Percutaneous alternative to the Maze procedure for the treatment of persistent or long-standing persistent atrial fibrillation (aMAZE trial): Rationale and design

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Background Pulmonary vein antrum isolation (PVI) as a treatment of paroxysmal atrial fibrillation (AF) is associated with a high rate of success; however, outcomes for treating persistent and long-standing persistent AF with PVI alone are substantially lower and often require multiple procedures to maintain long-term freedom from atrial arrhythmias. Foci and/or substrate outside the pulmonary veins, particularly in the left atrial appendage (LAA), has been identified as a key mechanism in the maintenance of persistent AF and long-standing persistent AF.

Objective The goals of the study are to evaluate the safety and effectiveness of the LARIAT System to percutaneously isolate and ligate the LAA and to determine if LAA ligation as adjunctive therapy to PVI improves maintenance of sinus rhythm in patients with persistent and long-standing persistent AF.

Study Design The trial is a prospective, multicenter, randomized controlled study. The trial design incorporates a Bayesian adaptive design that will randomize a maximum of 600 patients with persistent or long-standing persistent AF to LAA ligation and PVI vs PVI alone in a 2:1 randomization. The primary end points include 30-day safety of the LARIAT procedure and freedom from documented AF, atrial flutter, or atrial tachycardia of more than 30 seconds at 12 months after the PVI off antarrhythmic drugs. Key secondary outcomes include a composite of cardiovascular death and stroke, as well as quality of life.

Conclusion The aMAZE trial will determine if LAA ligation as adjunctive therapy to PVI increases the efficacy of maintaining sinus rhythm in patients with persistent and long-standing persistent AF. (Am Heart J 2015;170:1184-94.)

Catheter ablation as a treatment of paroxysmal AF is associated with a high rate of success, in excess of 70%. However, outcomes for treating persistent and long-standing AF with pulmonary vein antrum isolation (PVI) even after multiple procedures are substantially lower and usually less than 50% in maintain long-term freedom from atrial arrhythmias. The inability to effectively treat persistent AF has challenged cardiovascular surgeons and cardiac electrophysiologists to improve both surgical and catheter ablation approaches that provides a cure for persistent and long-standing persistent AF with an acceptable risk/benefit profile.

According to the Heart Rhythm Society Consensus Statement, the Cox-Maze III procedure is the criterion standard for nonpharmacologic treatment of AF. A key component of the Cox-Maze procedure is the exclusion of the left atrial appendage (LAA). Exclusion of the LAA is thought to eliminate a source of thrombus formation, lead to left atrial debulking, and eliminate focal and/or reentrant triggers arising from within and around the LAA. Although a high rate of maintaining sinus rhythm (SR) with a low incidence of stroke has been reported with the Cox-Maze procedure, few surgical maze procedures are performed due to the complexity...
and morbidity of the surgery. Even a multicenter minimally invasive surgical Maze study that demonstrated improved efficacy rates of maintaining SR compared with catheter-based PVI was associated with a considerably greater number of procedural-related adverse events compared with catheter ablation (23.0% vs 5.2%).

Electrical isolation of the pulmonary veins (PVs) is central to catheter ablation strategies for AF. However, there is no consensus regarding the optimal ablation approach for patients with persistent and long-standing persistent AF. Pulmonary vein antrum isolation plus ablation of complex fractionated electrograms and/or linear ablation lines have been advocated. The benefit of additional substrate modification in addition to PVI has been questioned with the results of the STAR AF II trial that demonstrated that PVI alone trended toward better efficacy rates of recurrence of atrial arrhythmias compared with PVI plus complex fractionated electrogram ablation or PVI and linear lines.

The objective of the aMAZE trial is to evaluate the safety and effectiveness of the LARIAT+ Suture Delivery System (Sentre HEART, Redwood City, CA) to percutaneously isolate and ligate the LAA from the LA as an adjunctive therapy to planned catheter ablation in the treatment for subjects with symptomatic persistent or long-standing persistent AF. The aMAZE trial will aim to demonstrate the ability of the LARIAT+ Suture Delivery System to (1) percutaneously isolate and ligate the LAA from the left atrium (LA) as an adjunct to planned PVI catheter ablation in the treatment for subjects with symptomatic persistent or long-standing persistent atrial fibrillation (AF); (2) demonstrate that the adjunctive percutaneous LAA ligation procedure does not result in an unacceptable risk of serious adverse events (SAEs) in these persistent or long-standing persistent AF subjects for whom a catheter ablation procedure is planned; and (3) assess freedom from episodes of AF, atrial flutter, or atrial tachycardia (AF/AFL/AT) >30-second duration during the observation period through 12 months after PVI.

**Rationale for the aMAZE trial**

The aMAZE trial will test the hypothesis that LAA exclusion will lead to increased efficacy of PVI in maintaining SR in patients with persistent and long-standing persistent AF. The ability to exclude the LAA with the LARIAT system is the first step in developing a percutaneous alternative to the Cox-Maze surgical procedure. Compared with other substrate modification strategies, excluding the LAA eliminates triggers arising from the LAA and eliminates the primary source of thrombus formation in patients with AF, thus hopefully leading to restoration and maintenance of SR and protection from embolic events.

Foci and/or substrate outside the PVs, particularly in the LAA, has been identified as a key mechanism in the maintenance of persistent AF. Left atrial appendage electrical isolation improves the clinical success in ablating persistent AF, but the thromboembolic risk of the residual electrically inert appendage is a concern. Endocardial and epicardial approaches to occlude or exclude the LAA have been explored in an effort to mitigate this mechanical standstill phenomenon. Endocardial device implants result in mechanical exclusion of the LAA; however, they do not achieve electrical isolation of the LAA. Left atrial appendage exclusion via the epicardial approach has been shown to result in a permanent transmural lesion, achieving both mechanical and electrical isolation of the LAA.

Left atrial appendage ligation allows for more extensive ablation of the left lateral ridge. This may lead to disruption of epicardial structures as the ligament of Marshall and autonomic ganglia plexi that lie between the LAA and LA within 3 mm from the endocardial surface. Interruption of the ligament of Marshall and autonomic nerve bundles may result in improved AF ablation outcomes. A decrease in AF burden occurs after LAA ligation. Badhwar et al demonstrated the feasibility and safety in 20 patients who underwent sequential LAA occlusion with the LARIAT followed by PVI. Left atrial appendage ligation as an adjunctive procedure to catheter ablation did not add significant risk to the ablation procedure. At 3 months, 68.4% of patients were in SR, and at 6 months, 75% were in SR. Left atrial appendage ligation also produced left atrial electrical remodeling with a reduction in dispersion. Lakkireddy et al compared patients undergoing LAA ligation and PVI to a matched group of patients who underwent PVI only. The combined LAA ligation and PVI resulted in a significant reduction of AF recurrence at 12 months. These studies suggest that there may be an additive effect of LAA isolation on the results of PVI in patients with persistent and long-standing persistent AF.

**Trial design**

This study is a Food and Drug Administration–approved, multicenter, prospective, randomized (2:1) controlled trial with an adaptive sample size designed to evaluate the safety and effectiveness of the LARIAT Suture Delivery System to percutaneously isolate and ligate the LAA from the LA as an adjunct to planned PVI catheter ablation in the treatment of symptomatic persistent or long-standing persistent AF (ClinicalTrials.gov, Registration No. NCT02513797).

The randomization schedule will be masked to the study subjects, site personnel, and sponsor. Randomization will be performed by the study statistician or designee using a computerized random number generator which will generate the randomization schedules for all strata in advance considering center, persistent vs long-standing persistent AF, and LA volume Index greater or less than 32 ml/m². Only the unmasked statistician and
Table I. Inclusion and exclusion criteria

### Inclusion criteria

1. Subjects must meet all of the following criteria to be eligible for the study:
2. Age $\geq 18$ and $\leq 80$ years at the time of screening
3. Documented diagnosis of symptomatic persistent or persistent long-standing nonvalvular AF
4. Persistent AF is defined as AF sustained for $\geq 7$ d and $\leq 1$ y
5. Long-standing persistent AF is defined as continuous AF $>1$-year duration
6. Failed at least one class I or III antiarrhythmic drugs
7. Life expectancy $\geq 1$ y
8. Willing and able to return to and comply with scheduled follow-up visits and testing
9. Willing and able to provide written informed consent

### Exclusion criteria

1. Subjects will be excluded if he/she meets any of the following:
2. Prior procedure involving opening of the pericardium or entering the pericardial space (eg, CABG, heart transplantation, and valve surgery) where adhesions are suspected
3. Prior epicardial or endocardial AF ablation procedure
4. Measured LA diameter $>6$ cm
5. Documented embolic stroke, TIA or suspected neurologic event within 3 mo prior to the planned intervention
6. Currently exhibits NYHA class IV heart failure symptoms
7. Documented history or right heart failure specifically when right ventricle exceeds the left ventricular size
8. Documented history of myocardial infarction within 3 mo prior to the planned study intervention
9. Documented history of unstable angina within 3 mo prior to the planned study intervention
10. Recent documented history of cardiogenic shock, hemodynamic instability, or any medical condition in which intra-aortic balloon pump therapy is clinically indicated
11. Documented symptomatic carotid disease, defined as $>70\%$ stenosis or $>50\%$ stenosis with symptoms
12. Diagnosed active local or systemic infection, septicemia, or fever of unknown origin at time of baseline screening
13. Chronic renal insufficiency defined as eGFR $<30$ mL/min per 1.73 m$^2$ within 3 mo prior to study treatment
14. End-stage renal disease or documented history of renal replacement/dialysis
15. Current documented history of clinically significant liver disease which predisposes the subject to significant bleeding risk (clinically defined by the treating physician)
16. Any history or thoracic radiation with the exception of localized radiation treatment of breast cancer
17. Current documented use of long-term treatment with corticoid steroids, not including use of inhaled steroids for respiratory diseases
18. Active pericarditis
19. Active endocarditis
20. Any documented history or autoimmune disease associated with pericarditis
21. Evidence of pectus excavatum (documented and clinically defined by the treating physician)
22. Untreated severe scoliosis (documented and clinically defined by treating physician)
23. Thrombocytopenia (platelet count $<100 \times 10^9/L$) based on most recent preprocedure assessment within 30 d prior to planned intervention
24. Anemia with hemoglobin concentration of $<8$ g/dL based on most recent preprocedure assessment (within 30 d prior to planned intervention)
25. Left ventricular ejection fraction $<30\%$ within 30 d prior to planned intervention
26. Known acquired or inherited propensity for forming blood clots (eg, malignancy and factor V Leiden mutation) established by prior objective testing
27. Documented presence of implanted congenital defect closure devices, (eg, ASD, PFO, or VSD device)
28. Previously attempted occlusion of the LAA (by any surgical or percutaneous method)
29. Inability, unwillingness, or contraindication to undergo TEE imaging
30. Body mass index $>40$ kg/m$^2$
31. Evidence of active Graves disease
32. Current untreated hypothyroidism

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designates will be privy to the masked randomization scheme.

Primary objectives
To demonstrate that adjunctive percutaneous LAA ligation to PVI as compared with the PVI alone significantly increases the freedom from episodes of persistent AF, AT, and AFL >30-second duration at 12 months after PVI. In addition, the primary safety end point in a noninferiority test against a performance criterion will be determined.

Secondary objectives
Secondary objectives will include the composite end point of cardiovascular death and stroke, as well as quality of life. Efficacy of LAA closure will also be evaluated.

Staged trial design
This trial will be conducted in 2 stages: limited, early stage (stage 1, up to 175 subjects) followed by a pivotal stage (stage 2, up to 600 subjects). All patients from both stages will be included in the primary analysis. After 100 patients are enrolled, an interim data review will be conducted and provided to the data safety monitoring committee (DSMC) for review. Enrollment will continue uninterrupted to a maximum of 175 subjects during this period of stage 1 analysis and review. To minimize operational bias, review of stage 1 results will be limited to individuals not involved in study operations.

The trial will proceed to stage 2 (pivotal) if the 30-day primary safety end point rate at this interim point did not exceed the predetermined performance goal for safety, and the DSMC review of overall safety and performance of the product suggests no significant safety or performance issues and that continuation on to stage 2 is warranted.

Study population
Adults aged ≥18 years and ≤80 years at the time of screening with a documented diagnosis of symptomatic persistent or persistent long-standing nonvalvular AF will be considered for inclusion in this trial. Subjects will be considered eligible for screening at the time written informed consent is obtained and will be assigned a subject ID in the electronic data capture system. Subjects who sign the informed consent form but are found ineligible during the screening process will be considered screen failures. Subjects who are deemed to be ineligible during the screening process will be considered screen failures. Subjects who are deemed to be eligible for screening will sign the informed consent for enrollment into the trial. Subjects will be considered enrolled at the time the enrollment consent is signed. Inclusion and exclusion criteria are listed in Table I.

### Table I. (continued)

| 33. | Any contraindication to suture, endovascular device, or other minimally invasive techniques including percutaneous, transseptal, and/or subxiphoid access |
| 34. | Subject is pregnant or plans/desires to get pregnant within the next 12 mo |
| 35. | Current enrollment in an investigation or study of an investigational device or investigational drug that would interfere with this study and the required follow-up |
| 36. | Mental impairment or other psychiatric conditions which may not allow patient to understand the nature, significance, and scope of the study |
| 37. | Any other criteria, medical illness, or comorbidity which would make the subject unsuitable to participate in this study as determined by the clinical site primary investigator |

Additional exclusion criteria: based on screening/preprocedure imaging

1. Subjects will also be excluded if they meet any of the following:
2. Based on screening computed tomography angiography performed within 90 d prior to study intervention as confirmed by the imaging core laboratory
3. LAA morphology: superior-posterior oriented LAA (ie, superior C shape) that has
   a. LAA LARIAT approach width >40 mm or
   b. LAA distal apex extending posterior to the ostium of the LAA
4. LAA positioned behind the pulmonary artery; or
5. All other LAA morphology: LAA LARIAT approach width >45 mm
6. Based on a periprocedural imaging (TEE at time of LARIAT or catheter ablation) as confirmed by institution’s designated LARIAT echocardiographer:
7. Intracardiac thrombus or
8. Significant mitral valve stenosis (ie, MV stenosis < 1.5 cm²)

Abbreviations: CABG, Coronary artery bypass grafting; TIA, transient ischemic attack; NYHA, New York Heart Association; IV, intravenous; eGFR, estimated glomerular filtration rate; ASD, atrial septal defect; PFO, patent foramen ovale; VSD, ventricular septal defect; MV, mitral valve.
### Table II. Medication regimen guideline recommendations

**LARIAT: Preprocedure**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Subjects may remain on prescribed dose; no need to discontinue</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Discontinue at least 7 d prior to scheduled LARIAT intervention. Exceptions are patients that have drug eluding stents For any subjects who may be currently taking OAC therapy:</td>
</tr>
<tr>
<td></td>
<td>• Discontinue within 5 d of the scheduled LARIAT procedure (ie, day 6) o Timing of discontinuation is based on the biological half-life (36-42 h) and the observed time for the PT/INR to return to normal after discontinuation • This discontinuation schedule will produce a period of several days with subtherapeutic anticoagulation. Thus, for these subjects at high thromboembolic risk, bridging may be appropriate (see bridging guidance below).</td>
</tr>
<tr>
<td>Oral anticoagulation therapy</td>
<td>If any one of the NOACs (dabigatran, rivaroxaban, apixaban):</td>
</tr>
<tr>
<td></td>
<td>• Discontinue within 2 d of the scheduled LARIAT procedure • The rapid offset and onset of NOAC activity obviate the need for bridging anticoagulation in most subjects; however, bridging may be appropriate for selected individuals at the discretion of the treating physician (see bridging guidance below).</td>
</tr>
<tr>
<td></td>
<td>Bridging anticoagulation Low-molecular-weight heparin or enoxaparin are the agents most commonly used for bridging anticoagulation. IV heparin should be off 6 h prior to LARIAT. Lovenox may be associated with increased bleeding and should be discontinued night before LARIAT procedure. Bridging can be used preoperatively, postoperatively or both depending on the underlying condition for which the patient is being anticoagulated. Timing depends on the agent used and the procedural bleeding risk. Resumption of bridging anticoagulation too early is associated with an increased risk for major bleeding.</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Colchicine has been found to be beneficial in reducing pain associated with pericarditis and the prevention of Dressler syndrome.</td>
</tr>
<tr>
<td></td>
<td>• Administration of colchicine at a dose of 0.6 mg BID for a period of 1 to 3 d prior to the scheduled LARIAT procedure is OPTIONAL • 0.6 mg/d (Halved dosage) is recommended for subjects weighing &lt;70 kg or who may be intolerant to the higher dose • Discontinue per treating physician’s discretion should patient experience gastrointestinal disturbance</td>
</tr>
</tbody>
</table>

**LARIAT: Intraprocedure**

| IV heparin | Target ACT of >250 s prior to any left atrial maneuvers |

**LARIAT: Postprocedure**

| Colchicine | Colchicine should be initiated after LARIAT procedure at a dosage of 0.6 mg BID for a minimum of 4 wks |
|           | • 0.6 mg/d (Halved dosage) is recommended for subjects weighing <70 kg or who may be intolerant to the higher dose |
|           | • Discontinue or decreasing the dose of colchicine per treating physician’s discretion should patient experience gastrointestinal disturbance |
| Acetaminophen (Tylenol) | • IV acetaminophen is recommended for pain management, particularly related to the pericardial drainage catheter. |
|           | • 1 g intravenously should be administered immediately after intervention and every 8 h after the procedure for 3 doses |
|           | • Maximum dosage: 1 g; 4 times daily |

**Optional agents**

| Opiates | Pain control may vary greatly from patient to patient. Opiates (ie, morphine) may be administered at treating physician’s discretion. |
|         | • NSAIDs may be added to the colchicine administration per the discretion of the treating physician and if patient’s renal function is normal. |
|         | • NSAIDs should not be initiated within the first 24 h after the LARIAT procedure. |
|         | • IV toradol (Is this also contraindicated in first 24 h) loaded 1-2 d before the initiation of oral NSAIDs may be beneficial. Any patient with renal insufficiency should not have toradol or other NSAIDs. |
| NSAIDs | Oral corticosteroids should be considered at the discretion of the treating physician if pericarditis persists for ≥7 d or with evidence of pericardial/pleural effusions. |
| Oral corticosteroids | The rate of thrombus formation reported to date after LAA ligation has been low and the true incidence, although unknown, is anticipated to be consistent with the risk of AF subjects taking coumadin therapy. |
| Thrombus prevention | Oral anticoagulants Keeping in mind preintervention bridging instructions stated above, OAC may be initiated on postoperative day 1 if there is <50 cc drainage per 8 h period. |
| ASA | ASA therapy (81 or 325 mg) should continue indefinitely, unless documented evidence shows that the risks of ASA therapy outweigh the risks of thromboembolism (should be discontinued if OAC therapy initiated). |
| Clopidogrel (Plavix) | DAPT with ASA plus clopidogrel is recommended for a minimum of 30 d after LARIAT procedure (should be discontinued if OAC therapy initiated). |

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Percutaneous suture ligation of LAA

The LARIAT+ device for exclusion of the LAA consists of 3 components: (1) a 15-mm compliant occlusion balloon catheter (EndoCATH), (2) 0.025- and 0.035-in. magnet-tipped guidewires (FindrWIRZ), and (3) a 12-F suture delivery device (LARIAT).19 The procedure has been previously described.19,20 Briefly, the procedure involves 4 basic steps: (1) pericardial and transseptal access, (2) placement of the endocardial magnet-tipped guidewire in the apex of the LAA with balloon identification of the LAA os, (3) connection of the epicardial and endocardial magnet-tipped guidewires for stabilization of the LAA, and (4) snare capture of the LAA with closure confirmation and release of the pre-tied suture for LAA ligation.

Post-LARIAT index procedure medication regimen

To protect subjects from complications such as bleeding or thromboembolic events and to mitigate against inflammation, recommended medications and dosages are provided in Table II, Medication Regimen Guideline Recommendations. Investigators may use their institutional procedures for anticoagulation/antiplatelet therapy, in recognition of various types of oral anticoagulants available as well as individual patient factors such as CHADS2 or CHA2DS2-VASc score.

Ablation protocol

Patients on warfarin will continue their oral anticoagulant (OAC) therapy. Patients taking one of the newer OAC agents will stop it the night before the PVI. The PVI will consist of a wide antrum circumferential ablation of the left and right PVs using a contact force irrigated radiofrequency energy as previously described.23 Briefly, a heparin bolus and infusion will be initiated to maintain an activated clotting time (ACT) of greater than 350. A 3-dimensional electroanatomic endocardial voltage map of the LA will be obtained with the ESI 3D mapping system (St Jude Medical Endocardial Solutions Inc, St. Paul, MN) or with the Biosense Webster Carto system (Biosense Webster, Diamond Bar, CA). Pulmonary vein antrum isolation will be performed using a contact force Smart Touch ablation catheter (Biosense Webster, Inc) or the TactiCath (St Jude Medical Endocardial Solutions Inc). After at least 30 minutes after the last energy delivery to a given PV, postablation mapping to confirm electrical isolation will be performed. A spiral catheter will be placed in each of the veins to assure complete PV isolation as demonstrated by lack of PV potential or dissociation of the PV potential with atrial electrograms and the inability to capture the left atrium when pacing circumferentially at 10 mA at 2 milliseconds within each PV. Adenosine will be administered to rule out "dormant" PV potentials.33 Acute PVI success will be defined as the ability to achieve SR with cardioversion and the demonstration of both entrance and exit block within all PVs.

Although additional substrate modification of the LA with ablation of complex fractionated atrial electrograms and/or addition of linear ablation lines has been advocated, the procedural method of catheter ablation in the aMAZE trial will be limited to only PVI. In limiting the ablation protocol to only PVI, the trial will have a consistent ablation lesion pattern and defined ablation end points of entrance and exit block from the PVs. Therefore, any efficacy benefit seen in the LAA ligation and PVI group can be attributed solely to exclusion of the LAA. The recent results of the STAR AF trial also suggest that PVI alone is a reasonable ablation strategy for the prevention of recurrence of atrial arrhythmias in patients with persistent AF.16

At the completion of the PVI, a right-sided cavo-tricuspid isthmus ablation will be performed. Conformation of cavo-tricuspid isthmus ablation will be verified by the demonstration of bidirectional block across the isthmus line.
Monitoring of the recurrence of AF

After a blanking period of 90 days after PVI, all antiarrhythmic drugs will be discontinued. Early recurrences of AF/AFL/AT within the first 3 months will not be classified as a treatment failure. Patients will be followed up as shown in Figure. Irrespective of symptoms, a 24-hour Holter will be performed at 6 and 12 months after PVI to detect recurrence of AF/AFL/AT. Subjects with symptoms reported after the 90-day blanking period will undergo event monitoring for assessment of atrial dysrhythmias.
Adaptive sample size design overview

The study design incorporates an adaptive sample size or “Goldilocks” design.54 Multiple interim analyses are performed with 1 of 3 decisions possible at each interim: (a) stop the study for futility, (b) stop accrual for predicted success then follow all subjects to their 12-month outcomes, and (c) continue to enroll subjects. Bayesian predictive probabilities of trial success are used for making interim decisions regarding both the primary efficacy and primary safety analyses.35 These predictive probability calculations account for observed data (efficacy, safety, and missing data patterns) and the number of patients without primary end point outcomes. For patients without 12-month outcomes but at least 6 months of follow-up, the predictive probabilities use the observed relationship between the 6- and 12-month outcomes to better predict trial success. Specific details regarding these Bayesian predictive probability calculations are beyond the scope of this article.

Interim analyses are planned after 100 subjects are enrolled and 67 LARIAT subjects have complete safety data (futility stopping only based on safety end point) and then when a total of 400, 450, 500, and 550 subjects have been enrolled. If the enrollment is not stopped at any of these points, enrollment will continue to the maximum predetermined maximum sample size of 600 subjects. A key attribute of the Goldilocks design is that although the final sample size may be 400, 450, 500, 550, or 600, there is only one (final) analysis for evaluating the primary efficacy and safety end points. This analysis occurs 12 months after the last patient is enrolled, provided that the study has not stopped for futility. This strategy ensures that even with early stopping of accrual, that all subjects provide complete safety and 12-month efficacy end points (if no dropouts).

Statistical analysis plan

Primary effectiveness end point

Freedom from episodes of AF > 30 seconds at 12 months after PVI was defined as follows: (1) no evidence of any episode of AF/AT/AFL >30-second duration, as documented by 24-hour Holter monitoring at any time after the 90-day blanking period after index PVI at 6 or 12 months or symptomatic atrial arrhythmias detected by event monitoring; (2) no additional catheter ablation procedures after index PVI (aside from ablation for right-sided AFL); and (3) no requirement for new class I or III antiarrhythmic drugs prescribed to treat AF after day 120 (90-day blanking period +30-day window).

The primary effectiveness end point for the LARIAT + PVI study is the 12-month rate of freedom from AF (\(p_L\)), which is estimated using Bayesian posterior distributions. The rate will be estimated in each treatment arm assuming that the number of AF-free subjects (\(x_L\)) out of the total number of subjects randomized to LARIAT + PVI (\(n_L\)) come from a binomial distribution, and the rate from a uniform beta prior distribution, producing a beta posterior distribution.

\[
x_L \sim \text{Binomial}(n_L, p_L) \\
p_L \sim \text{Beta}(1, 1) \\
p_L|x_L, n_L \sim \text{Beta}(1 + x_L, 1 + n_L - x_L)
\]

An analogous posterior distribution is calculated for the control group, the PVI-only arm:

\[
P_C|x_C, n_C \sim \text{Beta}(1 + x_C, 1 + n_C - x_C).
\]

Once these posterior distributions are obtained, the posterior probability distributions for the probability LARIAT + PVI offer a superior AF-free rate that will be calculated,

\[
\text{Pr}(p_L > p_C|x_L, n_L, x_C, n_C).
\]

The superiority criterion will be considered met if this probability exceeds \(C_E = 0.977\) (the critical value for efficacy). The 95% Bayesian posterior credible interval for the difference will also be calculated.

In addition to this superiority criterion, for the study to be considered successful, the lower bound of the 95% Bayesian posterior credible interval of \(p_L\) must be greater than or equal to 0.20, the predefined minimum performance threshold for efficacy.

Primary safety end point

The primary safety end point, incidence of significant device, or procedure-related SAEs at 30 days after LAA ligation in the LARIAT + PVI arm will be compared with an objective performance criterion.

The number of significant device or procedure-related SAEs at 30 days after LAA ligation, \(E_L\), in the total number of subjects in whom a LARIAT procedure is initiated \(n_L^*\) is used to calculate the safety end point rate assuming the safety event rate \(q_L\).

\[
q_L \sim \text{Beta}(0.5, 0.5).
\]

Therefore, the posterior distribution of \(q_L\) given the observed data is

\[
q_L|x_L^*, AE_L \sim \text{Beta}(0.5 + AE_L, 0.5 + n_L^* - AE_L)
\]

For the a priori-determined objective performance criteria, we will calculate the posterior probability

\[
\text{Pr}(q_L < 0.10 | n_L^*, AE_L).
\]

If this probability is greater than \(C_S = 0.957\), the safety end point will be considered met.
Sample size calculations/assumptions

The study is powered for a 15% absolute difference in primary effectiveness end point rates between treatment and control. For the primary safety end point, the study is designed to demonstrate the observed primary safety end point rate in the LARIAT arm is less than the prespecified performance goal of 10% (expected rate of 6% plus margin of 4%). The performance goal of 10% is clinically justifiable as demonstration that the rate of primary safety end point events is confidently below 10% ensures that the procedure has less major morbidity than the surgical Cox-Maze procedure historically used to treat persistent AF in subjects with stand-alone AF.

The study is considered a success if both the efficacy and safety criteria are met. Simulations are used to assess the power and type I error under a variety of scenarios and assumptions (regarding accrual, true safety/efficacy rates, 6-month and 12-month AF-free relationships, correlation between safety and efficacy outcomes, dropout rate, etc). The design has a type I error less than or equal to 0.025 for all null efficacy scenarios considered and less than or equal to 0.05 for all null safety scenarios considered. Power depends on the true AF-free effect size and true safety rates, but in general, effect sizes greater than or equal to 0.15 provide between 0.75 and 1.0 power when the treatment is safe. Details and results of the simulation study are beyond the scope of this article.

A minimum of 400 subjects allows for at least 267 treatment group subjects enrolled with approximately 250 available for assessment of the primary safety end point and at least 225 treatment group subjects enrolled with approximately 1-year follow-up for assessment of the primary effectiveness end point.

Analysis populations

The intention-to-treat population will consist of all enrolled subjects who are randomized. This population will be used as a secondary analysis population for the primary safety and effectiveness end points.

The modified intention-to-treat analysis set will consist of all randomized subjects who have undergone an attempt at the randomized procedure (LARIAT or PVI catheter ablation). The analyses of the primary study end points, all safety end points, and the technical success end point will be conducted using the modified intention-to-treat population.

The as-treated analysis set will consist of all randomized subjects who complete the PVI ablation procedure and (if randomized to treatment) have successful placement of the LARIAT device. This population will be used as a secondary analysis population for the primary safety and effectiveness end points and as the primary analysis for all secondary effectiveness end points.

The per-protocol population will consist of treated subjects who do not have a major protocol deviation and who do not have a missing end point assessment. This population will be used as a secondary analysis population for the primary safety and effectiveness end points.

Trial organization

The aMAZE trial will be funded by SentreHeart, Inc, but will not be actively involved in the management of the trial or data interpretation. A clinical research organization will independently collect all data, manage the database, and analyze the data in a restricted-access database. Independent groups of noninvestigator physicians will comprise the clinical events committee and DSMC. The clinical events committee will be responsible for the review and validation of reported potential safety end point events and all other device/procedure related SAEs that occur over the course of the study. The DSMC will establish a charter including a mission statement, operating procedures, and proposed monitoring criteria for the study, including any required interim analysis time points for assessing safety and proposed study stopping rules. The specific stopping rules shall remain confidential to the site and sponsor personnel in direct contact with sites to minimize bias. Third party core laboratories for echocardiography and computed tomographic imaging will be used to analyze and render reports for the imaging. A core laboratory with cardiac electrophysiology expertise will analyze and adjudicate all Holter monitoring and transtelephonic monitor transmissions for arrhythmia end point analysis. Statistical analysis will be managed by independent statisticians (Berry Consultants).

Any investigator receiving consultation fees and/or equity by the sponsor, SentreHEART, will not participate in the trial including but not limited to recruitment of patients, collection of data, analysis of data, and interpretation of the results. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. No extramural funding was used to support this work.

Conclusions

The aMAZE trial is a multicenter, prospective, randomized controlled trial designed to evaluate the safety of the LARIAT Suture Delivery System to percutaneously ligate the LAA from the LA and as an adjunct to planned PVI catheter ablation to increase effectiveness in maintaining SR in the treatment of symptomatic persistent or long-standing persistent AF. The ability to exclude the LAA with the LARIAT system is the first step in developing a percutaneous alternative to the Cox-Maze surgical procedure. The trial will investigate whether excluding the LAA eliminates triggers arising from the LAA and eliminates the primary source of thrombus formation in patients with AF, thus hopefully leading to restoration and maintenance of SR and protection from embolic
events in patients with persistent and long-standing persistent AF.

Disclosures
R.J. Lee is a consultant and equity holder in SentreHEART, Inc. Drs Ellis and Mattel are consultants to SentreHEART, Inc.

References

