

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Septal Occluder

Device Trade Name: GORE[®] CARDIOFORM Septal Occluder

Device Procode: MLV

Applicant's Name and Address: W.L. Gore & Associates, Inc.
32360 North Valley Parkway
Phoenix, AZ 85085

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P050006/S060

Date of FDA Notice of Approval: March 30, 2018

The original PMA (P050006) for the Helex Septal Occluder was approved on August 11, 2006 and is indicated for the percutaneous, transcatheter closure of ostium secundum atrial septal defects (ASDs). The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050006B.pdf) and is incorporated by reference here. A modified version of device, Gore Cardioform Septal Occluder, was approved in P050006/S044. The current supplement was submitted to expand the indication for the GORE[®] CARDIOFORM Septal Occluder to close a patent foramen ovale.

II. INDICATIONS FOR USE

The GORE[®] CARDIOFORM Septal Occluder is a permanently implanted device indicated for the percutaneous, transcatheter closure of the following defects of the atrial septum:

- Ostium secundum atrial septal defects (ASDs).
- Patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

III. CONTRAINDICATIONS

The GORE[®] CARDIOFORM Septal Occluder is contraindicated for use in patients:

- Unable to take antiplatelet or anticoagulant medications such as aspirin, heparin, or warfarin.
- With anatomy where the GORE® CARDIOFORM Septal Occluder size or position would interfere with other intracardiac or intravascular structures, such as cardiac valves or pulmonary veins.
- With active endocarditis, or other infections producing bacteremia, or patients with known sepsis within one month of planned implantation, or any other infection that cannot be treated successfully prior to device placement.
- With known intracardiac thrombi.

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the GORE CARDIOFORM Septal Occluder labeling.

V. **DEVICE DESCRIPTION**

The GORE® CARDIOFORM Septal Occluder consists of an implantable Occluder (Figure 1) and a Delivery System (Figure 2). The Occluder is comprised of a platinum-filled nickel-titanium (Nitinol) wire frame covered with expanded polytetrafluoroethylene (ePTFE). The ePTFE includes a hydrophilic surface treatment to facilitate echocardiographic imaging of the Occluder and surrounding tissue during implantation. When fully deployed, the Occluder assumes a double-disc configuration to prevent shunting of blood between the right and left atria. The Delivery System consists of a 75 cm working length 10 Fr outer diameter Delivery Catheter that is coupled to a Handle. The Handle facilitates loading, deployment, and locking of the Occluder. The Handle also allows repositioning and retrieval of the Occluder via the Retrieval Cord, if necessary. The Occluder is available in diameters of 20, 25, and 30 mm. The Occluder is delivered using conventional catheter delivery techniques and may be delivered with the aid of a 0.035” guidewire (or smaller), if desired.

Figure 1. GORE® CARDIOFORM Septal Occluder

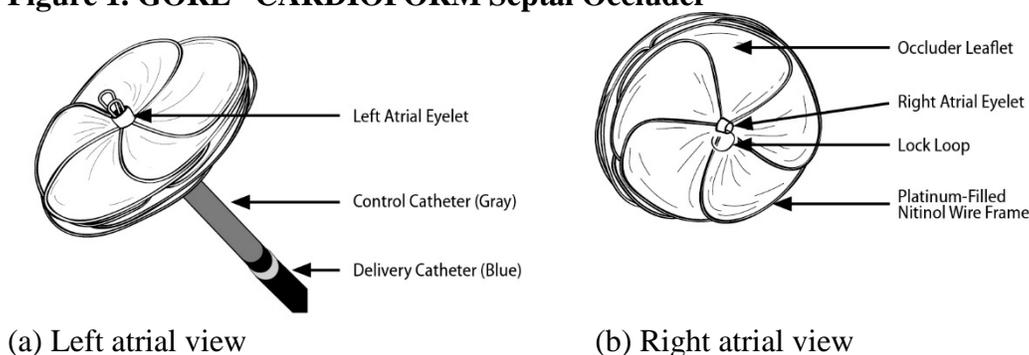
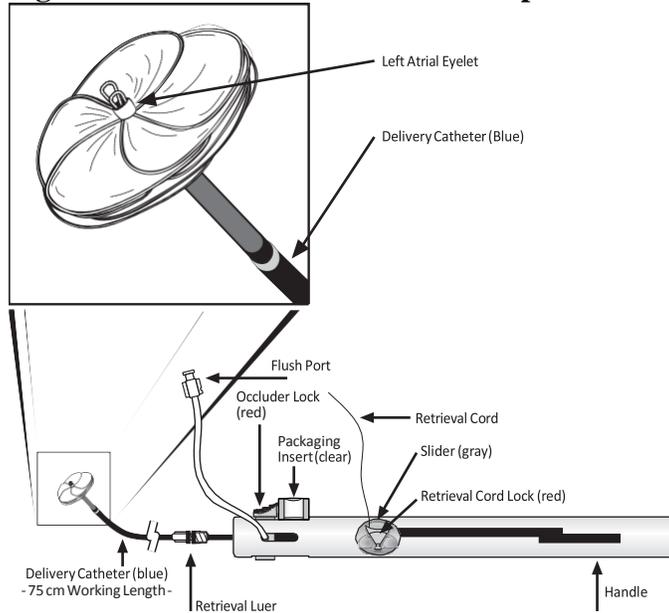


Figure 2. GORE® CARDIOFORM Septal Occluder with Delivery System



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for reducing the risk of recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism. Alternatives include medical management, surgical PFO closure, and transcatheter PFO closure using the St. Jude Medical AMPLATZER™ PFO Occluder. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The GORE® CARDIOFORM Septal Occluder is commercially available in the following countries:

- Australia
- Belgium
- Bulgaria
- Canada
- Croatia
- Czech Republic
- Lithuania
- Luxembourg
- Malta
- Netherlands
- Norway
- Poland

- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Ireland
- Italy
- Latvia
- Portugal
- Republic of Cyprus
- Romania
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- United Kingdom
- United States

The GORE® CARDIOFORM Septal Occluder has not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the device.

- Access site pain or complications requiring surgery, interventional procedure, transfusion, or prescription medication
- Air embolism
- Anxiety
- Arrhythmia, such as atrial fibrillation or flutter, requiring treatment
- Bleeding requiring surgery, interventional procedure, transfusion, or prescription medication
- Cardiac arrest
- Chest pain or discomfort
- Death
- Device disc expansion resulting in clinical sequelae or intervention
- Device embolization
- Device failure or ineffectiveness requiring repeat atrial septal defect interventions or procedures
- Device fracture resulting in clinical sequelae or surgical intervention
- Device thrombosis or thromboembolic event resulting in clinical sequelae
- Endocarditis
- Fatigue
- Headache or migraine
- Hypotension
- Myocardial infarction
- Palpitations
- Perforation or damage of a cardiovascular structure by the device
- Pericardial tamponade

- Renal failure
- Respiratory arrest
- Sepsis
- Significant pleural or pericardial effusion requiring drainage
- Stroke or TIA
- Thrombosis or thromboembolic event resulting in clinical sequelae

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical studies were performed on the device. Testing was referenced from PMA submission P050006 and related supplements for all non-clinical testing. No additional preclinical studies were conducted to support the proposed indication. A summary of previously reported preclinical studies can be found in the P050006 Summary of Safety and Effectiveness (see section I above).

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed the REDUCE pivotal clinical trial to establish a reasonable assurance of safety and effectiveness of PFO closure with the GORE® CARDIOFORM Septal Occluder to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism. The trial, conducted under IDE # G070185, enrolled subjects in the US, Denmark, Sweden, Norway, United Kingdom, Finland, and Canada. Data from this clinical trial were the basis for the PMA approval decision. A summary of the REDUCE trial is presented below.

A. Study Design

Patients were treated between December 2008 and February 2015. The database for this Panel Track Supplement reflected data collected through April 24, 2017 and included 664 patients, with 441 randomly assigned to the test arm and 223 to the control arm. At least two years of follow-up was available for all available subjects. There were 63 investigational sites, and 50% of subjects were enrolled in the US.

The REDUCE study was a prospective, randomized (2:1), open-label, multi-center clinical study. Device group subjects were treated with antiplatelet medical management and PFO closure with the GORE® CARDIOFORM Septal Occluder or GORE® HELEX® Septal Occluder (prior device generation approved under P050006). Control group subjects were treated with antiplatelet medical management alone. Subjects at each site were treated with the same antiplatelet therapy regardless of study arm. Investigators chose one of the following options: aspirin alone (75-325 mg once daily), combination aspirin (50-100 mg) and dipyridamole (225-400 mg), or

clopidogrel (75 mg once daily). Other combinations or the use of anticoagulants was not permitted.

There was an independent Data and Safety Monitoring Board (DSMB) responsible for conducting periodic reviews of aggregate data for patient safety and scientific integrity. An independent Clinical Events Committee (CEC), blinded to subjects' treatment assignments, was responsible for reviewing and adjudicating adverse events that had the potential to be study primary or secondary endpoint events. An independent MRI Core Lab, blinded to subjects' treatment assignments, provided analysis of brain imaging as a component of the brain infarct co-primary endpoint. An independent Echocardiography Core Lab conducted analyses of PFO closure, residual shunting, and device thrombus.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the REDUCE study was limited to patients who met the following key inclusion criteria:

- Patient ≥ 18 years and < 60 years of age
- Cryptogenic, ischemic stroke of presumed embolic etiology, verified by a neurologist within 180 days prior to randomization, meeting either criteria:
 - Ischemic stroke clinical symptoms persisting ≥ 24 hours; or
 - Clinical symptoms persisting < 24 hours and MRI evidence of infarction.
 - For MRI-incompatible patients (i.e., patients that are claustrophobic and/or have implants that are contraindicated for MR), CT scan accepted
- PFO, confirmed by TEE with bubble study demonstrating spontaneous right-to-left shunting or right-to-left shunting during Valsalva maneuver
- Absence of an identifiable source of thromboembolism in the systemic arterial circulation.
 - Vascular imaging that rules out other potential sources of cerebral thromboembolism (e.g., dissection of the aorta or neck vessels, carotid stenosis $> 50\%$ and/or presence of ulcerated plaques, or intracranial stenosis $> 50\%$)
- No evidence of hypercoagulable state, which requires anticoagulation therapy, based on the evaluation of, at a minimum:
 - Platelet count, Prothrombin Time (PT) or INR, aPTT, and antiphospholipid antibodies.
 - A history of thromboembolic events in first degree family members obtained for all patients. For patients who had a first-degree family member with such an event prior to age 55, or whose family history is unknown, the following additional tests were required and must be interpreted as normal: Factor V Leiden mutation, Prothrombin Gene G20210A mutation, protein C, protein S, and Antithrombin III.
 - Testing for prothrombotic disorders may be performed at the discretion of the treating physicians but was not required.

Patients were not permitted to enroll in the REDUCE study if they met any of the following exclusion criteria:

- Patient has a life expectancy of less than one year.
- Patient is experiencing severe disability, defined as modified Rankin Scale (mRS) score greater than or equal to 3, at the time of randomization.
- Neurological deficits not due to stroke that may affect neurologic assessments
- Other potential source(s) of cardio-embolism, for example: AFib, atrial flutter, prosthetic heart valve, severe native valve disease, LVEF <40%, severe ventricular wall motion abnormalities, intracardiac thrombus, mitral valve stenosis, prior cardiac surgery, or other major congenital cardiac abnormality
- Prior myocardial infarction
- Uncontrolled diabetes mellitus at the time of randomization, in the opinion of the investigator
- Pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg)
- Uncontrolled systemic hypertension at the time of screening, in the opinion of the investigator
- Presentation with a lacunar stroke syndrome (e.g., small deep infarction <1.5 cm in diameter and/or a typical lacunar syndrome such as pure motor hemiparesis, pure sensory stroke, clumsy hand-dysarthria syndrome, or ataxic-hemiparesis syndrome)
- Intracranial pathology that made the patient inappropriate for study participation based on discretion of the Investigator (e.g., brain tumor other than meningioma, AVM, cerebral hemorrhage, cerebral venous sinus thrombosis on CT or MRI, or cerebral aneurysm >7 mm)
- Active autoimmune disease (e.g., SLE, rheumatoid arthritis, polyarteritis nodosa, primary cerebral vasculitis)
- Active infection that could not be treated successfully prior to randomization
- Alcohol and/or drug abuse [e.g., on average >5 units or drinks (60 grams) of alcohol / day] or abuses alcohol and/or drugs in the opinion of the Investigator
- Pregnancy, lactating, or intent on becoming pregnant through 24-months after randomization
- Contraindication to study medications, including antiplatelet therapy
- Requirement for chronic anticoagulation therapy that cannot be discontinued prior to randomization, in the opinion of the Investigator
- Other anatomic or co-morbid conditions that could, in the investigator's opinion, limit the patient's ability to participate in the study or to comply with follow-up requirements, or impact the scientific soundness of the study results
- Major surgical procedure within 30 days preceding randomization
- Plans to have a major elective surgical procedure within 30 days after randomization or within 30 days of a PFO closure procedure
- Need for any concomitant procedure, based on the results of the screening evaluations, during the PFO closure procedure that may confound detection of device-related adverse events

- Known sensitivity to contrast media that cannot be controlled adequately with pre-medication
- In the opinion of the Investigator, anatomic criteria identified during the screening evaluation and/or the screening TEE that are unfavorable for successful placement of the GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder or the patient has contraindications for device placement, which may include:
 - Inability to accommodate a 10 Fr delivery catheter
 - The need for trans-septal puncture
 - Requires placement of more than one device
 - PFO estimated to be too large for successful device placement
 - Device would impinge on cardiac structure(s)
 - Anatomy would likely prevent discs from apposing the septal tissue

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at 1, 6, 12, 18, 24, 36, 48, and 60 months post-procedure. Adverse events and complications were recorded at all visits. The key timepoints are shown in Table 1.

Preoperatively, a neurologic examination (National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale) was performed to assess the subject's neurological status. Evaluation of antiplatelet study medications, concomitant medications and an electrocardiogram were also performed. Postoperatively, patient evaluation included changes in brain lesions and residual shunting through the PFO (in subjects randomized to the device). Adverse events and complications were recorded at all visits.

Table 1. Follow-up schedule

X = required for all subjects, ▲ = required for device group subjects, o = at discretion of investigator	Screening		Procedure / Peri-procedure	Month 1	Months 6 & 18	Month 12	Month 24 or Endpoint Event	Month 36 and 48	Month 60
Informed consent	X								
Demographics and medical history	X	RANDOMIZE							
Blood work (including hypercoagulability assessment ¹)	X		o						
Pregnancy Test	X ²		o						
MRA, MRI, CTA, duplex color Doppler, carotid ultrasound, transcranial Doppler, or conventional angiography of the head, neck, and aortic arch	X								

X = required for all subjects, ▲ = required for device group subjects, o = at discretion of investigator	Screening		Procedure / Peri-procedure	Month 1	Months 6 & 18	Month 12	Month 24 or Endpoint Event	Month 36 and 48	Month 60
Physical Exam (BP, HR, height/weight)	X		▲	X	X	X	X	o	o
ECG	X		▲	X	X	X	X	o	o
Brain MRI	X						X	o	o
TEE with bubble study at rest & with Valsalva	X		▲ ³				▲	o	o
TTE with bubble study			▲	▲	o	▲		o	o
Fluoroscopy			o	o	o	▲	o	o	o
Neurological assessments including NIH Stroke Scale (NIHSS), modified Rankin Score (mRS), and supplemental neurologist exam	X		▲	X	X	X	X	o	o
Telephone follow-up: Stroke-free questionnaire								X	X
Concomitant and antiplatelet study medication	X	X ⁴	▲	X	X	X	X	X	X
Adverse events	X		▲	X	X	X	X	X	X

¹ if standard of care at site or if subject has a 1st degree family history of embolic event prior to age 55

² if applicable

³ or ICE

⁴ start protocol-specific antiplatelet regimen within 48 hours of randomization

3. Clinical Endpoints

With regards to effectiveness, there were two co-primary endpoints for the study. The first was freedom from recurrent clinical ischemic stroke through at least 24 months. A recurrent ischemic stroke event was defined as the first occurrence of one of the following:

- Clinical finding of ischemic stroke that may be associated with MRI evidence of a new relevant brain infarction. An ischemic stroke was defined as a neurological deficit, presumed due to ischemia, persisting longer than 24 hours or until death.
- Transient neurological deficit, presumed due to ischemia, persisting less than 24 hours that also had MRI evidence of a new relevant brain infarction.

The second co-primary endpoint was the incidence of subjects with new brain infarction or clinical findings of ischemic stroke from screening through 24 months or last follow-up visit, whichever occurred first. New brain infarction was defined as the composite of clinical ischemic stroke (defined above) or radiographically-detected but clinically covert brain infarct. Any subject with at least one new T2

hyperintense MRI lesion with diameter ≥ 3 mm between the screening MRI and the 24-month MRI, or clinical findings of ischemic stroke through 24 months, and confirmed by the blinded MRI Core Lab or CEC, was classified as having a new brain infarction.

Secondary effectiveness endpoints consisted of an assessment of PFO closure in the device group subjects by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE).

With regards to safety, endpoints included the proportion of subjects who experienced adverse events (AEs) that are determined to be related to device, procedure, and/or antiplatelet medical management. The safety assessment included specific adverse events and groups of adverse events such as all-cause adverse events, device-related events, procedure-related events, antiplatelet medical therapy-related events, and any serious adverse events.

For the device group, device success was defined as the proportion of test arm subjects with successful implant and retention after procedure of the device. Clinical success was defined as the composite of device Success, PFO closure, and absence of a recurrent stroke or imaging-confirmed TIA at 24 months post-procedure in the test arm. In the control arm, clinical success was defined as the freedom from a recurrent stroke or imaging-confirmed TIA at 24 months post-randomization. The success/failure criteria also evaluated overall survival defined as time from randomization to death from any cause or last known contact, time to any stroke/TIA and device success.

Statistical Analysis Plan

The primary analysis population was the intent-to-treat (ITT) population.

Co-primary endpoint 1: The study was designed to test the null hypothesis that the hazard of a recurrent stroke or imaging-confirmed TIA in subjects treated with percutaneous PFO closure plus antiplatelet medical management was equal to or higher than subjects treated with antiplatelet medical management alone. The alternative hypothesis is that the hazard of a recurrent stroke/imaging-confirmed TIA was lower in subjects treated with percutaneous PFO closure plus antiplatelet medical management compared to antiplatelet medical management alone. In statistical terms:

$$H_0 : HR_{T/C}(t) \geq 1.0 \text{ for all } t$$

$$H_A : HR_{T/C}(t) < 1.0 \text{ for all } t$$

where:

$HR_{T/C}$ = hazard ratio comparing the test (T) arm (PFO closure and antiplatelet medical management) to the control (C) arm

(antiplatelet medical management only).

Co-primary endpoint 2: The study also tested the null hypothesis that the incidence of new brain infarction at 24 months in subjects treated with percutaneous PFO closure plus antiplatelet medical management was equal to or higher than subjects treated with antiplatelet medical management alone. The alternative hypothesis was that the brain infarction incidence was lower in subjects treated with percutaneous PFO closure plus antiplatelet medical management compared to antiplatelet medical management alone. In statistical terms:

$$H_0: P_C - P_T \leq 0$$

$$H_1: P_C - P_T > 0$$

where:

P_C = true proportion of subjects with incident brain infarct in the control group

P_T = true proportion of subjects with incident brain infarct in the test group

There was no pre-specified safety endpoint or a statistical hypothesis for safety. Serious adverse events as determined by the DSMB and were adjudicated for severity and relatedness to the device and procedure and defined as an event that:

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

B. Accountability of PMA Cohort

At the time of database lock, of 664 patients enrolled in the PMA study, 85.7% (569/664) patients were available for analysis at the completion of the study, the 24-month post-operative visit. The average follow-up time for subjects receiving PFO closure was 3.5 years with a total of 1,529 patient-years of exposure. The average follow-up time for control subjects was 3.2 years with 703 patient-years of exposure. The device group included 250 subjects implanted with the GORE® CARDIOFORM Septal Occluder and 158 subjects implanted with the GORE® HELEX® Septal Occluder.

Patients were required to take antiplatelet therapy for the duration of the clinical study. Single antiplatelet therapy was used in approximately 85% of patients in both the device group and medical management group. Aspirin alone was the most commonly

prescribed medication and used by 61.2% of patients in the Device Group and 54.7% of patients the medical management group.

There was a higher rate of subject discontinuation in the medical management group vs. the device group for the ITT recurrent stroke evaluation (14.8% vs. 8.8%, respectively; Figure 3). There were also more non-evaluable subjects for the brain infarct primary endpoint in the medical management group vs. the device group (20.6% vs. 13.2%, respectively; Figure 4).

For the ITT population, no study device was placed in 32 (7.3%) device group subjects, while 14 subjects (6.3%) in the medical management group had PFO closure during the trial (Figure 5).

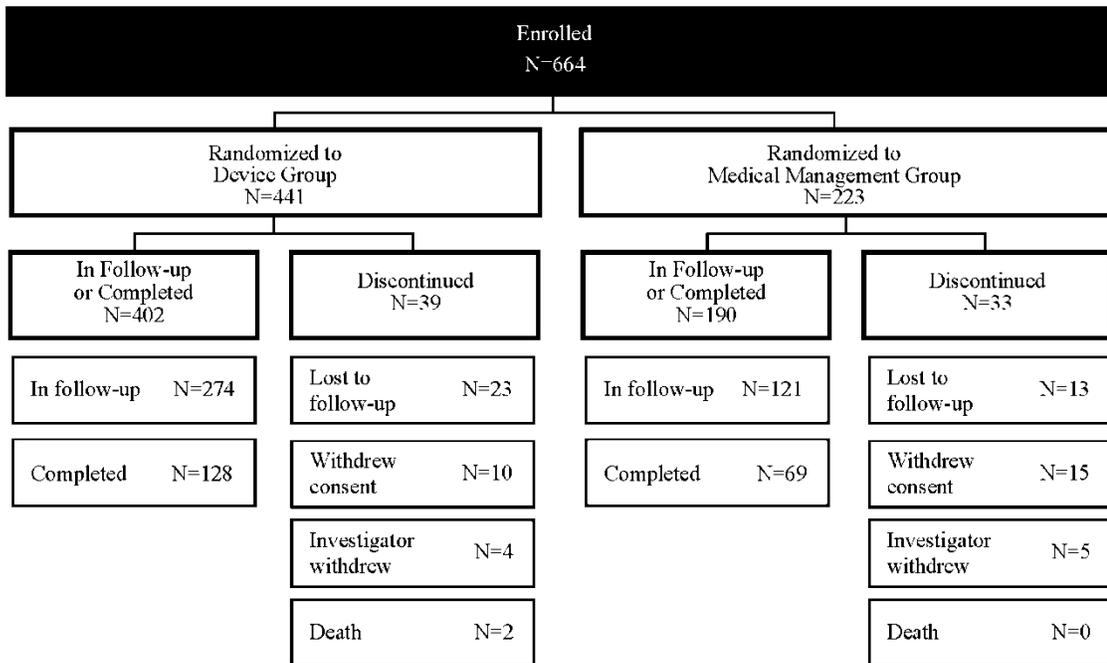


Figure 3: Patient Accountability Tree for Recurrent Stroke ITT Analysis
Note that completed includes recurrent strokes and finished 5-year follow-up.

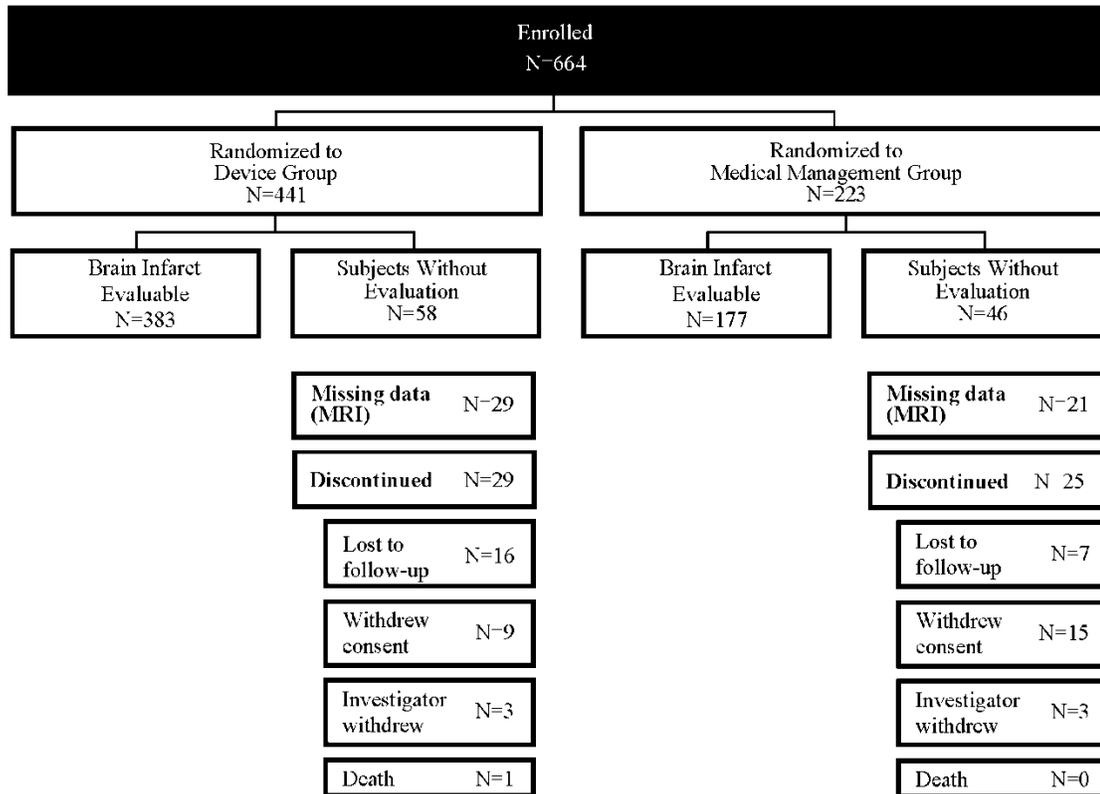


Figure 4. Subject accountability for brain infarct ITT analysis

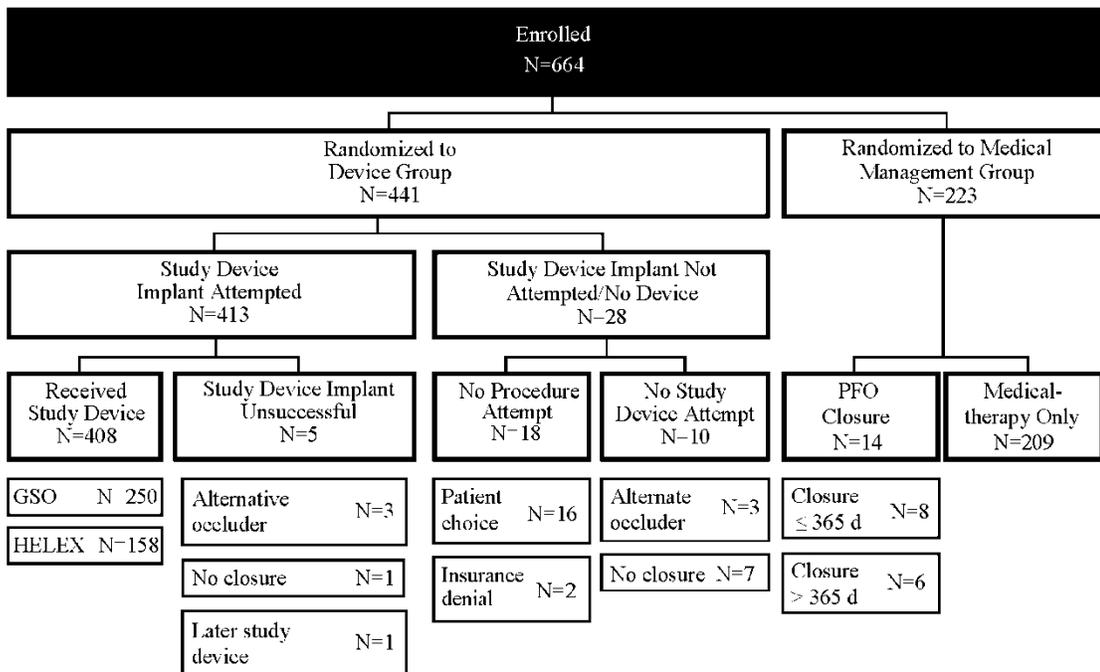


Figure 5. Post-randomization Disposition of Subjects

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PFO closure for stroke reduction study performed in the US. Patient demographics and risk factors are summarized in Table 2 and Table 3, respectively. The treatment groups were balanced with no significant differences for any of the characteristics or risk factors.

Table 2. Demographics, medical history, and PFO characteristics – ITT population

Variable	Device Arm (N=441)	Control Arm (N=223)	p-value ¹
Age-yr	45.4 ± 9.3	44.8 ± 9.6	0.41
Days from qualifying event to randomization	100 ± 52	101 ± 53	0.90
Male sex	261 (59.2%)	138 (61.9%)	0.56
Medical history			
Stroke or TIA prior to qualifying event	62 (14.1%)	23 (10.3%)	0.22
Previous stroke	42 (9.5%)	13 (5.8%)	0.44
Previous TIA	26 (5.9%)	11 (4.9%)	0.81
Qualifying event			
Stroke with symptoms ≥ 24 hrs	402 (91.2%)	199 (89.2%)	0.48
Stroke with symptoms < 24 hrs but with imaging confirmation of infarct	39 (8.8%)	24 (10.8%)	
Imaging evidence of qualifying infarction	438 (99.3%)	218 (97.8%)	0.13
Patent foramen ovale shunt grade ²	(n=425)	(n=216)	0.32
Grade I Trivial/Small (1-5 bubbles)	77 (18.1%)	43 (19.9%)	
Grade II Moderate (6-25 bubbles)	166 (39.1%)	94 (43.5%)	
Grade III Large (>25 bubbles)	182 (42.8%)	79 (36.6%)	
Atrial septal aneurysm	86/422 (20.4%)	n/a	

Continuous variables reported as means ± SD and categorical variables as n (%).

¹ p-value based upon Fisher's Exact Test for categorical variables and Wilcoxon Test for continuous variables.

² Shunt size was graded based on the estimated number of microbubbles detected in the left atrium within 3 cardiac cycles after appearance in the right atrium, as observed on (TEE), either at rest or with Valsalva maneuver.

Table 3. Baseline stroke risk factors – ITT population

Variable	Device (N = 441)	Control (N=223)	p-value ¹
Diabetes	18 (4.1%)	10 (4.5%)	0.839
Hypertension	112 (25.4%)	58 (26.0%)	0.925
Hyperlipidemia	213 (48.3%)	103 (46.2%)	0.622
Tobacco Use:			0.299
Current	63 (14.3%)	25 (11.2%)	
Previous: stopped > 12 months	87 (19.7%)	45 (20.2%)	

Variable	Device (N = 441)	Control (N=223)	p-value ¹
ago			
Previous: stopped < 12 months ago	42 (9.5%)	31 (13.9%)	
Never used	249 (56.5%)	122 (54.7%)	

¹ p-value based upon Fisher's Exact Test

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the enrolled cohort of 664 patients available at the time of the data lock. The key safety outcomes and adverse effects for this study are presented in Tables 4 to 5.

Adverse effects that occurred in the PMA clinical study:

Serious adverse events (SAEs) occurred in 164 subjects with no significant difference between treatment groups: 102 (23.1%) in the device group and 62 (27.8%) in the medical management group (P=0.22, Table 4). In the device group, device- and procedure-related SAEs occurred in 1.4% and 2.5% of subjects, respectively (Table 13). No unanticipated adverse device effects were reported in the trial.

Table 4. Summary of SAEs

	Device (N=441)	Control (N=223)
Device- or procedure-related death	0 (0.0%)	N/A
Any SAE	102 (23.1%)	62 (27.8%)
Related to procedure	11 (2.5%)	N/A
Related to device	6 (1.4%)	N/A

Six (6) device-related SAEs occurred in 6 subjects (1.4%) and 18 procedure-related SAEs occurred in 11 subjects (2.5%), and are summarized in Table 5. Of the 16 device group subjects (3.6%) with device- and/or procedure-related SAEs, one (0.2%) had a recurrent stroke (associated with a device-related thrombosis).

Table 5. Device- and procedure-related SAEs in the device group (N=441)

Device-related SAE	n (%)
Atrial fibrillation	2 (0.5%)
Device-related thrombosis	2 (0.5%)
Device embolization	1 (0.2%)
Tachycardia	1 (0.2%)
Procedure-related SAE	n (%)
Device embolization	2 (0.5%)

Hypotension	2 (0.5%)
Anxiety	1 (0.2%)
Aortic dissection	1 (0.2%)
Arteriovenous fistula	1 (0.2%)
Cardiac tamponade	1 (0.2%)
Chest discomfort	1 (0.2%)
Complication of device removal	1 (0.2%)
Fatigue	1 (0.2%)
Hemiparesis	1 (0.2%)
Incision site hematoma	1 (0.2%)
Incision site hemorrhage	1 (0.2%)
Non-cardiac chest pain	1 (0.2%)
Post procedural hemorrhage	1 (0.2%)
Puncture site hemorrhage	1 (0.2%)
Respiratory arrest	1 (0.2%)

The risks of serious bleeding were similar in both groups (1.8% vs. 2.7%, $p=0.57$). Four device subjects experienced procedure related bleeding which included bleeding within 30 days post-procedure at the vascular access site ($n=3$) or cardiac tamponade ($n=1$). Four device subjects experienced other bleeds which includes bleeding in the reproductive, visual, gastrointestinal, and musculoskeletal systems. The risks of deep vein thrombosis (DVT) and pulmonary embolism (PE) were also similar in both groups (0.7% vs. 0.9%, $p=1.0$). There was a higher incidence of atrial fibrillation (AF) in the device group than in the control group (6.6% vs. 0.4%, $p<0.001$). The majority of subjects with AF or flutter in the device group had events which were categorized as non-serious (66%) and 83% were, detected within 45 days post-procedure. One device subject (0.2%) with AF had a recurrent stroke. Refer to Table 6 below for a summary of atrial fibrillation and atrial flutter events.

Table 6. Atrial fibrillation and atrial flutter events

	Device Group (N=441)			Control Group (N=223)		
	# Patients	# Events	Rate per 100 pt-yrs	# Patients	# Events	Rate per 100 pt-yrs
Atrial Fibrillation	29	31	2.0	1	1	0.1
Implant Procedure-Related	7	7	0.5	N/A	N/A	N/A
Non-Procedure-Related	22	24	1.6	N/A	N/A	N/A
Atrial flutter	2	2	0.1	0	0	0

Wire Frame Fracture

Wire frame fracture was noted on 12-month fluoroscopy in 4.6% of Device Group subjects. No fractures were associated with device instability or clinical sequelae.

2. Effectiveness Results

The analysis of effectiveness was based on the 664 evaluable patients at the 24-month time point. Key effectiveness outcomes are presented in Figure 6 and Table 7 to Table 9. Recurrent clinical ischemic stroke occurred in 6 subjects (0.39 per 100-patient-years) in the device group and 12 (1.71 per 100-patient-years) in the control group (hazard ratio (HR) 0.23; 95% confidence interval [CI], 0.09-0.62; one-sided adjusted P=0.001) (Figure 6, Table 7). This result achieved statistical significance at the pre-specified alpha=0.025 for co-primary endpoint 1. The number needed-to-treat to prevent one recurrent stroke in 2 years was approximately 28 patients.

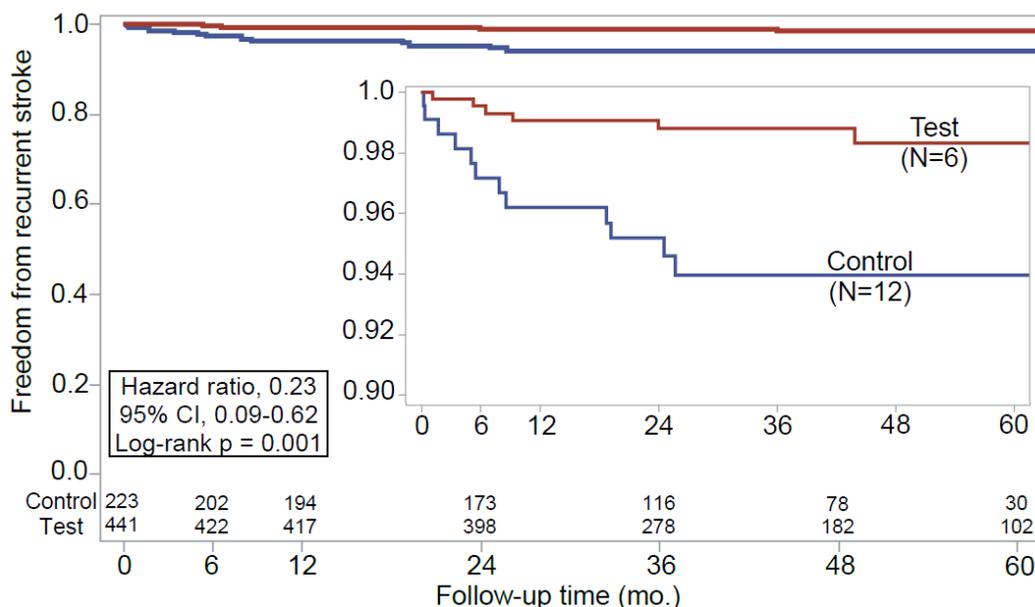


Figure 6. Intention-to-treat Kaplan-Meier plot of freedom from recurrent stroke coprimary endpoint

The composite new brain infarction endpoint (Table 7) occurred in 22 device subjects (5.7%) and 20 medical management subjects (11.3%; absolute difference 5.6%; 95% CI 0.3-10.8%; relative risk [RR] 0.51; 95% CI 0.29-0.91; nominal one-sided p=0.018). This 49% relative risk reduction in favor of the device group achieved statistical significance at the pre-specified alpha=0.025 with multiplicity adjusted one-sided p=0.024. The number needed-to-treat to prevent one new brain infarct in 2 years was approximately 18 patients. Of device group subjects with

new brain infarcts, 5 (1.3%) had recurrent clinical strokes, and 17 (4.4%) had silent brain infarcts only. Of control group subjects with new brain infarcts, 12 (6.8%) had recurrent clinical strokes, and 8 (4.5%) had silent brain infarcts only.

Table 7. Composite new brain infarction endpoint

Primary Endpoint	# Subjects (%)		Relative Risk (95% CI)	Relative Risk Reduction	p-value ²
	Device (N=383) ¹	Control (N=177) ¹			
New Brain Infarction	22 (5.7%)	20 (11.3%)	0.51 (0.29-0.91)	49%	0.018
Recurrent Clinical Stroke	5 (1.3%)	12 (6.8%)	-	-	-
Silent Brain Infarct Only	17 (4.4%)	8 (4.5%)	-	-	-

¹The sample sizes (N=383 in the Device Group and N=177 in the control Group) represent the number of evaluable patients; 58 Device Group subjects (13.2%) and 46 control Group subjects (20.6%) were not evaluable for the New Brain Infarction co-primary endpoint due to early discontinuation or missing MRI assessments.

²One-sided binomial proportions test

Two additional populations were considered for exploratory analysis, including a per-protocol cohort and an as-treated cohort. For per-protocol (PP) analysis, only subjects who were randomized and treated according to critical protocol requirements were analyzed, according to treatment assigned at randomization. Specifically, subjects randomized to the device group who received PFO closure with a study device, and subjects randomized to the control group who received no PFO closure by any means at any time, were included in the PP analysis. For as-treated (AT) analysis, subjects who were randomized and treated were analyzed by treatment received, regardless of treatment assigned at randomization. Specifically, randomized subjects who received PFO closure by any means were analyzed in the “PFO Closure” group, and randomized subjects who received no PFO closure by any means were analyzed in the “No PFO Closure” group. Results for both co-primary endpoints for the PP and AT cohorts were similar to Intention-To-Treat (ITT) results (Table 8).

Table 8. Recurrent stroke and new brain infarct effect size by analysis cohort

Endpoint	Analysis Cohort	Effect size	95% CI	Nominal one-sided p-value
Recurrent stroke	ITT	HR 0.23	0.09 to 0.62	0.0008
Recurrent stroke	PP	HR 0.25	0.09 to 0.65	0.0011
Recurrent stroke	AT	HR 0.25	0.09 to 0.66	0.0013

Endpoint	Analysis Cohort	Effect size	95% CI	Nominal one-sided p-value
New brain infarct	ITT	RR 0.51	0.29 to 0.91	0.018
New brain infarct	PP	RR 0.56	0.31 to 1.01	0.037
New brain infarct	AT	RR 0.58	0.32 to 1.03	0.043

Table 9 provides a summary of the results of Technical Success, Clinical Success, Device Success, and PFO Closure for the Device Group along with a summary of the results of Clinical Success for the control Group.

Table 9. Secondary endpoint summary

Performance Outcome	Device n/N (%)	Control n/N (%)
Device Success	408/423 (96.5%)	-
Clinical Success	308/334 (92.2%)	186/198 (93.9%)
Technical Success ¹	408/413 (98.8%)	-
Complete PFO Closure ²		
12 months	232/307 (75.6%)	-
24 months	257/315 (81.6%)	-
Effective PFO Closure ³		
12 months	290/307 (94.5%)	-
24 months	309/315 (98.1%)	-

¹ proportion of device group subjects with successful implant and retention of a study device after study device implant attempt

² note that PFO closure results (both complete and effective) are provided for device group subjects who received a study device

³ freedom from large shunt (> 25 bubbles), adjudicated by echo core lab

Overall survival, defined as time from randomization to death from any cause or last known contact, was similar between groups (p=0.335) with 24-month survival of 99.8% and 100% in the device and medical management groups, respectively. Freedom from any stroke / TIA showed a trend in favor of the device group (p=0.096) with a 24-month estimate of freedom from any stroke or TIA of 95.1% vs. 91.8% for device vs. medical management groups, respectively.

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with outcomes: age, sex, shunt size, and geographic region. Analyses to evaluate possible treatment interactions in relation to baseline covariates suggested that closure had similar effects on recurrent stroke (Figure 7) and brain infarct (Table 10) in relation to age, sex, shunt size, and geographic region.

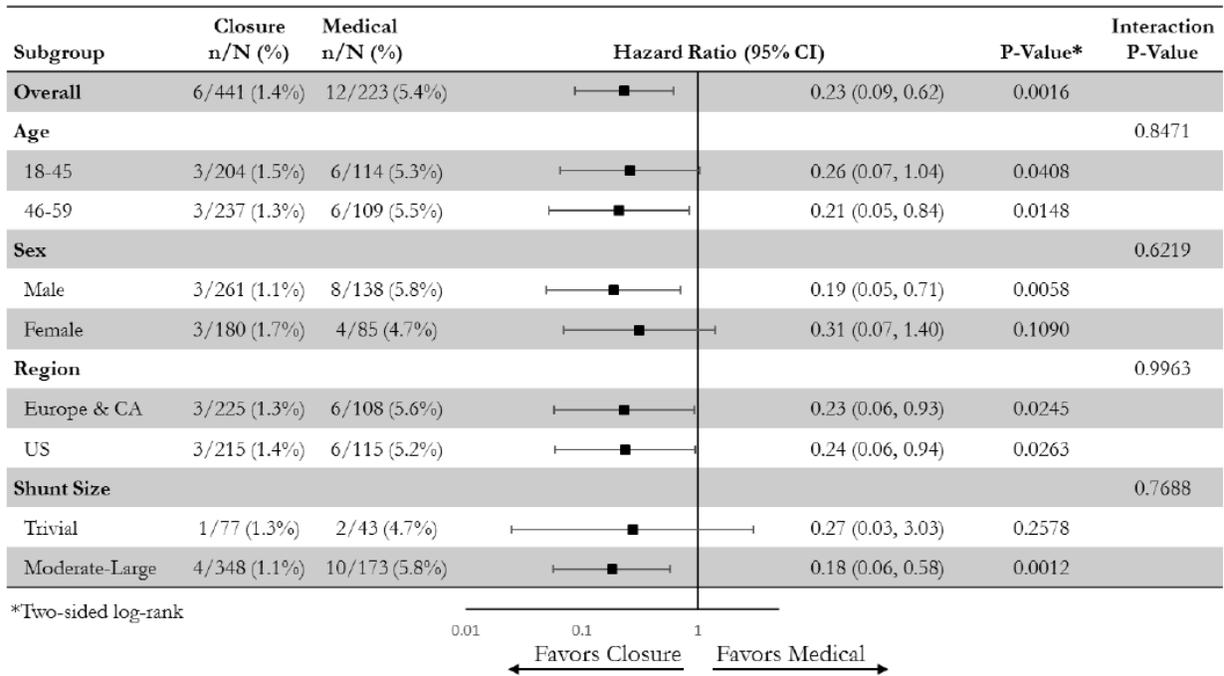


Figure 7. Subgroup analysis for recurrent stroke endpoint

Table 10. Subgroup analysis for brain infarct endpoint

Subgroup	Device n/N (%)	Control n/N (%)	Relative Risk (95% CI)	P- Value*	Interaction P-Value
Overall	22/383 (5.7%)	20/177 (11.3%)	0.51 (0.29, 0.91)	0.0368	
Age					0.8312
18-45	10/172 (5.8%)	10/93 (10.8%)	0.54 (0.23, 1.25)	0.1789	
56-59	12/211 (5.7%)	10/84 (11.9%)	0.48 (0.22, 1.06)	0.1087	
Sex					0.1480
Male	11/224 (4.9%)	15/111 (13.5%)	0.36 (0.17, 0.77)	0.0154	
Female	11/159 (6.9%)	5/66 (7.6%)	0.91 (0.33, 2.53)	0.8636	
Region					0.6226
Europe/ Canada	8/205 (3.9%)	9/96 (9.4%)	0.42 (0.17, 1.05)	0.0940	
US	14/178 (7.9%)	11/81 (13.6%)	0.58 (0.28, 1.22)	0.1846	
Shunt Size					0.7014
Trivial	5/63 (7.9%)	4/31 (12.9%)	0.62 (0.18, 2.13)	0.4728	
Moderate/ Large	16/308 (5.2%)	16/141 (11.3%)	0.46 (0.24, 0.89)	0.0373	

*Two-sided binomial test (normal approximation)

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 416 investigators of which none were full-time or part-time employees of the sponsor and 13 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none of the investigators
- Significant payment of other sorts: 13 investigators
- Proprietary interest in the product tested held by the investigator: none of the investigators
- Significant equity interest held by investigator in sponsor of covered study: none of the investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the REDUCE Clinical Study, effectiveness was established in the primary ITT analysis for both co-primary endpoints, freedom from recurrent stroke and incidence of new brain infarction. PFO closure was associated with a statistically significant 77% relative risk reduction in recurrent stroke. PFO closure was also associated with

a statistically significant 49% relative risk reduction in incidence of new brain infarction.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. There was no significant difference in overall rate of SAEs between the control (medical management) and device groups, and there was a low rate of device- or procedure-related SAEs (3.6%). Subjects in the device group had a higher incidence of atrial fibrillation or flutter (6.6%), but the majority had events which were non-serious. There were no device- or procedure-related deaths.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The REDUCE study demonstrated a statistically significant 77% relative reduction in recurrent ischemic stroke for PFO closure plus antiplatelet medical therapy compared to antiplatelet medical therapy alone.

Additional factors to be considered in determining probable risks and benefits for the GORE® CARDIOFORM Septal Occluder device included the rate of serious adverse events. The risk of device or implantation procedure-related serious adverse events in patients undergoing an GORE® CARDIOFORM Septal Occluder was 3.9% in the REDUCE trial. There were no device or implantation procedure-related deaths. There was an increased risk of atrial fibrillation or flutter in patients treated with the device compared with medical therapy.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, for percutaneous transcatheter closure of the patent foramen ovale (PFO) in patients described in the indications for use statement, the probable benefits of the GORE® CARDIOFORM Septal Occluder outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The REDUCE study demonstrated a statistically significant 77% relative risk reduction in recurrent ischemic stroke for PFO closure plus antiplatelet medical therapy compared to antiplatelet medical therapy alone. The rate of device or implantation procedure-

related serious adverse events in patients undergoing PFO closure with the GORE® CARDIOFORM Septal Occluder was low. There were no device or implantation procedure-related deaths. There was an increased risk of atrial fibrillation or flutter in patients treated with the device compared with medical therapy.

XIII. CDRH DECISION

CDRH issued an approval order on March 30, 2018. The final conditions of approval cited in the approval order are described below.

OSB Lead PMA Post-Approval Study – GORE® CARDIOFORM Septal Occluder New Enrollment PAS: This prospective, multi-center, single arm post-approval study will evaluate the acute, subacute, and long-term safety and effectiveness of GORE® CARDIOFORM Septal Occluder and assess the training program for new operators.

The primary effectiveness endpoint, which is the proportion of subjects with ischemic stroke at 2 years, will be compared to a performance goal (PG) of 3.8%. The primary safety endpoint, which is the cumulative incidence of device- or procedure-related serious adverse events through 30 days, will be compared to a PG of 6.4%. The study will provide 80% power at a one-sided significance level of 5% to reject the null hypothesis for effectiveness and safety. Secondary endpoints include technical success, procedural success, clinically significant arrhythmias, and effective PFO closure, defined as a complete PFO closure or a trivial or small residual shunt, at 1 year. Patients will be followed through 5 years post-procedure. Follow-up visits for all subjects will be performed at baseline, pre-discharge, 1, 6, and 12 months post-implant and then annually through 5 years post-procedure.

ODE Lead PMA Post-Approval Study – Continued Follow-up of IDE Cohort: The study will consist of all IDE patients enrolled in the REDUCE trial who are currently alive. The study objective is to characterize the safety and effectiveness of the GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluders annually through 5 years post-procedure. For continued follow up of patients from REDUCE, the safety and effectiveness endpoints are listed in the protocol as follows: The primary effectiveness endpoint is freedom from recurrent ischemic stroke or imaging confirmed TIA through at least 24 months post-randomization (co-primary endpoint 1) and incidence of subjects with new brain infarct or clinical findings of ischemic stroke from screening through 24 months or last follow-up visit, whichever occurs first (co-primary endpoint 2). The safety endpoint is the proportion of subjects who experience adverse events (AEs) that are determined to be related to device, procedure, and/or antiplatelet medical management. Additional secondary endpoints include clinical success, overall survival, time to any stroke/TIA, and device success as defined in the clinical protocol. All available patients in REDUCE will be followed through 5 years.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.