Study Design of the CLOSURE I Trial

A Prospective, Multicenter, Randomized, Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex Septal Closure System Versus Best Medical Therapy in Patients With Stroke or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale

Anthony J. Furlan, MD; Mark Reisman, MD; Joseph Massaro, PhD; Laura Mauri, MD, MSc; Harold Adams, MD; Gregory W. Albers, MD; Robert Felberg, MD; Howard Herrmann, MD; Saibal Kar, MD; Michael Landzberg, MD; Albert Raizner, MD; Lawrence Wechsler, MD; for the CLOSURE I Investigators

Background and Purpose—Some strokes of unknown etiology may be the result of a paradoxical embolism traversing through a nonfused foramen ovale (patent foramen ovale [PFO]). The utility of percutaneously placed devices for treatment of patients with cryptogenic stroke or transient ischemic attack (TIA) and PFO is unknown. In addition, there are no clear data about the utility of medical interventions or other surgical procedures in this situation. Despite limited data, many patients are being treated with PFO closure devices. Thus, there is a strong need for clinical trials that test the potential efficacy of PFO occlusive devices in this situation. To address this gap in medical knowledge, we designed the CLOSURE I trial, a randomized, clinical trial comparing the use of a percutaneously placed PFO occlusive device and best medical therapy versus best medical therapy alone for prevention of recurrent ischemic neurologic symptoms among persons with TIA or ischemic stroke.

Study Design—This prospective, multicenter, randomized, controlled trial has finished enrollment. Two-year follow-up for all 910 patients is required. The primary end point is the 2-year incidence of stroke or TIA, all-cause mortality for the first 30 days, and neurologic mortality from 31 days of follow-up, as adjudicated by a panel of physicians who are unaware of treatment allocation. This article describes the rationale and study design of CLOSURE I.

Conclusions—This trial should provide information as to whether the STARFlex septal closure system is safe and more effective than best medical therapy alone in preventing recurrent stroke/TIA and mortality in patients with PFO and whether the STARFlex septal closure device can demonstrate superiority compared with best medical therapy alone.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00201461.

(Stroke. 2010;41:2872-2883.)

Key Words: patent foramen ovale ■ cryptogenic stroke ■ atrial septal closure ■ right-to-left shunt ■ percutaneous closure
The annual rate of recurrent transient ischemic attack (TIA) or stroke in patients with PFO being treated with medical therapy varies from 3.8% to 12%.

The best medical therapy (BMT) for stroke prevention in patients with PFO is unknown. The American Academy of Neurology guidelines for prevention of secondary stroke associated with PFO currently recommend therapy with daily aspirin. However, this recommendation reflects the absence of definitive evidence that warfarin is beneficial for preventing stroke in patients with PFO. As well, certain subgroups may warrant warfarin, including patients with acute deep vein thrombosis and pulmonary embolism.

There has never been a randomized trial of BMT for secondary stroke prevention in patients with PFO. Although warfarin has been the traditional medical therapy for secondary stroke prevention in patients with PFO, the Patent Foramen Ovale in Cryptogenic Stroke Study found no significant difference in the 2-year recurrent stroke and TIA rate between patients being treated with aspirin versus warfarin. Notably, the Patent Foramen Ovale in Cryptogenic Stroke Study was a substudy of the Warfarin versus Aspirin Recurrent Stroke Study and was not powered to address the issue of BMT for PFO. In addition, patients up to age 85 were eligible for inclusion in the Warfarin versus Aspirin Recurrent Stroke Study, and the mean age of those with PFO was 58. Warfarin therapy must be monitored and carries an increased risk of bleeding, which can be a significant concern in many patients with PFO. There are essentially no data on the efficacy of clopidogrel or aspirin plus extended-release dipyridamole for secondary stroke prevention in PFO.

Surgical closure of PFO is well established, but there are conflicting reports concerning its safety and efficacy. The recurrence rates after surgical closure are widely variable, but an ≈4% per year recurrence of stroke or TIA is reported. In most centers, surgical therapy for PFO (including robotic surgery) has been supplanted by percutaneous endovascular closure. Case series suggest that the annual TIA or stroke recurrence rate after percutaneous PFO closure has been consistently <5%. The benefits of percutaneous PFO closure include avoidance of open-heart surgery and, usually, long-term anticoagulation. Pain after an implant procedure is significantly less than after surgery, general anesthesia is avoided, the hospital stay is usually overnight, and the recovery time is minimal because only venous access is needed. Major complications from percutaneous intervention occur in ≈1.5% of patients and include embolization of the device from the septum, malapposition of the device, trigger of arrhythmias, infection, and cardiac perforation and erosion at the site of device implantation.

The STARFlex septal closure system (STARFlex) represents the next generation of the CardioSEAL device and was not commercially available at the onset of the CLOSURE I trial. STARFlex is a catheter-delivered, flexible, cardiovascular implant device designed to close atrium-level defects and thus, stop shunting. The device has 2 opposed “clamshell” disklike occluders, each having an umbrella shape joined by an interconnecting point. STARFlex is delivered to the defect and is deployed with 1 occluder on each side of the PFO. For this indication, the product is available in 3 sizes (23, 28, and 33 mm).

Several devices designed for PFO closure are undergoing clinical trials, but no device has received US Food and Drug Administration (FDA) premarket approval for this indication. The prior humanitarian device exemption for PFO closure was voluntarily withdrawn in October 2006. Nonetheless, off-label percutaneous closure of PFOs is widely available, with the use of occlusion devices designed and approved for either atrial or ventricular septal defects. CLOSURE I is the first completed (enrollment), randomized, controlled trial comparing the safety and efficacy of percutaneous PFO closure plus medical therapy versus BMT alone for secondary TIA and stroke prevention in patients with PFO. The purpose of this article is to describe the CLOSURE I trial methodology.

**Study Objective**

The primary objective of CLOSURE I is to determine whether percutaneous PFO closure with STARFlex in combination with medical therapy is superior to medical therapy alone for the prevention of recurrent TIA, stroke, and mortality in patients with cryptogenic TIA or stroke and a PFO.

**Study Overview**

CLOSURE I is a prospective, multicenter, randomized, open-label, 2-arm superiority trial. The original end point was the 2-year rate of TIA, stroke, or death. Recruitment into PFO trials has proven notoriously difficult owing to a variety of factors, including off-label device use. Based on a conservative estimate of the expected event rate (6%) from the literature available before 2003, CLOSURE I was originally designed to enroll 1600 patients. However, after 4 years (2003–2006), CLOSURE I had recruited only 611 patients. Recruitment feasibility was discussed with the FDA in March 2007. Various options were considered with the FDA, including combining data from different ongoing, randomized trials. The Executive Committee asked the Harvard Clinical Research Institute (HCRI) to investigate the effect of a reduced sample size on the statistical power of the trial. The HCRI determined that a sample size of 800 would provide sufficient power to determine a significant risk reduction between BMT and the device arm from 6% to 2%. A revised expected event rate of 2% in the device arm (as opposed to an event rate of 3% for the original design) was considered realistic, based on a literature meta-analysis not available when the study was initially designed. In April 2007, the FDA approved a proposed revision to the statistical plan that decreased the sample size from 1600 to 800 patients on the basis of an expected event rate of 6% in the BMT arm and 2% in the device arm. This decision was not based on any examination of the data; no end point data were inspected before this decision was made. A prespecified and FDA-approved interim analysis was performed by the Data Safety Monitoring Board (DSMB) at 33% of the original enrollment point (600 patients). The purpose of this analysis was to assess whether interim results indicated that the revised final sample size of 800 would yield sufficient power for a significant trial and, if not, to increase the sample size. As a
result of this interim analysis, the DSMB recommended increasing the sample size to 900.

Patients with cryptogenic TIA or stroke within 6 months and a PFO were screened for study eligibility under the direction of a treating neurologist. To be included, a PFO must have been documented by transesophageal echocardiography (TEE) amenable to percutaneous closure with STARFlex. Transcranial Doppler was not required by the protocol. In addition, no planned valvuloplasties, coil occlusion procedures, pacemakers, or placement of permanent intracardiac devices could be performed during the index procedure. Clinical follow-up for all patients was performed at 1 month (telephone call) and at 6, 12, and 24 months after the procedure/first dose.

Before commencement of the study and before any device supplies were shipped to the investigator, the investigator must have provided the sponsor (NMT Medical Inc) written documentation of the investigational review board approval of both the protocol and the patient informed-consent form, which must have complied with all requirements outlined by the sponsor and the study protocol.

Definitions of TIA and Stroke
CLOSURE I adopted the modernized, imaging-based definition of ischemic stroke as one of the components of its primary end point.\(^4\) Ischemic stroke was defined as an acute, focal neurologic event that showed evidence of corresponding tissue injury on brain imaging.\(^4\) The modernized definition of TIA is an acute, focal neurologic event of <24 hours’ duration with negative evidence of acute ischemic brain injury on imaging, preferably diffusion-weighted magnetic resonance.\(^4\) In the absence of diffusion-weighted magnetic resonance imaging, a sudden, focal event lasting <24 hours would still be classified as a TIA.

CLOSURE I included TIA as a primary end point component because, on the basis of a literature review, it was estimated that the sample size required would be impossible to attain if stroke were the sole primary end point. However, to improve diagnostic accuracy, CLOSURE I used a very limited definition for TIA. For the purposes of both study entry and primary end point, a definite TIA was defined as a sudden, focal neurologic event lasting at least 10 minutes without evidence of acute ischemic brain injury on diffusion-weighted magnetic resonance imaging and consisting of hemiplegia/paresis, monoplegia/paresis, quadriplegia/paresis, language disturbance other than isolated slurred speech, blindness in 1 or both eyes, or significant difficulty walking. Dysarthria, vertigo, sensory symptoms, confusion, memory loss, syncope, lightheadedness, and diplopia in isolation were not accepted as evidence for TIA. Atypical symptoms such as a marching evolution, positive phenomena such as visual scintillations, or prominent unilateral throbbing headache suggesting migraine were characterized as “transient neurologic events of unknown etiology” and were not considered TIA. Such events were considered secondary end points.

The diagnosis of either definite TIA or stroke was made by a board-certified study neurologist at each study site and required blinded adjudication by the Clinical Events Committee completely independent of the trial and the sponsor.

The Clinical Events Committee is chaired by a board-certified vascular neurologist and includes participation of board-certified invasive and noninvasive cardiologists and neurologists who are not study participants.

Inclusion and Exclusion Criteria
The study population includes patients with a documented, definite TIA or stroke and a PFO, with or without ASA, within 6 months of randomization and in the absence of other potential causes of TIA or stroke (Table 1). Major exclusion criteria include a potential source of TIA or stroke other than PFO, including atherosclerosis and other cardiac disease; hypercoagulability requiring treatment with warfarin; and a known hypersensitivity or contraindication to warfarin, aspirin, or clopidogrel. Patients meeting all inclusion criteria and no exclusion criteria were approached regarding the trial and asked to sign an investigational review board–approved informed-consent form. Only after the informed-consent form was signed were patients eligible for randomization.

Changes in the Event-to-Randomization Window and Enrollment of Patients With Laboratory Hypercoagulation Abnormalities
A review of study screening logs indicated that the 3-month event-to-randomization window had caused many candidates to be excluded from study enrollment. To increase recruitment, the event-to-randomization window was increased from 3 to 6 months. The FDA approved this protocol change on June 1, 2004, and it was incorporated in version 4 of the protocol in June 8, 2004. As a point of reference, 79 patients had been enrolled at the end of May 2004. This decision was supported by a detailed literature review of the timing of recurrent events.\(^4\) In the study by Mas and Zuber,\(^6\) the risk of recurrent TIA or stroke among patients with PFO remained high throughout a 4-year follow-up. After 4 years, the risk of recurrent stroke or TIA was 5.6% among patients with PFO alone and 19.2% among patients with both PFO and ASA. Although the rate was slightly higher in the first 6 months, the majority of recurrent cerebrovascular events occurred beyond this time.\(^1\)

Elevations of hypercoagulation parameters such as anticardiolipin antibodies are common in patients with PFO. However, hospital laboratories define the clinical significance of these abnormalities differently. The Executive Committee recommended that modest abnormalities in hypercoagulation tests (as defined by the local hospital laboratory), which in the judgment of the local investigator did not warrant long-term warfarin and were of uncertain clinical significance, should not be an exclusion criterion. In addition, the protocol was clarified to state that patients were excluded if warfarin therapy was thought to be required for hypercoagulopathy or other indication, such as acute deep vein thrombosis or pulmonary embolism. This protocol change was approved by the FDA on June 1, 2004, and was incorporated in version 4 of the protocol on June 8, 2004 (the Figure).

Randomization and Stratification
Patients were randomized (1:1) to 1 of the 2 treatment arms: STARFlex plus medical therapy or medical therapy only, by
### Table 1. Study Inclusion and Exclusion Criteria

**Inclusion Criteria:** Candidates will be included in the study only if ALL the following conditions are met:

**Before randomization**
1. The patient is ≥18 years of age and ≤60 years of age.
2. Patients must have a positive contrast Valsalva bubble study by TEE, demonstrating right-to-left shunting through the PFO during the Valsalva maneuver. An ASA may or may not be identified.
3. Patients must be available for follow-up in accordance with the protocol.
4. Patients must be able to provide informed consent, or if unable, a legal guardian must provide informed consent.
5. The vascular access from the femoral vein is expected to accommodate the 10F delivery system.
6. Critical cardiac structures are not expected to come in contact with the device (e.g., atrioventricular valves and pulmonary veins). (It is recommended that the device be ~1 mm from the structure.)
7. The risks and benefits of both treatments have been fully explained to the patient by the neurologist.
8. Patients must have discontinued use of hormonal contraceptives before enrollment in the study and agree to avoid future use during the entire study period. (Hormone replacement therapy use is allowed if NOT being used for contraception purposes.)
9. Stroke or definite clinical TIA within 6 months without other identifiable cause.
10. A patient presenting with a definite clinical TIA meeting the following criteria: patients experience a sudden, focal neurologic event lasting at least 10 minutes without evidence of acute ischemic brain injury on diffusion-weighted magnetic resonance imaging, with symptoms consisting of hemiplegia/paresis, monoplegia/paresis, quadruplegia/paresis, language disturbance other than isolated slurred speech, blindness in 1 or both eyes, or significant difficulty walking. Dysarthria, vertigo, sensory symptoms, confusion, memory loss, syncope, lightheadedness, or diplopia will not be accepted in isolation. Such symptoms must be accompanied by focal weakness or combinations of multiple symptoms localizable to the anterior or posterior circulation to be accepted as TIs. Atypical symptoms such as a marching evolution, positive phenomena such as visual scintillations, or prominent unilateral throbbing headache suggesting migraine will be characterized as “transient neurologic events of unknown etiology” and will NOT be called TIs.

**After randomization (device patients only)**
1. The size of the PFO (measured by indentation with a soft balloon) must be amenable to selection of a STARFlex device as described in the instructions for use.

**Exclusion Criteria:** Candidates will be excluded from the study if ANY of the following conditions are present:

1. A contrast Valsalva bubble study demonstrating no shunting from right to left through the PFO.
2. There is a potential source of embolic stroke or TIA other than the PFO, including but not limited to:
   - Carotid artery stenosis >50% (or less if stenosis is ulcerated or associated with thrombus).
   - >50% intracranial stenosis appropriate to the patient’s symptoms.
   - Complex aortic arch atheroma exhibiting high-risk features for embolism.
   - Aortic arch, carotid artery, or vertebral artery dissection.
   - Severe mitral valve stenosis.
   - Severe aortic stenosis.
   - Mitral or aortic valve vegetations.
   - Mitral or aortic valve calcified annulus, classified as a >5-mm mitral annulus calcification thickness.
   - Prosthetic heart valves in any location.
   - Left ventricular ejection fraction <30% by echocardiography or ventriculography.
   - Left ventricular aneurysm.
   - Recent anterior wall myocardial infarction within the 3-month period preceding the neurologic event.
   - Chronic atrial fibrillation, paroxysmal atrial fibrillation, or flutter defined as a history of ≥2 documented episodes lasting >30 seconds each and unrelated to a reversible cause, such as acute myocardial infarction, cardiac surgery, myocarditis, hyperthyroidism, or acute pulmonary disease. Patients meeting this definition will be excluded regardless of persistent or paroxysmal nature of the arrhythmia.*
3. Based on echocardiographic assessment, a large, redundant ASA that cannot, in the judgment of the investigator, be covered by the STARFlex device without (1) causing the device to interfere with other intracardiac structures or (2) prohibiting the ability of the operator to adequately deploy the distal/proximal arms in the left/right atrium prior to final placement on the septum.
4. Congenital cardiac defects not repaired before enrollment, including:
   - Atrial septal defect.
   - Ventricular septal defect.
   - Coarctation of the aorta.
   - Patent ductus arteriosus.
5. Thrombus in or occlusion of the venous lumen between the femoral vein access site (or superior access site, if used) and the right atrium.
6. A previously implanted atrial septal device.
7. Echocardiographic evidence of an intra-atrial or ventricular thrombus.

(Continued)
Table 1. Continued

8. History of recent (within the past 6 months) or current intravenous drug abuse.
9. Known active endocarditis or documented bacteremia.
10. Serum creatinine >2.0 mg/dL.
11. Active infections requiring current antibiotic therapy. (If temporary illness, patients may enroll after discontinuation of antibiotics, once asymptomatic for 4 weeks.)
12. Women with suspected or known pregnancy.
13. Known hypersensitivity or contraindication (ie, tissue plasminogen activator administration or any endovascular intervention for acute stroke within 7 days) to warfarin treatment.
14. A known contraindication to aspirin, heparin, or clopidogrel or sensitivity to contrast media that cannot be adequately premedicated.
15. Any medical condition (other than index stroke), such as acute deep vein thrombosis, requiring anticoagulation with warfarin.
16. A platelet count <100 000 cells/mm³ or >700 000 cells/mm³, a white blood cell count <3000 cells/mm³, or a disorder of platelet function, such as thrombocytosis.
17. Any patient with a coagulopathy (ie, prothrombin G20210A, protein C, protein S, antithrombin III deficiency, factor V Leiden deficiency) if the patient requires long-term warfarin therapy as a result. These tests must be performed before randomization.
18. Patients with a moderate or high positive titer, as defined per study site, of antiphospholipid antibodies that would require long-term warfarin therapy as a result. Testing for antiphospholipid antibodies are to include, at a minimum, lupus anticoagulant and anticardiolipin antibodies. These tests must be performed before randomization.
19. Patients with known vasculitis or neurologic disorder that would interfere with interpretation or diagnosis of stroke or TIA, including systemic lupus erythematosus, giant-cell arteritis, or multiple sclerosis.
20. Patients unable to perform a satisfactory Valsalva maneuver.
21. Patients in whom TEE is contraindicated.
22. Active peptic ulcer or upper gastrointestinal bleeding within the prior 6 months.
23. Concurrent medical condition with a life expectancy of <24 months.
24. Currently participating in an investigational drug or another device study that has not completed the primary end point or that clinically interferes with the current study endpoints. (NOTE: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.)
25. The presence of a permanent pacemaker.
26. The presence of an inferior vena cava filter.
27. Hemodynamic conditions generally contraindicating closure of a PFO or any other right-to-left decompressive shunt (ie, normal right ventricular function and pulmonary valve replacement >10 indexed Wood units if right ventricular pressure is less than half of systemic pressure, or pulmonary valve replacement >8 indexed Wood units if right ventricular pressure is more than half of systemic pressure).
28. When echocardiography suggests moderate or greater tricuspid regurgitation.
29. Suspected/recognized cirrhosis or portal hypertension or known pulmonary arteriovenous malformation.
30. Baseline (within 1 month before randomization) Modified Rankin Score of 3 or more.

*As per American College of Cardiology/American Heart Association guidelines of atrial fibrillation terminology (J Am Coll Cardiol. 2006;48:854–906).

using an interactive voice-response system. Block randomization was performed with stratification by study site and by the presence or absence of an ASA viewed by TEE. Once a patient was randomized, he or she was considered to be enrolled in the study and was included in the primary analysis, according to the general intent-to-treat principle that all randomized patients are to be analyzed according to the groups to which they were initially randomized. Study treatment was considered to begin at the start of the device implant procedure for device patients and at first dosing for medical therapy patients.

Study Treatments

For patients randomized to the device arm, the STARFlex device was implanted via percutaneous intervention. The implant procedure was scheduled as soon as possible from the

Figure. Study flow diagram. mth indicates month.
A broad-spectrum IV antibiotic should be given during implantation, with at least 1 additional IV dose given 6 hours after implantation. Patients receiving a device should receive appropriate subacute bacterial endocarditis prophylaxis for 6 months after implantation. The decision to prescribe prophylactic treatment after 6 months for minor invasive procedures is subject to physician judgment.

Aspirin† (coated or uncoated) 325 or 81 mg PO within 24 hours before procedure

Clopidogrel 300 mg PO within 24–48 hours of procedure

Warfarin Should be stopped at least 24 hours before procedure

* A broad-spectrum IV antibiotic should be given during implantation, with at least 1 additional IV dose given 6 hours after implantation. Patients receiving a device should receive appropriate subacute bacterial endocarditis prophylaxis for 6 months after implantation. The decision to prescribe prophylactic treatment after 6 months for minor invasive procedures is subject to physician judgment.

† Aspirin at 81 mg is allowed only for well-documented gastrointestinal intolerance.

‡ Warfarin use before the procedure and during routine follow-up is not allowed.

point of randomization, preferably within 1 week. Either TEE or intracardiac echocardiography was used during placement of the device. Patients were medicated for the implant procedure in accordance with the standard of care at the hospital where the implant occurred. In the device arm, patients followed a standardized antiplatelet regimen of clopidogrel 75 mg daily for 6 months plus aspirin for the duration of the trial. Concomitant medications for the device arm are shown in Table 2.

Patients randomized to medical therapy were treated with 1 of the following medications throughout the duration of the study: (1) warfarin with a target International Normalized Ratio of 2.0 to 3.0 with an ideal target of 2.5; (2) aspirin 325 mg daily; (3) aspirin 81 mg daily only, allowed for documented gastrointestinal intolerance; or (4) aspirin 81 mg daily with warfarin. Clopidogrel, ticlopidine, and aspirin plus extended-release dipyridamole were not allowed in the medical arm.

Because there is no consensus on the most effective medical therapy in preventing recurrent ischemic events in these patients, the choice of aspirin or warfarin in the medical arm was left to the discretion of the site principal investigator. Crossover between any of the medical regimens was allowed, but documentation of the reason for change was required. Heparin was permitted during the initial warfarin treatment period to provide sufficient anticoagulation.

Migraine

When a patient had a history of migraine headaches, an optional migraine survey was completed at randomization and at study follow-up intervals. Questions on the migraine history survey included details of frequency and characteristics of migraine. As described earlier, every attempt was made to exclude migrainous neurologic events from randomization.

Core Laboratory Descriptions and Functions

The purpose of the core laboratories was to minimize study bias and to create consistency of interpretation completely independent of the sponsor. Three core laboratories were identified for this study: an echocardiography core laboratory (University of Pennsylvania), a chest x-ray core laboratory reader (Valerie Mandell, MD; Taylor Chung, MD), and a magnetic resonance imaging core laboratory (Perceptive Informatics). Data from these labs were transmitted to the HCRI, the data coordinating center, and were used by the independent Clinical Event Committee in adjudication of events.

Echocardiography

An initial TEE with contrast bubble study and Valsalva maneuver was performed to establish the diagnosis of PFO and to evaluate the patient for associated atrial sepal abnormalities, such as ASA. TEE or intracardiac echocardiography was required during implantation. Follow-up TEE was required at the 6-month follow-up visit. Follow-up TEE in those patients with residual leaks classified as grade II (moderate) or more after the 6-month visit was performed at each study-related follow-up visit until resolution. All TEEs were evaluated at the echocardiography core laboratory at the University of Pennsylvania completely independent of the sponsor.

The core laboratory classified PFOs on the basis of the appearance of bubbles in the left atrium either spontaneously or after provocative maneuver within 5 cardiac cycles after opacification of the right atrium: (1) None: No bubbles appearing in the left atrium on Valsalva maneuver. (2) Trace: The distinct appearance of between 1 and 10 bubbles in the left atrium either spontaneously or after provocative maneuver within 5 cardiac cycles. (3) Moderate: The distinct appearance of a moderate quantity (≥10 to 25) of bubbles in the left atrium, such that a distinct circumscribable section of the left atrial cavity can be described. (4) Substantial: The distinct appearance of a significant quantity (≥25 or more) of bubbles in the left atrium, with some of said bubbles reaching the contralateral left atrial wall, such that complete filling of the left atrial chamber can be described.

ASA was defined as an aneurysm associated with a PFO that had a mobility of 10 mm or greater total excursion of the septum. Effective closure (secondary end point) was defined as procedural success with a grade 0 (none) or 1 (trace)
International Normalized Ratio was monitored at least monthly by local coagulation laboratories for warfarin-treated patients in the medical arm.

**Study End Points**

The primary end point for CLOSURE I is the incidence of TIA, stroke, or mortality (all-cause mortality through the first 30 days of follow-up and neurologic mortality from 31 days through 2 years) up to 2 years after randomization. Secondary end points assessed per treatment group included major bleeding, all death, stroke, and transient neurologic events of uncertain etiology up to 2 years after randomization. Migraine headache frequency was assessed at each follow-up visit for those who participated in the optional migraine substudy. All end points occurring after randomization, before the end of the 2-year follow-up period for a given patient, and those reported to the data coordinating center database lock will be included in the primary and secondary efficacy analyses and the safety analyses (Tables 3 and 4).

**Statistical Considerations**

**Determination of Sample Size**

This randomized study was designed to determine the superiority of the STARFlex device over BMT with regard to the composite primary end point. Specifically, the formal statistical null and alternative hypotheses are as follows:

<table>
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<tr>
<th>End Point</th>
<th>CLOSURE I Definition</th>
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<tr>
<td>Stroke</td>
<td>Defined as an acute, focal neurologic event that is magnetic resonance imaging–positive, regardless of duration of clinical symptoms. (Note that during the course of the trial, in the rare event that imaging cannot be performed for confirmation of a stroke, stroke will be defined as a persistent, focal neurologic deficit lasting &gt;24 hours.)</td>
</tr>
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<td>TIA</td>
<td>Defined as a sudden, focal neurologic event lasting at least 10 minutes without evidence of acute ischemic brain injury on diffusion-weighted magnetic resonance imaging and consisting of hemiplegia/paresis, monoplegia/paresis, quadriplegia/paresis, language disturbance other than isolated slurred speech, blindness in 1 or both eyes, or significant difficulty walking. Dysarthria, vertigo, sensory symptoms, confusion, memory loss, syncope, lightheadedness, or diplopia will not be accepted in isolation. Such symptoms must be accompanied by focal weakness or combinations of multiple symptoms localizable to the anterior or posterior circulation to be accepted as TIA.s. Atypical symptoms such as a marching evolution, positive phenomena such as visual scintillations, or prominent unilateral throbbing headache suggesting migraine will be characterized as “transient neurologic events of unknown etiology” and will NOT be called TIA.s. Transient neurologic events of unknown etiology will be secondary end points.</td>
</tr>
<tr>
<td>Death</td>
<td>Divided into 3 categories</td>
</tr>
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<td></td>
<td>1. Neurologic death is defined as death related to acute ischemic or hemorrhagic stroke, either directly from increased intracranial pressure or indirectly from complications, including pneumonia/sepsis, pulmonary embolism, heart failure, cardiac arrhythmia, and myocardial infarction. These nonbrain causes of death will be adjudicated by the Clinical Events Committee as complications after a stroke.</td>
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<tr>
<td></td>
<td>2. Cardiac death is defined as death due to any of the following: Acute myocardial infarction. Cardiac perforation/pericardial tamponade. Arrhythmia or conduction abnormality. Stroke suspected of being directly related to the procedure. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery. Any death in which a cardiac cause cannot be excluded.</td>
</tr>
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<td></td>
<td>3. Other death is defined as a death not due to cardiac or neurologic causes (as defined above).</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Defined as the occurrence of intracranial, intraocular, or retroperitoneal hemorrhage or any hemorrhage requiring a transfusion or resulting in a hematocrit decrease of &gt;15% or a hemoglobin decrease of &gt;5 g/dL.</td>
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<td>Transient neurologic events of uncertain etiology</td>
<td>Defined as atypical symptoms, such as a marching evolution, positive phenomena such as visual scintillations, or prominent unilateral throbbing headache suggesting migraine will be characterized as “transient neurologic events of unknown etiology” and will NOT be called TIA.s.</td>
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Follow-Up visits were conducted under the supervision of a study neurologist for patients randomized to medical therapy. Follow-up visits for patients with a STARFlex device were conducted under the supervision of a study neurologist and interventional cardiologist. Follow-up visits to assess clinical end points and adverse events were planned for month 1 (at 23 to 37 days by telephone call), month 6 (150 to 210 days), month 12 (10 to 14 months), and month 24 (22 to 26 months). TEE and radiographic assessments occurred at the 6-month visit for patients randomized to the device arm only. The International Normalized Ratio was monitored at least

residual shunt on TEE. To evaluate effective closure, TEE was performed immediately after implantation, at the 6-month follow-up visit, and on subsequent follow-up visits at 12 and 24 months, if necessary, to evaluate persistent shunting. Owing to the materials comprising the implant (in particular, the knitted polyester fabric) and the healing process that occurs over time, patients may not attain effective closure status immediately after implantation. In addition, the echo core laboratory noted whether echocardiographic densities consistent with thrombus, fibrinous strands, or vegetation were seen on the device or surrounding areas of the interatrial septum.

**Table 3. Major Endpoint Definitions**

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<td>Death</td>
<td>Divided into 3 categories</td>
</tr>
<tr>
<td></td>
<td>1. Neurologic death is defined as death related to acute ischemic or hemorrhagic stroke, either directly from increased intracranial pressure or indirectly from complications, including pneumonia/sepsis, pulmonary embolism, heart failure, cardiac arrhythmia, and myocardial infarction. These nonbrain causes of death will be adjudicated by the Clinical Events Committee as complications after a stroke.</td>
</tr>
<tr>
<td></td>
<td>2. Cardiac death is defined as death due to any of the following: Acute myocardial infarction. Cardiac perforation/pericardial tamponade. Arrhythmia or conduction abnormality. Stroke suspected of being directly related to the procedure. Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery. Any death in which a cardiac cause cannot be excluded.</td>
</tr>
<tr>
<td></td>
<td>3. Other death is defined as a death not due to cardiac or neurologic causes (as defined above).</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Defined as the occurrence of intracranial, intraocular, or retroperitoneal hemorrhage or any hemorrhage requiring a transfusion or resulting in a hematocrit decrease of &gt;15% or a hemoglobin decrease of &gt;5 g/dL.</td>
</tr>
<tr>
<td>Transient neurologic events of uncertain etiology</td>
<td>Defined as atypical symptoms, such as a marching evolution, positive phenomena such as visual scintillations, or prominent unilateral throbbing headache suggesting migraine will be characterized as “transient neurologic events of unknown etiology” and will NOT be called TIA.s.</td>
</tr>
</tbody>
</table>

**Follow-Up**

Follow-up visits were conducted under the supervision of a study neurologist for patients randomized to medical therapy. Follow-up visits for patients with a STARFlex device were conducted under the supervision of a study neurologist and interventional cardiologist. Follow-up visits to assess clinical end points and adverse events were planned for month 1 (at 23 to 37 days by telephone call), month 6 (150 to 210 days), month 12 (10 to 14 months), and month 24 (22 to 26 months). TEE and radiographic assessments occurred at the 6-month visit for patients randomized to the device arm only. The International Normalized Ratio was monitored at least monthly by local coagulation laboratories for warfarin-treated patients in the medical arm.
where $\lambda$ is the hazard rate of the primary end point in the 2-year period.

The original protocol assumed that the incidence of the primary end point would be 6% for BMT\textsuperscript{3,6,8,11,13} patients and 3% for the patients receiving the STARFlex device (that is, the expected relative risk ratio of BMT to STARFlex would be 50%). Under this assumption and an expected loss to follow-up of 7% during 2 years for each treatment group, an evaluable sample size of 1600 patients (800 per randomized treatment) yielded $\approx 80\%$ power to declare the treatments significantly different at a 2-sided, 0.05 level of significance.

Owing to slow patient recruitment and new information in the literature on expected event rates with PFO device closure and after consultation with the FDA, in March 2007 the expected event rate in the device arm was revised to 2% (the expected rate in the BMT arm remained at 6%), and the sample size was reduced to 800. No endpoint data were inspected before this decision was made. These revised event-rate assumptions reduced the evaluable sample size from 1600 to 800 patients (400 per treatment group) at 80% power and a 2-sided significance level of 0.05, also accounting for the anticipated loss to follow-up. The 2-year lost-to-follow-up rate was reduced from 7% to 6% per group. The protocol was revised at this time, incorporating this new sample size. In April 2007, the FDA granted approval to the revised CLOSURE I statistical plan. Further details are discussed in the Statistical Methods section.

### DSMB, Planned Interim Analysis, and Independent Event Analysis

A fully independent, 4-member DSMB periodically reviews and evaluates the incidence of adverse events and can recommend stopping the study at any time for a safety concern. A planned, formal, interim, unblinded efficacy analysis was conducted in June 2007. The plan called for the
DSMB to inspect the probability value from a log-rank test comparing treatments with respect to the time to primary end point after \( \approx 8046 \) patient-months of follow-up were available (115 patients with 6 months of follow-up, an additional 235 patients with 12 months of follow-up, and an additional 189 patients with 24 months of follow-up) to determine whether the study should be stopped for extreme efficacy of either treatment group or for futility. If the study was not prematurely stopped and if the conditional power for obtaining a significant beneficial treatment effect of STARFlex was \(<80\%\), the plan called for the DSMB to recommend increasing the sample size per group for the final analysis to obtain a conditional power of at least \(80\%\) for the final analysis. The algorithm for assessing futility and for recalculating sample size was based on the sample size recalculation for a survival analysis algorithm discussed in Li et al.44,45

The aforementioned formal interim analysis was conducted in June 2007. At that time, the DSMB recommended increasing the total randomized sample size to 900 patients (450 per group). The details of the interim analysis and the reasons behind this recommendation are held by the DSMB and will not be disseminated to NMT Medical Inc or any personnel involved with the study until the final database is locked.

The last patient was enrolled in October 2008. With the consent of the FDA, a blinded statistical analysis reviewed by a committee independent of the study or the sponsor was performed in March 2009. The independent analysis concluded that the number and timing of primary outcome events was sufficient to provide at least \(80\%\) power to detect a statistically significant pre-protocol treatment effect if the analysis were performed on patient-follow-up available as of October 2009. The Executive Committee subsequently recommended to NMT Medical Inc to lock the database in April 2010 (that is, 6 months later than the event-driven independent statistical review recommendation). The primary purpose of this analysis is to provide results to the FDA to begin the premarket approval review process of the STARFlex device. All patients without 2 years of follow-up at this initial database lockup will continue to be followed up through 2 years, with a subsequent locking and analysis of the database in October 2010 to include all patients. Results of the analysis for this final database will be provided to the FDA before it completes its review of the premarket approval review; it is understood that final FDA approval of STARFlex rests on the results of the analysis on the final database.

Statistical Methods

For the primary analysis on the primary end point, the time to primary end point and rate of the primary end point (incidence of 24-month stroke or TIA; all-cause mortality for the first 30 days of follow-up or hospital discharge, whichever is longer; and neurologic mortality from \( \geq 31 \) days of follow-up) will be compared between treatments according to the techniques described next at an overall 2-sided 0.05 level of significance. (The significance level for the treatment comparison on the primary end point is spread across the planned unblinded interim analysis and the final analysis by the methodology of Li et al.44: 0.00464 at the interim and 0.04659 at the final analysis.) For the aforementioned analyses, a statistically significant STARFlex effect will be declared when the 2-sided probability value is \( \leq 0.04659 \) (to account for the interim analysis as discussed previously) and the primary end point rates are in the appropriate direction.

The primary analysis population will be on the intent-to-treat analysis set (all randomized patients); patients will be analyzed according to the treatment to which they were randomized. Secondary analyses populations are the (1) per-protocol (that is, evaluable) analysis set, defined as all randomized patients who received the treatment to which they were randomized, who had no major inclusion/exclusion criteria violations, and who had a follow-up of at least 22 months; and (2) the modified intent-to-treat analysis set, defined as all randomized patients who received a study treatment and who had no major inclusion/exclusion criteria violations, regardless of length of follow-up. The major inclusion/exclusion criteria violations were no PFO or no prior TIA or stroke.

To account for missing primary end point data owing to nonneurologic death after 31 days or premature withdrawal from the study before achieving an end point or before the 24-month follow-up period, the following imputation approaches will be carried out: (1) Available data imputation (incidence analysis), whereby only patients who achieved the primary end point or who had at least 22 months of follow-up (the earliest allowable time point for the 2-year follow-up visit) are included in the denominator of the primary end point rates. The treatment comparison on primary end point rate will be performed by logistic regression. (2) Available data imputation (survival analysis), whereby all randomized patients who did not achieve the primary end point will be censored at the 24-month time point or at the date of the last known follow-up, whichever is earlier. Treatment comparisons will be performed by the log-rank test and Cox proportional-hazards regression. (3) Multiple imputation. Patients with missing primary end point result because of premature withdrawal from the study will have their outcome imputed (yes/no) with the logistic-regression, multiple-imputation approach by using SAS PROC MI, whereby the imputation-model covariates include randomized treatment and clinically relevant demographic characteristics. A total of 5 imputed data sets will be generated, and treatment comparisons on the primary end point will be performed on each imputed data set by logistic regression. Results will be compiled across the 5 imputed data sets by using SAS PROC MIANALYZE to obtain 1 overall assessment of the treatment difference on the primary end point. (4) Diseased-case imputation, whereby all randomized patients who prematurely withdrew will be assumed to have the primary end point. The treatment comparison will be carried out by logistic regression.

The results of the imputation approaches will be descriptively compared to assess sensitivity of the results to the various imputation methods. It is expected that the fourth imputation method (diseased case) may dilute the true difference between treatments, but it is provided as a somewhat conservative approach. Assessments of treatment-group difference on the secondary end points and within subgroups will be performed by the \( \chi^2 \) test and logistic regression. All secondary end points and analyses within subgroups will be tested without multiple
comparison correction but will be clearly labeled as secondary findings or hypothesis-generating findings.

**Safety**

An intention-to-treat safety analysis will be performed on the basis of the incidence of all anticipated and unanticipated adverse events that occur during the study. Although a mechanical malfunction, such as the presence of device arm

<table>
<thead>
<tr>
<th>Site</th>
<th>Clinical Center</th>
<th>City</th>
<th>State/Province</th>
</tr>
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<tr>
<td>95</td>
<td>Johns Hopkins Hospital</td>
<td>Baltimore</td>
<td>Md</td>
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<tr>
<td>96</td>
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<td>Ridgewood</td>
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<td>LeMesa</td>
<td>Calif</td>
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<tr>
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<td>Charlottesville</td>
<td>Va</td>
</tr>
<tr>
<td>162</td>
<td>MidAmerica Neuroscience Institute/Liberty Hospital</td>
<td>Lenexa</td>
<td>Kan</td>
</tr>
</tbody>
</table>

fractures, may result in an adverse event, it will be considered with the safety assessments. The safety analysis will also include chest x-ray evidence of device arm fractures (STARFlex patients only) and identification of a bleeding episode. A separate on-treatment safety analysis will also be performed. All confidence intervals will be 2-sided with a 95% confidence interval, and all probability values will be 2-sided, unless otherwise specified, and will be presented to 3 decimal places. Computations will be performed according to widely accepted statistical or graphical software. The HCRI will perform the final statistical analysis.

Study Organization
This CLOSURE I study is sponsored by NMT Medical Inc (Boston, Mass). The HCRI (Boston, Mass) serves as the academic contract research organization, data coordinating center, and data analysis center. The Executive Committee assists in the periodic review of the progress of the trial and provides important feedback to the sponsor.

Enrollment Characteristics
Enrollment has been completed for this study, and long-term follow-up is ongoing. The total number of patients enrolled was 910 from 87 clinical sites (Table 5) in the United States and Canada. (The final data set for the study is 909 patients. One patient was randomized/enrolled during an investigational review board–approval lapse; the site’s investigational review board ruled that the data should be monitored for safety purposes only and could not be part of the final analysis data set.) The first patient was enrolled on June 23, 2003, and the final patient was enrolled on October 24, 2008.

Appendix: Trial Operations

Study Sponsor
NMT Medical Inc, Boston, Mass.

National Principal Investigator
Anthony J. Furlan, MD, Gilbert Humphrey Professor and Chairman, Department of Neurology, Neurological Institute–University Hospitals Case Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio.

Co-National Principal Investigator
Mark Reisman, MD, Director of Cardiovascular Research and Education, Swedish Heart and Vascular Institute, Seattle, Wash.

Executive Committee
Neurology: Chairperson Anthony Furlan, MD, University Hospitals Neurological Institute, Case Western Reserve University, Cleveland, Ohio; Gregory Albers, MD, Stanford University Medical Center, Palo Alto, Calif; Harold Adams, MD, University of Iowa, Iowa City, Iowa; Lawrence Wechsler, MD, University of Pittsburgh Medical Center, Pittsburgh, Pa; Robert A. Felberg, MD, Geisinger Medical Center, Danville, Pa.
Cardiology: Co-Chairperson Mark Reisman, MD, Swedish Medical Center, Seattle, Wash; Michael Landzberg, MD, Brigham and Women’s Hospital, Boston, Mass; Howard Herrmann, MD, University of Pennsylvania, Philadelphia, Pa; Saibal Kar, MD, Cedars Sinai Medical Center, Los Angeles, Calif; Albert Raizner, MD, Methodist DeBakey Heart Center, Houston, Tex.

Data Coordinating Center and Data Analysis
HCRI, Boston, Mass.

Data Safety Monitoring Board
Chairman J.P. Mohr, MD; Thomas Brott, MD; John F. Keane, MD; Martin Larson, ScD.

Clinical Events Committee
Marc Fisher, MD, Chairman, and coordinated by HCRI, Boston, Mass.

Core Laboratories
Echocardiography core laboratory: University of Pennsylvania Cardiac Care at Radnor, Pa; chest x-ray core laboratory reader: Valerie Mandell, MD; Taylor Chung, MD; magnetic resonance core laboratory: Perceptive Informatics, Inc, Waltham, Mass.

Disclosures
Anthony Furlan: consultant/advisory board, NMT Medical Inc; Mark Reisman: research grant, NMT Medical, Inc, and Coherex; consultant/advisory board, Boston Scientific, Cordis; Joseph Massaro: consultant/advisory board, HCRI data coordination center for CLOSURE I; Laura Mauri: consultant/advisory board, consultant for Cordis, HCRI data coordination center for CLOSURE I; Harold Adams, research grant, Merck; Schering-Plough; consultant/advisory board, NMT Medical Inc; Gregory Albers: research grant, NMT Medical Inc; consultant/advisory board, NMT; Howard Herrmann: research grant, Gore Medical; consultant/advisory board, NMT Medical Inc; Saibal Kar: ownership interest, NMT Medical Inc; consultant/advisory board, NMT Medical Inc; Albert Raizner, consultant/advisory board, NMT Medical Inc; Lawrence Wechsler: consultant/advisory board, NMT Medical Inc; Robert Felberg: no disclosures.

References


Study Design of the CLOSURE I Trial: A Prospective, Multicenter, Randomized, Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex Septal Closure System Versus Best Medical Therapy in Patients With Stroke or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale

Anthony J. Furlan, Mark Reisman, Joseph Massaro, Laura Mauri, Harold Adams, Gregory W. Albers, Robert Felberg, Howard Herrmann, Saibal Kar, Michael Landzberg, Albert Raizner and Lawrence Wechsler
for the CLOSURE I Investigators

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