for obtaining informed consent must comply with the ethical principles defined in the current version of the Declaration of Helsinki.



Prior to enrolling in the clinical trial and conducting study-specific procedures, subjects must be consented, as required by applicable regulations and the center's EC/IRB.

The principal investigator (PI) or his/her authorized designee will conduct the informed consent process. This process will include a verbal discussion with the subject on all aspects of the clinical trial that are relevant to the subject's decision to participate. The subject should be allowed adequate time to review and ask questions and must not be coerced or induced to participate.

Documentation of the informed consent shall be recorded on the electronic Case Report Form (eCRF) and in the subject's medical records. The original signed informed consent shall be filed in the subject's study chart, and a copy given to the subject.

The subject shall be provided with the informed consent form that is written in a language understandable to the subject and has been approved by the center's EC/IRB. Failure to obtain informed consent from a subject prior to study enrollment should be reported to SJM within 5 working days and to the reviewing center's EC/IRB, consistent with the center's EC/IRB reporting requirements.

A template of the informed consent form is provided in Appendix E. Any changes to the template must be approved by SJM prior to EC/IRB review and approval.

6 DEVICE UNDER INVESTIGATION (UNITED STATES) AND CONTROL DEVICE

6.1 Device Description

6.1.1 Amulet Device

The AMPLATZER™ Amulet™ Left Atrial Appendage Occluder (Amulet) is a percutaneous transcatheter device intended to prevent thrombus embolization from the left atrial appendage (LAA) in patients who have nonvalvular atrial fibrillation.

The Amulet device (Figure 1) received CE Mark in 2013, but is an investigational product (not approved by the FDA) in the US. It is constructed from a nitinol mesh and consists of a lobe and a disc connected by a central waist. The lobe ranges in diameter from 16 to 34 mm (Table 1) and has stabilizing wires for device placement and retention in the LAA. The disc is larger in diameter than the lobe, ranging from 22 to 41 mm; both the disc and the lobe contain polyester fabric to facilitate closure of the LAA. There are threaded screw attachments at either end of the device for connection to the delivery and loading cable. Radiopaque markers at either end of the device and at the location of the stabilizing wires allow for predictable placement of the device. The stabilizing wires and polyester patch are secured to the device using polyester thread. A platinum/iridium thread is attached to the nitinol braid. Both the lobe and the disc will be in contact with the tissue and fluids (blood) of the heart. Accessories packaged with the Amulet device include the loader, loading cable, loading cable vise, delivery cable, delivery cable vise, and hemostatic valve.

The Amulet device is recommended for delivery using the AMPLATZER TorqVue 45 x45 Delivery Sheath (12F and 14F) which has CE Mark and FDA clearance.

Figure 1: The Amulet device and key components

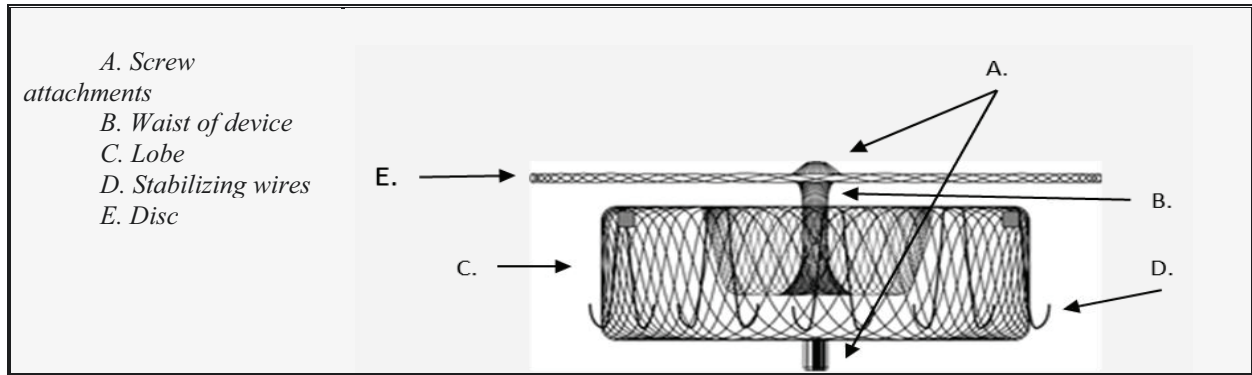


Table 1: Model numbers and key dimensions of the Amulet device and delivery system

Part Number (Commercially Available Product)	Part Number (IDE Product)	Amulet Device Size/ Lobe Diameter	Disc Diameter (mm)	Lobe Length (mm)	# of stabilizing wires	TorqVue Delivery System
9-ACP2-007-016	9-ACP2-IDE-016	16mm	22	7.5	6	12F*
9-ACP2-007-018	9-ACP2-IDE-018	18mm	24	7.5	6	12F*
9-ACP2-007-020	9-ACP2-IDE-020	20mm	26	7.5	8	12F*
9-ACP2-007-022	9-ACP2-IDE-022	22mm	28	7.5	8	12F*
9-ACP2-010-025	9-ACP2-IDE-025	25mm	32	10	8	12F*
9-ACP2-010-028	9-ACP2-IDE-028	28mm	35	10	10	14F
9-ACP2-010-031	9-ACP2-IDE-031	31mm	38	10	10	14F
9-ACP2-010-034	9-ACP2-IDE-034	34mm	41	10	10	14F

*Per the IFU, if a 14 Fr delivery sheath is selected for use with a 16 mm-25mm device, tightly connect the 14 Fr sheath adaptor to the delivery sheath hub

**The TorqVue delivery sheath is available in both an 80cm and 100cm length. The 80cm sheath is marketed under the name AMPLATZER™ Amulet™ Delivery Sheath outside of the US.

6.1.2 Commercially Released Boston Scientific LAAC Device (Control)

The Boston Scientific WATCHMAN device has both CE Mark and FDA approval, and the WATCHMAN FLX is CE Marked. The WATCHMAN family of devices was chosen as the comparator/control since the intended population is identical to that for the Amulet device. Table 2 provides a comparison between the Amulet and Boston Scientific LAAC device.

Per the directions for use (DFU), the Boston Scientific left atrial appendage closure (LAAC) technology is intended for percutaneous, transcatheter closure of the left atrial appendage and consists of the access system (access sheath and dilator) and delivery

system (delivery catheter and LAAC device). The access system and delivery system permit device placement in the left atrial appendage (LAA) via femoral access and inter-atrial septum crossing into the left atrium. The Boston Scientific device is a self-expanding nitinol structure with a polyethylene terephthalate (PET) porous membrane on the proximal face. The device is constrained within the delivery system until deployment in the LAA. Appropriate device sizing is determined by LAA measurement using fluoroscopy (fluoro) and transesophageal echocardiography (TEE/TOE).

The Boston Scientific LAAC device (WATCHMAN) is designed to be permanently implanted at or slightly distal to the ostium of the LAA to close the appendage to inflow. The placement procedure can be done under local or general anesthesia in a hospital catheterization or electrophysiology laboratory setting.

In the event another Boston Scientific LAAC device becomes commercially available, use of the device will be allowed upon approval from FDA and SJM, and data captured accordingly on the eCRFs.

Table 2 provides a comparison between the Amulet and Boston Scientific WATCHMAN device.

Table 2: Comparison of the Amulet and Boston Scientific WATCHMAN Device

Characteristic	Amulet	WATCHMAN
Manufacturer	St. Jude Medical	Boston Scientific
Mechanism of Action	Disc seals orifice of LAA	Closes off distal body of LAA
Sizes (diameter)	16, 18, 20, 22, 25, 28, 31, and 34 mm	21, 24, 27, 30, and 33 mm
Delivery system	AMPLATZER TORQVUE 45x45 (sheath sizes 12 Fr or 14 Fr)	WATCHMAN Access Sheath (12 Fr)
Required Medication Post-procedure	<p>Aspirin (or alternate antiplatelet) at least 6 months post-implant</p> <p>Clopidogrel (or alternate antiplatelet) per standard of care</p> <p>Endocarditis prophylaxis</p>	<p>Warfarin* and aspirin until LAA seal \leq 5 mm</p> <p>Warfarin cessation, aspirin indefinitely</p> <p>Clopidogrel and aspirin up to 6 months post-procedure</p> <p>Endocarditis prophylaxis</p> <p>*Subjects enrolled outside the US may take other anticoagulants/vitamin K antagonists in lieu of warfarin</p>
Availability	US: Investigational use only	US: FDA approved
	CE Mark	CE Mark



	TGA Approved	TGA Approved
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6.2 Operator Training and Experience and Implant Facility Requirements

Common complications related to LAAO therapy include pericardial effusion, cardiac perforation, cardiac tamponade, device embolization, systemic thromboembolism, and vascular access-related injury. Operator training and experience are important to reduce these complications and advance procedural success rates.

Intended users of both the Amulet and Control devices are interventional cardiologists and electrophysiologists trained in percutaneous and transseptal procedures, who have completed company-specified physician training programs.

The following are required for the implanting facility to participate in this trial:

- Hospital with an established structural heart disease and/or electrophysiology program
- Hospital with a cardiac catheterization lab or electrophysiology (EP) lab with fluoroscopy capability
- Non-invasive imaging (i.e. transesophageal echocardiography) with echocardiography support
- Anesthesiology support for administration of general anesthesia specific to this procedure

6.3 Medication Requirements

6.3.1 Pre-Procedure (All Subjects)

Subjects must begin aspirin (81-100 mg) one day prior to implant procedure.

6.3.2 Post-Procedure

Amulet Subjects:

Aspirin (81-100 mg) and clopidogrel (75 mg) OR aspirin (81-100 mg) and Oral Anticoagulation (OAC, including NOACs) daily until the 45-day TEE/TOE is performed. An alternative antiplatelet to clopidogrel may be used if a subject is a non-responder to clopidogrel, as documented in the subject’s medical record/study chart.

- If the residual flow into the LAA is > 5 mm, OAC therapy (if warfarin, INR of 2.0 - 3.0) and aspirin (81-100 mg) is required until the 45-day TEE/TOE is performed.

Appropriate endocarditis prophylaxis is recommended for 6 months following device implantation. The decision to continue beyond 6 months is at the discretion of the principal investigator.

Control Subjects:



Post-procedure, subjects should take aspirin (81-100 mg) and warfarin*, adjusted to achieve international normalized ratio (INR) of 2.0-3.0 until the 45-day study visit.

Appropriate endocarditis prophylaxis is recommended for 6 months following device implantation. The decision to continue beyond 6 months is at the discretion of the principal investigator.

*Subjects enrolled outside the US may take other anticoagulants/vitamin K antagonists in lieu of warfarin

6.3.3 45-Day Visit

Amulet Subjects:

If at the 45-day visit the TEE/TOE shows adequate closure of the LAA (residual jet \leq 5mm) cessation of OAC is required. Subjects should then begin clopidogrel (75 mg) daily until the 6-month visit and continue aspirin 81-100mg daily. An alternative antiplatelet to clopidogrel may be used if a subject is a non-responder to clopidogrel, as documented in the subject's medical record/study chart. Cessation of clopidogrel is required at the 6-month visit (aspirin 81-100mg to be continued indefinitely).

If at the 45-day visit the TEE/TOE shows inadequate closure of the LAA (jet $>$ 5mm), the subject should remain on OAC and aspirin until the 6-month TEE/TOE is performed.

Control Subjects:

If at the 45-day visit the TEE/TOE shows adequate closure of the LAA (residual jet \leq 5 mm) cessation of warfarin is required. Subjects should then begin clopidogrel (75 mg) daily until the 6-month visit and continue aspirin 81-100mg daily. An alternative antiplatelet to clopidogrel may be used if a subject is a non-responder to clopidogrel, as documented in the subject's medical record/study chart. Cessation of clopidogrel is required at the 6-month visit (aspirin 81-100mg to be continued indefinitely).

If at the 45-day visit the TEE/TOE shows inadequate closure of the LAA (residual jet $>$ 5 mm), the subject should remain on aspirin (81-100 mg) and warfarin, adjusted to achieve INR of 2.0-3.0, until the 6-month TEE/TOE is performed. Subjects should discontinue clopidogrel at the 6-month visit if the TEE/TOE shows adequate closure of the LAA (residual jet \leq 5 mm), and remain on aspirin 81-100 mg indefinitely.

6.3.4 6-Month Visit (applicable to subjects with residual flow $>$ 5 mm at 45-day visit)

If the residual flow into the LAA is \leq 5 mm at the 6-month visit, cessation of oral anticoagulation is required. Subjects should continue 81-100 mg aspirin daily (continue indefinitely).

If the residual flow into the LAA is $>$ 5 mm at the 6-month visit, oral anticoagulation medication and aspirin (81-100 mg) must continue until the next TEE/TOE confirms closure.

6.3.5 12-Month Visit and Later

When closure is confirmed, cessation of oral anticoagulation is required. Subjects should then maintain aspirin (81-100 mg) indefinitely. If closure is not confirmed at the 12-month visit, additional echocardiograms and OAC therapy is at the physician's discretion.

A TEE/TOE is required at the 12-month visit for all subjects, regardless of previous TEE/TOE results.

6.4 Device Accountability

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

6.4.1 CE Mark Product: Worldwide Sites

There are no additional tracking requirements for the Amulet device in countries where the device and delivery system have CE Mark or other regional regulatory approvals.

6.4.2 Investigational Product (US)

There are no additional tracking requirements for the Amulet delivery system since it is commercially available in the US.

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.

6.4.2.1 Device Handling & Storage (Investigational Product)

SJM requires that all investigational products be stored according to the labeling, in a secure area to prevent unauthorized access or use. This will prevent non-investigational use of products that are provided for this trial.

7 PROCEDURES

This trial will be conducted in accordance with this clinical investigational plan. All persons participating in the conduct of the trial will be qualified by education, training, and/or experience to perform study-related tasks.

The trial will not commence at a site until SJM receives written approval from the IRB/EC/HREC, FDA, competent authorities (CA), if applicable, and all required documents have been collected from the participating sites. **Figure 2** describes the study flowchart for the trial. **Table 3** outlines the testing and assessments required per study visit interval.

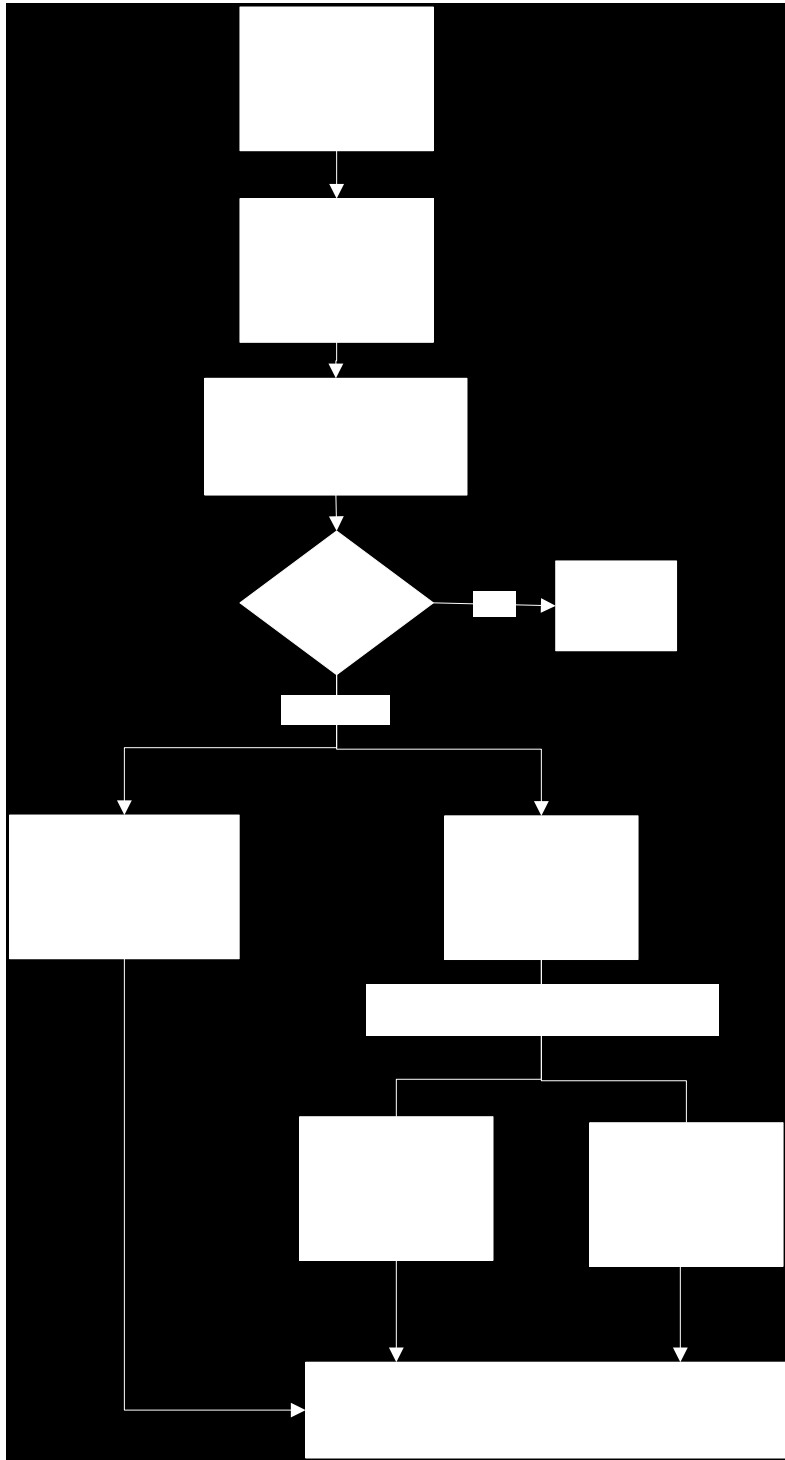


Figure 2: Study flowchart

7.1 Screening/Enrollment/Baseline

The following baseline and enrollment activities are required as part of the screening process. All baseline activities should be done after informed consent is obtained, except where otherwise noted.

- History and physical (may be done per standard of care up to 30 days prior to consent)
- Cardiovascular and medical exam (may be done per standard of care up to 30 days prior to consent)
- Neurological exam (assessment by a neurologist for subjects with a history of TIA and/or stroke, per institutional standard of care)
- Neurologic assessment: Modified Rankin Scale (mRS), NIHSS, Barthel Index (must be performed by NIHSS-, Barthel- and mRS-certified personnel)
- Questionnaire for Verifying Stroke-Free Status (QVSFS)
- CT/MRI for subjects with documented history of TIA/stroke (previous imaging done post-neurological event per standard of care is acceptable; otherwise must be done after consent)
- 12-lead ECG (may be done per standard of care up to 30 days prior to consent)
- CHADS₂ Score
- CHA₂DS₂-VASc score
- HAS-BLED score
- INR Assessment (INR target range 2-3) if subject is taking warfarin (or other oral anticoagulants requiring INR assessments)
- Medication assessment including the use of antiplatelet and anticoagulation medication
- Pregnancy test (required for females of childbearing potential only)
- EQ-5D-5L (Health Questionnaire)
- TEE/TOE to confirm eligibility (echoes done up to 90 days prior to consent will be accepted as baseline)

The principal investigator or delegated study personnel is responsible for screening potential subjects to determine subject eligibility for the trial. Enrollment information (date of consent, inclusion/exclusion information, etc.) will be recorded in the subject's medical record and on the Baseline and Inclusion/Exclusion eCRF. Every effort must be made to submit the Inclusion/Exclusion eCRF within one week of screening.

All subjects screened (including those who sign the informed consent) for the trial should be entered onto a Screening Log. If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the randomized trial.

If a subject is consented and undergoes study-specific testing (i.e. testing that otherwise would not be conducted unless participating in this trial) but does not qualify for the trial,

the subject will be considered a consented screen failure and will not continue in the trial. Data collected through the time of screen failure are required to be submitted on the applicable eCRFs.

7.2 Roll-in Phase

At US sites, or sites where the implanting physicians do not have Amulet implant experience, up to 3 subjects per sponsor-approved implanter may be implanted with the Amulet device prior to randomization as part of the roll-in phase, in order to provide initial experience to the site. These data will not be included in the formal endpoint analyses, but data from these subjects will be included in the clinical investigation report and reported to regulatory authorities. Roll-in subjects are required to meet all eligibility criteria (including echo criteria, as if they were to be randomized) and will have the same data collection and follow-up schedule as randomized subjects.

7.3 Randomization

When it is determined the subject has met all inclusion criteria and no exclusion criteria (including echocardiographic exclusion criteria), the subject may undergo the procedure as a roll-in or will be randomized in a 1:1 ratio to either the Amulet or Control device according to a computer-generated randomization scheme. Randomization will be stratified by investigational site.

Trained SJM representatives may be present during the Amulet implant procedure. Representatives from Boston Scientific may be present during the Control implant procedure. Site personnel should contact SJM to schedule the implant procedure and proctor as necessary.

Subjects must follow pre-procedure care instructions (Section 6) and begin aspirin (81-100 mg) one day prior to the procedure. The LAA closure procedure shall take place no later than 14 days from the date of randomization.

Adverse events will be reported from the time of consent through the end of subject participation. Adverse Event eCRFs should be completed, as applicable.

7.4 Procedure

7.4.1 Amulet device

- **Procedure must be performed no later than 14 days from the date of randomization**
- Subjects taking anticoagulants may continue un-interrupted use, at the physician's discretion. A bridging regimen is not recommended.
- Procedure will be performed under TEE/TOE and angiographic guidance
- On angiogram assessment, if a subject has an LAA landing zone measured with a width of less than 11 mm (at its widest point) or greater than 31 mm at its widest point, the subject will not proceed with device implantation.

- On angiogram assessment, if a subject has insufficient space (minimum 10 mm or 12 mm depending on device size) distal to the LAA orifice to accommodate placement of the device lobe, the subject will not proceed with device placement.
- Refer to the Instructions for Use for the recommended device size, delivery sheath selection, and Amulet implantation procedure.

7.4.2 Boston Scientific LAAC device (Control)

Refer to the directions for use (DFU) for procedural instructions for the commercially available Boston Scientific LAAC device.

Note: Subjects that are randomized but do not have a procedure or do not receive a device will be followed for adverse events and ascertainment of endpoints. Follow-up visit schedules for subjects who do not have a procedure will be determined by the date of randomization. Follow-up schedules for subjects who have a device implant attempted (but not implanted) will be determined by the date of the implant procedure attempt. These subjects will continue to be followed in the trial (as per Table 3: Study Visits and Assessments) but will have no protocol-specific medication or follow-up echo testing requirements.

7.4.3 Post-Procedure

Post-procedure care should involve the following (refer also to Table 3):

- Perform a TTE prior to discharge to ensure the device is positioned correctly and no pericardial effusion is present
- Initiate medications per Section 6.3
- Instruct the subject on when to seek medical attention
- Schedule follow-up, including echocardiography, for evaluation of residual shunt (flow) and adverse events (including thrombus formation)
 - If a thrombus on the device is detected at any time during the trial, 4-6 weeks of anticoagulation treatment with warfarin is recommended, followed by a TEE to evaluate resolution of thrombus.
- In applicable geographies, provide the subject with the temporary subject identification card.

7.5 Scheduled Visits

For subjects who are implanted with a device, follow-up visit schedules will be determined by the date of the implant procedure. All enrolled subjects will have the following required visits: pre-hospital discharge (implanted subjects only), 45-days, 3-months (phone contact), 6-months, 9-months (phone contact), 12-months, 18-months, 24-months, and annually by phone until 5 years. Refer to Table 3 for follow-up testing and assessments.

Note: As an endpoint visit, the 18-month visit window is - 7/+45 days based on the date of implant procedure.

7.6 Neurological Events

The Questionnaire to Verify Stroke-Free Status (QVSFS) is to be completed at baseline and at each study visit (including phone visits) to screen for presenting TIA/stroke signs and symptoms. A positive response to any question will trigger further evaluation and a neurology consult, as necessary. If a stroke or TIA is suspected, or the subject experiences any cognitive or behavioral changes at any time during the trial, the subject must be seen by a stroke/TIA neurologist for evaluation and an appropriate investigation must be performed, including neurovascular imaging and other tests as indicated.

- If a stroke or TIA is suspected/confirmed by neurologist: complete an MRI (CT if MRI- contraindicated) as soon as possible and within 10 days (if possible) of the event, preferably using the following sequences: Fluid-Attenuated Inversion Recovery (FLAIR), Diffusion-Weighted Imaging (DWI), Susceptibility-Weighted Imaging (SWI), Gradient Recalled Echo (GRE) gradient, Apparent Diffusion Coefficient (ADC) maps
- If ischemic stroke is confirmed through imaging, a TEE/TOE is required as soon as possible, but within 7 days of the neurological imaging. Echo imaging should be submitted to the core laboratory.

In the event of a confirmed stroke or TIA by a stroke neurologist, neurological assessments (NIHSS, mRS and Barthel Index) shall be completed. Neurological assessments should be repeated 90 days (+/- 10 days) after the event.

Every effort will be made to keep treating neurologists blinded to the subject's treatment assignment. This will require collaboration between the study investigators and neurologists with respect to review of the echoes and source documentation, whenever possible.

7.7 Subject Study Completion

When the subject's participation in the clinical trial is complete, the subject will return to medical care as per physician's recommendation. Subject participation in the roll-in phase and randomized trial will be considered complete upon completion of the 5-year follow-up visit, subject has withdrawn consent or died, or upon notification from SJM that the trial is completed, whichever is earlier.

7.8 Criteria and Procedures for Subject Withdrawal or Discontinuation

Subjects must be informed of their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical trial until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject withdraws consent
- Subject is deceased (cause must be documented)
- Subject is lost to follow-up. Subjects considered lost-to-follow-up are those who have missed at least one visit and cannot be reached and/or are unresponsive to attempts to be contacted. Attempts may include the following:
 - Phone calls to the subject from the study site personnel. Attempts to contact subject must be documented in the subject's study chart and/or medical record.
 - Mailing a letter to the subject's last known address.

Additional requirements based on geography or IRB/EC will be followed when considering a subject as lost-to-follow-up.

If a subject withdraws from the clinical trial, the site will record the subject's reasons for withdrawal on a Withdrawal eCRF.

Table 3 outlines the study visits and assessments for all enrolled subjects.

Table 3: Study visits and assessments

Study Evaluation	Baseline	Procedure ²	Discharge	45-day visit (± 5 days)	3-month visit (± 30 days) Phone Contact	6-month visit (± 30 days)	9-month visit (± 30 days) Phone Contact	12-month visit (±30 days)	**18- month	24-month visit (±30 days)	Annual visits 3, 4 and 5 years (±60 days) Phone Contact	Stroke Assessment
Informed Consent Process	X											
History & Physical	X											
Cardiovascular & Medical Exam	X											
Neurological exam	X											
CHADS ₂ and CHA ₂ DS ₂ -VASc scores	X											
HAS-BLED score	X											
Reason for seeking an alternative to Warfarin/OAC therapy	X											
INR assessment (as applicable while on warfarin/oral anticoagulants requiring INR assessments)	X			X		X		X	X	X		X
12-lead ECG	X											
Pregnancy Test ¹	X											
Medication Assessment	X		X	X	X	X	X	X	X	X	X	X
MRI (CT if contraindicated)	X ³											X
Modified Rankin Scale, NIHSS & Barthel Index ⁴	X											X
QVSFS	X			X	X	X	X	X	X	X	X	
EQ-5D-5L	X			X		X		X	X			
Angiography		X										
TTE			X									
TEE/TOE	X*	X		X		X ⁵		X ⁶				X ⁷
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X

* Echoes performed within 90 days prior to consent will be accepted; otherwise TEE/TOE must be conducted after consent

¹ Pregnancy test for women of childbearing potential

² Procedure must occur within 14 days from the date of randomization. Follow-up visit windows for implanted subjects will be calculated based on the date of procedure.

³ MRI (CT if contraindicated) is required for subjects with a documented history of TIA or stroke. Previous imaging done post-neurological event is acceptable; otherwise must be repeated

⁴ Perform additional Neurological assessments after a confirmed stroke or TIA and repeat within 90 days of stroke confirmation.

⁵ TEE/TOE is not required if closure was confirmed at 45 days (defined as residual jet ≤5mm)

⁶ TEE/TOE is required for all subjects at 12 months

⁷ TEE/TOE is required at stroke visit only if stroke is confirmed through MRI/CT



Study Document No: SJM-CIP-10114, Ver. C

[REDACTED]
Study Name: AMPLATZER™ Amulet™ Left Atrial
Appendage Occluder Randomized Controlled Trial

**As an endpoint visit, the 18-month visit window is -7/ +45 days based on the date of implant procedure.

Note: Subjects that are randomized but do not have a procedure or do not receive a device will be followed according to Table 3; however, medication requirements and follow-up TEE/TOEs are not required

Table 4 outlines the electronic case report forms (eCRFs) to be completed for all subjects (as applicable), and as per the study visit intervals.

Table 4: Required eCRF completion for all subjects

Visit Interval	Required eCRFs	eCRF Completion Timeframe
Baseline	<ul style="list-style-type: none"> • Screening log • Inclusion/Exclusion • Baseline • Medication • EQ-5D-5L • QVSFS 	
Procedure [^]	<ul style="list-style-type: none"> • Procedure • Medication • Health Care Utilization 	After study implant procedure [^] Reminder: Procedure must occur within 14 days of randomization
Discharge	<ul style="list-style-type: none"> • Follow up • Medication 	At hospital discharge
Follow-up	<ul style="list-style-type: none"> • Follow up ** • Medication • EQ-5D-5L^{^^} • QVSFS 	<ul style="list-style-type: none"> • Office visits: 45-day, 6-month, 12-month, 18-month and 24-month • Phone contact: 3-month, 9-month, 3-year, 4-year and 5-year • ** Reminder: Submit TEE/TOE images for core lab review • ^{^^}Reminder: 45-day and 6-month, 12-month, 18-month
Stroke Assessment Visit	<ul style="list-style-type: none"> • Stroke/TIA Assessment • Adverse Event • Medication 	At the time of suspected stroke/TIA
Adverse Event (“Unscheduled” visit)	<ul style="list-style-type: none"> • Adverse Event • Medication • Stroke/TIA Assessment* 	At the time of occurrence or notification of event * If Stroke/TIA is suspected
Hospitalization	<ul style="list-style-type: none"> • Health Care Utilization 	In conjunction with implant procedure and reportable SAEs if hospitalization occurs
Protocol Deviation	<ul style="list-style-type: none"> • Protocol Deviation 	At the time of occurrence or notification of event
Withdrawal	<ul style="list-style-type: none"> • Subject Withdrawal 	When a subject is withdrawn from the study for any reason
Death	<ul style="list-style-type: none"> • Adverse Event • Death • Out of Service 	At the time of occurrence or notification of event
N/A	<ul style="list-style-type: none"> • Out of Service 	If a device is opened, but not used/implanted; at the time of subject death

Additional eCRFs and assessments noted below should be completed upon occurrence, and/or as applicable:

- Withdrawal eCRF
- Adverse Event eCRF
- Protocol Deviation eCRF (enter with the applicable visit interval, as appropriate)
- Death eCRF
- Out of Service eCRF
- mRS and Barthel Index: complete 90 days (+/- 10 days) after confirmed stroke /TIA
- Health Care Utilization eCRF

8 COMPLIANCE TO CIP

8.1 Statements of Compliance

The study will be performed in accordance with all applicable US Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) and 21 CFR Parts 50, 54, 56, and 812 and the Declaration of Helsinki. Sites will comply with the study protocol and any additional requirements imposed by their IRB, EC, HREC in Australia, or other, based on requirements per geography and institution.

The investigator will not start enrolling subjects or request informed consent from any subject prior to obtaining IRB/EC/HREC approval and authorization from the sponsor, in writing, for the study.

If any action is taken by an IRB/EC/HREC, and regulatory requirements with respect to the trial, that information will be forwarded to SJM.

IRB/EC/HREC approval letter should clearly identify (where applicable, based on geography):

- Date of the meeting
- Duration of approval or expiration date of approval
- Approved version of the clinical protocol
- Approved version of the informed consent form and any other advertising or subject recruitment materials
- Approved version of the Instructions for Use (IFU)

Any amendments to the Clinical Investigation Plan (CIP) will be submitted to the FDA. Approval of the amendments shall be obtained in written form from the FDA and IRB/EC/HREC (or other, as applicable) prior to implementation.

8.2 Adherence to the Clinical Investigation Plan

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical trial according to the Clinical Investigational Plan, IRB/EC/HREC requirements or the Investigator Agreement. The

investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the CIP. Relevant information for each deviation will be documented on a Deviation eCRF. The site will submit the eCRF to SJM.

Regulations require investigators obtain approval from SJM and the IRB/EC/HREC (as required) before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the investigator's control, must be reported on an eCRF.

To obtain approval, the principal investigator may call or email and discuss the potential deviation with SJM or designee prior to initiating any changes. The Investigator will notify SJM and the reviewing IRB/EC/HREC within 5 working days of becoming aware of the event:

- Any deviation to protect the life or physical well-being of a subject in an emergency
- Any failure to obtain informed consent

Investigators or the designee must notify SJM as soon as possible, and complete a Deviation eCRF.

The Investigator is required to adhere to local regulatory requirements for reporting deviations to IRB/EC/HREC (or other, as applicable).

8.3 Repeated and Serious Non-Compliance

Protocol deviations will be collected and monitored by SJM for trending. In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the sponsor, a clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

9 ADVERSE EVENT, SERIOUS ADVERSE EVENTS, COMPLAINTS

9.1 Definitions

9.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under study. This definition includes events related to the investigational device or the comparator/control device, as well as events related to the procedures involved in the clinical protocol.

9.1.2 Serious Adverse Event (SAE)

A serious adverse event is an adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
 - A life-threatening illness or injury OR
 - A permanent impairment to a body structure or a body function OR
 - An in-patient (defined as >24 hours) or prolonged hospitalization OR
 - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
 - A malignant tumor
 - Fetal distress, fetal death, or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the clinical protocol, is not considered a serious adverse event.

9.1.3 Unanticipated Adverse Device Effects (UADE)

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.

If an unanticipated adverse device effect occurs in the United States, the investigator must notify SJM and the IRB/EC/HREC (or other, as required) immediately, but no later than 10 working days of the investigator's knowledge of the event, as required by 21 CFR §812.150. SJM will take the necessary steps to investigate the event, and will be responsible for notifying FDA and all other participating IRBs/ECs (or other, as required) and investigators.

9.2 Procedure for Recording and Reporting Adverse Events, Device Complaints, Serious

Adverse Events and Unanticipated Adverse Device Effects

Safety surveillance within this trial (and the safety reporting performed by the investigator), starts as soon as the subject is consented. For all subjects, adverse events will be collected from the time of informed consent. Safety surveillance and safety reporting will continue until the last study visit has been performed, or the subject is deceased, or the subject concludes participation in the trial. The following types of adverse event will be collected for all subjects:

- All serious adverse events
- All device and procedure-related adverse events
- Unanticipated adverse device effects

In particular, the following adverse events regardless of seriousness or relatedness will be collected:

- Bleeding events through 18 months
- Embolic events (e.g. stroke, TIA, systemic embolism) through 18 months

Investigators are responsible for promptly reporting adverse events to SJM by completing the Adverse Event eCRF. Serious adverse events and unanticipated adverse device effects need to be reported within 10 working days after the investigator first learns of the events.

Adverse events will be assessed by the investigator for relationship to the device and to the implant procedure. In the event that emergent reporting of an adverse event to the sponsor is necessary, clinical sites will complete an eCRF through the electronic database to report SAEs as soon as possible.

Additional information may be requested by the sponsor, when required, in order to support AE reporting to regulatory authorities.

The investigator must notify the IRB/EC/HREC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the sponsor.

9.3 Subject Death

All subject deaths are to be documented and reported to the sponsor within 10 days of becoming aware of the event. A Death eCRF should be completed and include additional information surrounding the death and cause of death. An autopsy may be requested for subjects with an investigational device. Corresponding source documentation (i.e. death certificate, autopsy results, etc.) will be requested, as appropriate.

9.4 Complaints

A complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. All complaints should be submitted [REDACTED]

In the event that the

complaint is not submitted [REDACTED] then the Clinical Adverse Event eCRF for an event which meets the definition of a complaint may be submitted via email to [REDACTED]

Any complaint on the Control device should be submitted to Boston Scientific and handled per Boston Scientific's complaint handling process.

10 RISKS AND BENEFITS

10.1 Description of Subject Population

The subject population will include participants that are ≥ 18 years old and diagnosed with non-valvular atrial fibrillation who are at high risk of stroke.

10.2 Anticipated Clinical Benefits

The potential benefit of LAA closure is that subjects may not need to be on long-term warfarin/other OAC therapy and thus will not be exposed to complications associated with long-term warfarin/other OAC therapy, particularly bleeding complications.

The potential benefit of participating in this clinical trial is close follow-up of the subject by their treating physicians. Potential benefits of the Amulet device (which are being assessed in this trial) are higher implant success rate, higher rate of device closure, lower rate of complications, and lower rate of stroke than the Control device. Future patients with non-valvular atrial fibrillation at high risk of stroke may benefit from the results of this clinical trial.

10.3 Anticipated Adverse Events

There are potential risks associated with the left atrial appendage occlusion procedure with the Amulet device as well as the commercially available Control device. The potential risks include but are not limited to, the following:

- Air embolus
- Allergic reaction to contrast dye or medications used in the trial
- Allergic reaction to the device implanted
- Anemia
- Anesthesia reaction
- Arrhythmia
- Atrial septal defect
- Bacterial endocarditis
- Bleeding
- Brachial plexus injury
- Bruising
- Cardiac arrest
- Cardiac perforation



- Cardiac tamponade
- Congestive heart failure
- Death
- Delivery system failure
- Device embolization
- Device migration
- Device thrombus
- Dyspepsia
- Embolic event
- Erosion
- Fever
- Foreign body embolization
- Gastrointestinal pain and/or bleeding
- Hypertension/hypotension
- Hypoventilation
- Infection
- Multi-organ failure
- Myocardial infarction
- Myocardial ischemia
- Perforation
- Pericardial effusion
- Peripheral thromboembolism
- Pleural effusion
- Renal failure/dysfunction
- Respiratory failure
- Respiratory insufficiency
- Seizure
- Sepsis
- Septicemia
- Significant residual flow
- ST elevation
- Stroke
- Systemic embolism
- Syncope
- Thrombophlebitis

- Thrombus formation
- Tissue damage
- Transient ischemic attack
- Valvular regurgitation/insufficiency
- Vascular access site injury
- Vessel trauma/injury

Refer to the Boston Scientific LAAC device labeling for risks associated with the Control device.

10.4 Risks Associated with Participation in the Clinical Study

Risks associated with participation in this clinical trial are no different from the risks associated with undergoing LAAC implant with a commercially available transcatheter device.

The risks associated with the Amulet device implant procedure are similar to those of other cardiac catheterization procedures. Radiation risks associated with the procedure are comparable to a diagnostic catheterization procedure.

The risks associated with the implanted Amulet device are similar to other implantable cardiac left atrial appendage occlusion devices.

10.5 Possible Interactions with Concomitant Medical Treatments and/or Concurrent Medical Interventions

The potential risks associated with blood thinning medicines (warfarin, other OACs, aspirin, and clopidogrel) include, but are not limited to: increased bleeding time, bleeding from the stomach or bowels, cranial bleed, drowsiness, dizziness, headache, heartburn, stomach pain, loss of appetite, nausea, vomiting, hives, rash, itching, bruising, swelling, fast heartbeat, chest pain, infection.

The potential risks associated with a transesophageal echocardiography (TEE/TOE) include, but are not limited to sore throat, bleeding, breathing or heart problems, gagging, vomiting, pain when swallowing, dental injury and damage or tear to esophagus.

The risks are no different from the risks associated with medications prescribed upon undergoing LAAC implant with a commercially available transcatheter device.

10.6 Steps to Control or Mitigate Risks

To minimize potential clinical risks to subjects participating in this clinical trial:

- This study will undergo review and approval by site Institutional Review Boards (IRBs) or Ethics Committees (ECs). The IRB/EC will review all study-related documents such as the protocol, informed consent form, and participant recruitment announcements.
- The FDA (and other competent authorities, as applicable) will review the protocol and informed consent form.

- Investigators will be selected based on their knowledge of, and experience treating patients with AF.
- Implanters will be trained on the Amulet and Control device and protocol.
- Investigators will be provided with the detailed instructions for use.
- A Clinical Events Committee (CEC) will review all adverse events as defined in the CEC charter (see Section 17.2).
- A Data and Safety Monitoring Board (DSMB) will advise the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial (see Section 17.3).

10.7 Risk-to-Benefit Rationale

Risks associated with participating in this clinical study are no different from risks associated with undergoing LAAC implant with a commercially available transcatheter device. The potential benefit of participating in this clinical study are close follow-up of the subject by their treating physicians. Potential benefits of the Amulet device are: higher implant success rate, higher rate of device closure, lower rate of complications and lower rate of stroke than the Watchman device. Future patients with non-valvular atrial fibrillation at high risk of stroke may benefit from the results of this clinical trial.

11 DATA MANAGEMENT

SJM will be responsible for data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

SJM respects and protects personally identifiable information collected and maintained for the trial. As part of our commitment, SJM is certified to the U.S. - European Union Framework Agreement regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed, and will be secured against unauthorized access.

Electronic eCRFs will be used in this trial, as noted below and in the Data Management Plan (DMP).

The principal investigator or institution will provide direct access to source data for monitoring, audits, IRB/EC/HREC review and regulatory authority inspections. As required, the principal investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical trial.

11.1 Data Management Plan

A Data Management Plan (DMP) will be established to ensure consistency of handling the study data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries.

CRF data will be captured in a secure validated electronic database management system hosted by SJM. Only authorized site personnel will be permitted to enter the data through the electronic data capture (EDC) system deployed by SJM. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.2 Document and Data Control

11.2.1 Traceability of Documents and Data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the eCRFs and in all required reports.

11.2.2 Recording Data

Source documents will be maintained by the investigational site team throughout the duration of the clinical trial. The data reported on the eCRFs will be derived from source documents. Discrepancies or inconsistencies in data between the eCRFs and source documents will be queried by SJM. Authorized site personnel will have the opportunity to explain the discrepancy via the Data Clarification Form (DCF/query) process in the database and/or via writing, as applicable.

12 MONITORING

It is the responsibility of SJM as the sponsor of the trial to ensure it is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the SJM Clinical Monitoring standard operating procedure.

Prior to beginning the trial, SJM will contact the investigator or designee to discuss the study and data requirements. An SJM monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for monitoring.

13 FDA INSPECTIONS

The investigator and/or delegate should contact SJM immediately upon notification of a FDA inspection at the site.

An investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the sponsor or IRB/EC/HREC have not been submitted or are incomplete, inaccurate, false or misleading.

14 STATISTICAL CONSIDERATIONS

The following section describes statistical methods for the clinical investigation and justification of the design. Additional details on statistical analyses, including sensitivity analyses, poolability analyses and analysis of descriptive endpoints, are maintained in a separate Statistical Analysis Plan (SAP).

14.1 Endpoints

14.1.1 Primary Safety Endpoint and Hypothesis

The primary safety endpoint is a composite endpoint of procedure-related complications, or all-cause death, or major bleeding (defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC) definition) through 12 months. The primary safety endpoint will be reported and analyzed based on event adjudication by the CEC. Let $p_1(\text{Amulet})$ be the probability of a primary safety endpoint event with the Amulet device, while $p_1(\text{Control})$ is the corresponding probability with the Control device. The following hypothesis will be tested:

$$H_0: p_1(\text{Amulet}) - p_1(\text{Control}) \geq \Delta_1$$

$$H_1: p_1(\text{Amulet}) - p_1(\text{Control}) < \Delta_1$$

where Δ_1 is the absolute value of the non-inferiority margin for the safety endpoint. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

14.1.2 Primary Effectiveness Endpoint and Hypothesis

The primary effectiveness endpoint is a composite endpoint of ischemic stroke or systemic embolism through 18 months. Let $p_2(\text{Amulet})$ be the probability of a subject experiencing a primary effectiveness endpoint event in the Amulet group, while $p_2(\text{Control})$ is the corresponding probability in the Control group. The following hypothesis will be tested:

$$H_0: p_2(\text{Amulet}) - p_2(\text{Control}) \geq \Delta_2$$

$$H_1: p_2(\text{Amulet}) - p_2(\text{Control}) < \Delta_2$$

where Δ_2 is the absolute value of the non-inferiority margin for the effectiveness endpoint.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

14.1.3 Primary Endpoint of Device Closure and Hypothesis

The primary endpoint of device closure is the device closure rate at the 45-day visit. Device closure is defined as residual jet around the device ≤ 5 mm, documented by TEE/TOE. Closure will be determined by Doppler flow and adjudicated by an independent Echocardiography Core Laboratory. Let $p_3(\text{Amulet})$ be the 45-day closure probability in the Amulet group, while $p_3(\text{Control})$ is the corresponding probability in the Control group. The following hypothesis will be tested:

$$H_0: p_3(\text{Amulet}) - p_3(\text{Control}) \leq -\Delta_3$$

$$H_1: p_3(\text{Amulet}) - p_3(\text{Control}) > -\Delta_3$$

where Δ_3 is the absolute value of the non-inferiority margin. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

14.1.4 Secondary Endpoints and Hypothesis

The following secondary endpoints will be tested if the above three primary endpoint non-inferiority hypotheses are met:

14.1.4.1 Composite endpoint of all stroke, systemic embolism, or cardiovascular/unexplained death through 18 months

The following hypothesis will be tested:

$$H_0: p_4(\text{Amulet}) - p_4(\text{Control}) \geq \Delta_4$$

$$H_1: p_4(\text{Amulet}) - p_4(\text{Control}) < \Delta_4$$

where $p_4(\text{Amulet})$ and $p_4(\text{Control})$ are the probabilities of subjects in the two groups experiencing a composite endpoint of all stroke, systemic embolism, or cardiovascular (CV)/unexplained death through 18 months and Δ_5 is the absolute value of the non-inferiority margin. [REDACTED]

14.1.4.2 Major Bleeding through 18 months

The following hypothesis will be tested:

$$H_0: p_5(\text{Amulet}) - p_5(\text{Control}) \geq 0$$

$$H_1: p_5(\text{Amulet}) - p_5(\text{Control}) < 0$$

where $p_5(\text{Amulet})$ and $p_5(\text{Control})$ are the 18-month major bleeding probabilities in the two groups [REDACTED]

[REDACTED] Major bleeding is defined as Type 3 or greater based on the BARC definition. [REDACTED]

14.1.4.3 Superiority test of the primary safety endpoint

If non-inferiority of safety of Amulet over control is demonstrated, a reflex test for superiority will be performed to determine if the Amulet device is superior to the Control device. The hypothesis is as follows:

$$H_0: p_1(\text{Amulet}) - p_1(\text{Control}) \geq 0$$

$$H_1: p_1(\text{Amulet}) - p_1(\text{Control}) < 0$$

The hypothesis will be tested at the 2.5% significance level. [REDACTED]

14.1.4.4 Superiority test of the primary effectiveness endpoint

If non-inferiority of effectiveness of Amulet over Control is demonstrated, a reflex test for superiority will be performed to determine if the Amulet device is superior to the Control device. The hypothesis is as follows:

$$H_0: p_2(\text{Amulet}) - p_2(\text{Control}) \geq 0$$

$$H_1: p_2(\text{Amulet}) - p_2(\text{Control}) < 0$$

The hypothesis will be tested at the 2.5% significance level. [REDACTED]

14.1.4.5 Superiority test of device closure rate at the 45-day visit

If non-inferiority of device closure endpoint of Amulet over control is demonstrated, a reflex test for superiority will be performed to determine if the Amulet device is superior to the Control device. The following hypothesis will be tested:

$$H_0: p_3(\text{Amulet}) - p_3(\text{Control}) \leq 0$$

$$H_1: p_3(\text{Amulet}) - p_3(\text{Control}) > 0$$



The hypothesis will be tested at the 2.5% significance level.

[Redacted text block]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

15 ECONOMIC AND QUALITY OF LIFE ANALYSIS

In conjunction with the clinical trial, resource utilization and quality of life data will be collected and compared among the Amulet and Control device recipients using descriptive statistics. The economic and quality of life analysis will be fully integrated into the clinical trial.

16 DOCUMENT RETENTION

Principal investigators will maintain the clinical study documents as required by SJM and applicable regulatory requirements. They will take measures to prevent accidental or premature destruction of these documents. The principal investigator may transfer custody of records to another person/party and document the transfer at the investigational site.

[REDACTED]

The principal investigator must ensure the availability of source documents from which the information on the case report forms was derived.

17 STUDY COMMITTEES

17.1 Steering Committee

A Steering Committee (SC), composed of medical practitioners who are experts in the field of atrial fibrillation, interventional cardiology, neurology, and/or LAA Occlusion, will be appointed by SJM. Specific responsibilities of the members will depend upon the consulting expertise needed by SJM. The SC will advise SJM on trial design, trial conduct, analysis, and reporting of trial results (including publications), as outlined in the SC charter.

17.2 Clinical Event Committee

The Clinical Event Committee (CEC) is a physician group who will review and adjudicate adverse events that occur during the trial, specifically those pertaining to the primary and secondary endpoints. The CEC will be blinded to the treatment group. With respect to review and adjudication of neurological events, events will be captured on the AE and Stroke/TIA assessment eCRFs and will include the NIHSS, mRS, and Barthel index scores (collected at both the time of event and 90 days after the event). Source documentation related to the event will be collected, including brain and echo imaging, for complete review by the CEC. Membership, roles, and responsibilities are defined in the CEC charter.

17.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be utilized to advise the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DSMB members will not be investigators in the trial.

At any time during the trial, the DSMB may offer opinions or provide formal recommendations concerning aspects of the study that impact subject safety (e.g., safety-related changes or input regarding study-related adverse event rates). An agreed-upon charter between both SJM and the DSMB members will govern the roles and responsibility of this committee.

17.4 Echocardiography Core Lab

An independent Echocardiography Core Laboratory will be utilized to analyze echo imaging, as required, during the trial. Echoes performed during and after the implant procedure, or as necessary and at the request of SJM, will be uploaded to a web-based platform and reviewed by the core lab. Members of the Echocardiography Core Lab will have no affiliation with the Amulet IDE Clinical Trial.

18 INVESTIGATION SUSPENSION OR TERMINATION

18.1 Premature Termination

The sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.

If for any reason SJM suspends or prematurely terminates the trial at an individual investigational site, SJM will inform the responsible regulatory authority, as appropriate, and ensure that the IRB/EC/HREC are notified, either by the principal investigator or by SJM. If the suspension or premature termination was in the interest of safety, SJM will inform all other principal investigators.

If suspension or premature termination occurs, SJM will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical study, and the principal investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

18.2 Study Conclusion

The study will be concluded when:

- All sites are closed AND
- The final report generated by SJM has been provided to sites or SJM has provided formal documentation of study closure

19 PUBLICATION POLICY

A Publication Agreement will be signed between the principal investigator and the sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

The investigator or site may not publish any information that the sponsor believes to be confidential information. The publication of the initial results of the Amulet IDE trial shall be subject to the review and release of sponsor's publication committee, which shall confer with the site regarding such publication.

Publication guidelines will be followed according to the International Committee of Medical Journal Editors (ICMJE). Upon receiving IDE approval from the FDA, this clinical trial will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, regardless of trial results, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act. If this clinical trial is terminated early, SJM will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

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Appendix A: Abbreviations

Select or add abbreviations used

Abbreviation	Term
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ACP	AMPLATZER™ Cardiac Plug
AE	Adverse Event
AF	Atrial Fibrillation
ASA	Atrial Septal Aneurysm
ASD	Atrial Septal Defect
BARC	Bleeding Academic Research Consortium
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CE	Conformité Européenne
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CIP	Clinical Investigational Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CT	Computed Tomography
DFU	Directions for Use
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EP	Electrophysiology
FDA	Food and Drug Administration
GP	General Practitioner
HREC	Human Research Ethics Committee
IB	Investigator Brochure
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LA	Left Atrium
LAA	Left Atrial Appendage
LAAC	Left Atrial Appendage Closure
LAO	Left Atrial Appendage Occlusion
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NA	Not Applicable
NIHSS	National Institute of Health Stroke Scale
NOAC	Novel Oral Anticoagulant
NSAID	Non-Steroidal Anti Inflammatory Drug

NVAF	Non Valvular Atrial Fibrillation
NYHA	New York Heart Association Classification
OAC	Oral Anticoagulation
PAS	Post-Approval Study
PET	Polyethylene Terephthalate
PFO	Patent Foramen Ovale
PI	Principal Investigator
PMA	Pre-Market Approval
RNT	Randomized Not Treated
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SE	Systemic Embolism
SJM	St. Jude Medical
TEE/TOE	Transesophageal echocardiography
TIA	Transient Ischemic Attack
UCB	Upper Confidence Bound
US	United States
UADE	Unanticipated Adverse Device Effect
WMA	World Medical Association

Appendix B: List of Clinical Investigation Sites, EC/IRB/HRECs

[REDACTED]

Appendix C: Declaration of Helsinki

This clinical investigation will be conducted under the guidance of the current Declaration of Helsinki, which can be found at the following website:

<http://www.wma.net/en/20activities/10ethics/10helsinki/>.

Appendix D: Informed Consent Form Template

[REDACTED]

Appendix E: Report of Priors

[REDACTED]

[REDACTED]

[REDACTED]

Appendix F: Amulet Product Labeling/Instructions for Use (IFU)
[REDACTED]

Appendix G: Physician Training Plan

[REDACTED]

Appendix H: Case Report Forms

[REDACTED]

Appendix I: Modified Rankin Scale

Subject Identifier: _____

Rater Name: _____

Date: _____

Score	Description _____
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0-6): _____**Comments:**

Appendix J: The Barthel Index
[REDACTED]

Appendix K: CHADS₂ score & CHA₂DS₂-VASc score

The CHADS₂ scoring system criteria is specified below:

CHA₂DS	Score
Congestive heart failure	1
Hypertension	1
Age \geq 75	1
Diabetes mellitus	1
Stroke/TIA	2

The CHA₂DS₂-VASc scoring system criteria is specified below:

CHA₂DS₂-VASc	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age \geq 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior myocardial infarction, peripheral artery disease or aortic plaque]	1
Age 65-74	1
Sex category [i.e. female gender]	1

Appendix L: HAS-BLED score

The HAS-BLED scoring system criteria is specified below:

HAS-BLED	Score
Hypertension history (uncontrolled, > 160 mmHg systolic)	1
Abnormal renal function/renal disease (dialysis transplant, creatinine > 2.6 mg/dL or > 200µmol/L)	1
Liver disease (cirrhosis, bilirubin > 2x normal AST/ALT/AP > 3x normal)	1
Stroke history	1
Bleeding, anemia, or predisposition to bleeding	1
Labile INR (Unstable/high INRs, or poor time (< 60% time in therapeutic range))	1
Elderly - Age \geq 65 years	1
Drugs - Medication usage predisposing to bleeding (antiplatelet agents, NSAIDs)	1
Alcohol usage history (> 8 drinks/week)	1

Appendix M: Bleeding Academic Research Consortium Definitions (BARC)⁵²

All bleeding events will be classified according to the BARC definitions.

Bleeding

Classified as Type 0 – 5 according to the following BARC definitions

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 (minor): 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 (major):

Type 3a:

- Any transfusion with overt bleeding
- Overt bleeding plus a hemoglobin drop of ≥ 3 to < 5 g/dL (provided hemoglobin drop is related to 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 drugs

Type 3c:

- Intracranial hemorrhage including subdural hemorrhages (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: Coronary artery bypass graft (CABG)–related bleeding:

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding

- Transfusion of ≥ 5 units whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output ≥ 2 L within a 24-hour period

Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will not be classified as a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e. within a 48-hour timeframe) but does not meet type 4 severity criteria, it will not be classified as a bleeding event.

Type 5: Fatal bleeding

Fatal bleeding is bleeding that directly causes death with no other explainable cause.

BARC fatal bleeding is categorized as either definite or probable as follows:

Type 5a:

Probably fatal bleeding: bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging

Type 5b:

Definite fatal bleeding: bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc.] or imaging) or confirmed on autopsy

The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.

Bleeding Academic Research Consortium (BARC) indicates fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory but again would not be classified as fatal bleeding.

Appendix N: Echo Acquisition Protocol
[REDACTED]

Appendix O: Additional Definitions

- **Technical success:** Exclusion of the LAA with no device-related complications and no leak >5mm on color Doppler TEE⁵³
- **Procedural success:** Technical success with no procedure-related complications, except for uncomplicated (minor) device embolization⁵³
- **Device success:** Device deployed and implanted in correct position⁵³
- **Device-related complication:** Adverse events which are adjudicated as device-related and require either an invasive surgical or percutaneous intervention. Examples of device-related complications may include embolization requiring percutaneous/surgical intervention, pericardial effusion or cardiac tamponade requiring pericardiocentesis or surgery, device-related infection, etc.
- **Procedural complication:** Adverse events which are adjudicated as procedure-related and require either an invasive surgical or percutaneous intervention. Examples of procedural complications may include embolization requiring percutaneous/surgical intervention, pericardial effusion or cardiac tamponade requiring pericardiocentesis or surgery, etc.
- **Major vascular complication:**⁵⁴
 - Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm
 - 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
 - Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage
 - The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment
 - Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram
 - Surgery for access site-related nerve injury
 - Permanent access site-related nerve injury

- **Stroke:**⁵³ An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. The event classifies as a stroke rather than a TIA based on any of the following:
 - Duration of neurological dysfunction >24 h[ours]
 - Duration of neurological dysfunction <24 h[ours] in case of imaging-documented new hemorrhage or infarction
 - A neurological dysfunction resulting in death
- **TIA:**⁵³ Any neurological dysfunction not satisfying the above criteria for stroke, specifically if lasting ,24 hours without imaging-documented acute brain infarction
- **Systemic embolism:**⁵³ 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.
- **AF classification**⁵⁵
 - **Paroxysmal AF** – AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency.
 - **Persistent AF** – Continuous AF >7 days in duration
 - **Permanent AF** – AF that cannot be corrected. The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.

Appendix P: QVSFS