FDA Executive Summary

Prepared for the
May 24, 2016 meeting of the
Circulatory System Devices Panel

P120021
AMPLATZER™ Patent Foramen Ovale (PFO) Occluder
St. Jude Medical

Introduction

This is the FDA Executive Summary for the AMPLATZER PFO Occluder, a first-of-a-kind transcatheter patent foramen ovale (PFO) closure device. The device is a permanent cardiac implant and is intended for percutaneous, transcatheter closure of a PFO in patients who have had a cryptogenic ischemic stroke due to a presumed paradoxical embolism (thromboembolism from the venous circulation to the arterial circulation through the PFO). The RESPECT pivotal clinical trial to evaluate the safety and effectiveness of the AMPLATZER PFO Occluder was fully approved by the Agency on September 13, 2000 under Investigational Device Exemption (IDE) G990318. On November 30, 2012, St. Jude Medical submitted a Premarket Approval Application (PMA) requesting marketing approval of the device under P120021. This submission has been reviewed by the Division of Cardiovascular Devices (DCD), Office of Device Evaluation, within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This memorandum will summarize FDA's review of the PMA, highlighting the areas for which we are seeking the Panel's expertise and input. These topics will include the device performance and clinical experience to date, focused on the RESPECT IDE trial. At the conclusion of your review and discussion of the data, FDA will ask for your assessment of the safety and effectiveness and benefit-risk profile of the AMPLATZER PFO Occluder to prevent recurrent stroke in patients with a PFO and a history of cryptogenic stroke.

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1 PROPOSED INDICATIONS FOR USE

The sponsor has proposed the following Indications for Use statement:

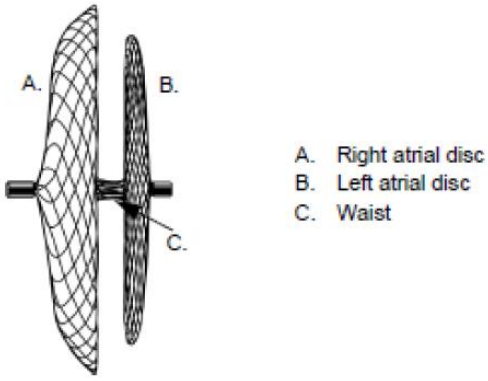
The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to presumed paradoxical embolism.

FDA Comment: The Panel will be asked to comment on whether the proposed Indications for Use statement is appropriate.

2 DEVICE DESCRIPTION

The AMPLATZER PFO Occluder (the Device) is a self-expandable, double disc device made from a Nitinol wire mesh (**Figure 1**). The two discs are linked together by a short connecting waist which allows for each disc to articulate in relation to the defect and conform to the septal wall. To enhance the closing ability, the discs contain a thin polyester fabric.

Figure 1. AMPLATZER PFO Occluder



The Device contains radiopaque marker bands on the distal and proximal ends. An end screw on the proximal end facilitates delivery and deployment. The Device is available in three sizes: 18/18 mm, 18/25 mm, and 25/35 mm (numbers corresponds to the left and right atrial disc diameters, respectively). Per the Instructions for Use, device size selection should be based on imaging techniques that measure the distance from the defect to the aortic root and the distance from the defect to the superior vena cava orifice.

The 510(k) cleared AMPLATZER TorqVue Delivery System is used to deliver the Device. It is comprised of a delivery sheath which is used to cross the atrial septum through the PFO from the right atrium to the left atrium. A loader containing the Device and delivery cable are advanced through the delivery sheath until the Device reaches the

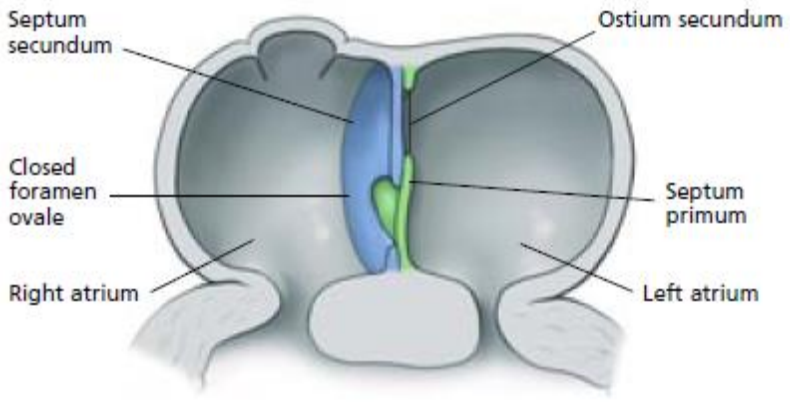
tip of the sheath. Once in the proper position, the delivery sheath is retracted to first deploy the left atrial disc followed by deployment of the right atrial disc. If device positioning is not satisfactory, the Device can be recaptured into the sheath and deployment can be reattempted, or the Device can be removed. After deployment, the Device is detached from the delivery cable.

3 CLINICAL BACKGROUND INFORMATION AND REGULATORY HISTORY

Patent Foramen Ovale (PFO)

The foramen ovale is a flap-like opening between the atrial septum primum and septum secundum at the location of the fossa ovalis. During fetal development, oxygenated blood from the inferior vena cava crosses through the foramen ovale to provide oxygenated blood for the systemic circulation. At birth, establishment of the pulmonary circulation increases left atrial pressure, pressing the flap against the septum and closing the communication. Complete closure of the foramen ovale occurs in 70-75% of individuals by age 2 (**Figure 2**).

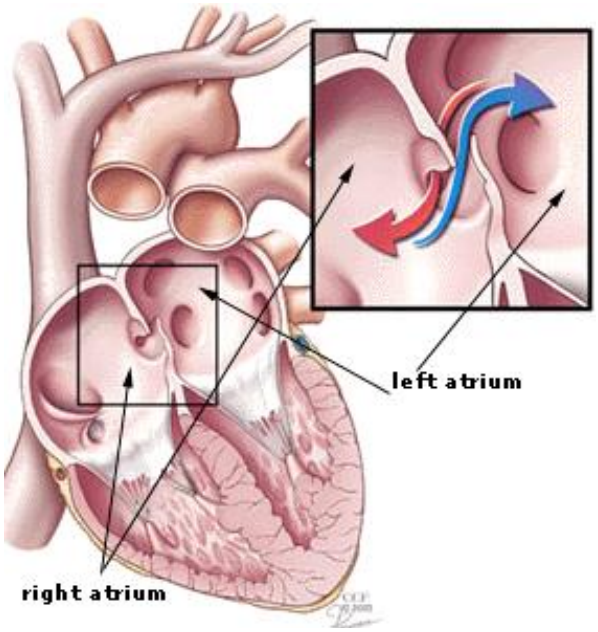
Figure 2. Foramen Ovale Anatomy[1]



The foramen ovale remains patent (a PFO) into adulthood in 25-30% of individuals. (Hagen PT, 1984) Although a PFO is an incidental finding of no clinical consequence in most individuals, it can permit the shunting of blood across the inter-atrial septum between the venous and arterial circulations (as shown in **Figure 3**). The presence of a shunt across a PFO is the presumed mechanism for paradoxical thromboembolization leading to ischemic stroke, and there are established criteria to grade the severity of shunting across the PFO.

[1] Krasuski RA. When and how to fix a 'hole in the heart': Approach to ASD and PFO. Cleveland Clinic J Med. 2007; 74: 137-47.

Figure 3. Shunting across PFO[2]



A PFO may also be associated with an atrial septal aneurysm (ASA), which consists of redundant atrial septal tissue in the region of the fossa ovalis. ASAs are generally associated with a larger separation between the septum primum and septum secundum and a higher grade inter-atrial shunt compared to PFOs without an associated ASA.

Stroke

Stroke is the fourth leading cause of mortality and a leading cause of serious, long-term disability in the US. (Roger VL, 2012) Strokes are categorized as ischemic (>80% of all strokes), hemorrhagic, or undetermined. Most ischemic strokes are due to thromboembolism from an intracardiac source, large vessel athero- or thromboembolism, small vessel occlusive disease, or vasculitis. The following are potential etiologies of ischemic stroke:

- Thromboembolic stroke in the setting of atrial fibrillation
- Thromboembolic stroke due to left ventricular mural thrombus
- Thromboembolic stroke due to non-bacterial thrombotic endocarditis
- Thromboembolic stroke associated with prosthetic heart valves
- Atheroembolic stroke due to thoracic aortic or carotid artery atherosclerotic disease
- Intracranial arterial disease
- Arterial dissection
- Hypercoagulable states

[2] http://my.clevelandclinic.org/services/heart/disorders/congenital-heart/patent-foramen

- Thromboembolic stroke via a right-to-left shunt

In patients under 55 years of age, up to 30% of ischemic strokes are reported to be cryptogenic (no identified cause). (Sacco RL E. J., 1989) The diagnosis of cryptogenic stroke is one of exclusion and highly dependent on the comprehensiveness of the evaluation to exclude alternative known stroke etiologies. With continued advances in diagnostic testing and monitoring (e.g., cardiovascular and neurovascular imaging, extended or cardiac monitoring with cutaneous or implanted devices to detect sub-clinical atrial fibrillation, and markers for hypercoagulable states), it is likely that more strokes that were previously classified as cryptogenic will have an identifiable etiology that is independent of the presence of a PFO.

PFO and the risk of a first stroke

A PFO is a common incidental anatomic finding in the general population, and its presence does not confer a risk of stroke among asymptomatic individuals. The multiethnic Northern Manhattan Study (NOMAS) showed that a PFO was not associated with increased stroke risk in men and women, or in those younger or older than 60 years of age. (Di Tullio MR, 2007) Similarly, PFO was also not an independent predictor of stroke among normal individuals >45 years of age in the Olmsted County SPARC Study. (Meissner I, 2006) Further, no consistent association has been established between the risk of stroke and PFO size, severity of right-to-left shunting, or the presence of an ASA. (Sacco RL A. R., 2006) (Homma S S. R., 2005) (Mas JL, 2001) (Wöhrle, 2006) Although there have been case reports of thrombi originating in the venous circulation traversing a PFO in stroke patients (Srivastava TN, 1997), venous thrombosis has been only rarely identified in patients with PFO and stroke. (O'Gara PT, 2009)

PFO and the risk of cryptogenic stroke

Several observational studies have reported a higher prevalence of PFO in cryptogenic stroke patients vs. normal individuals or individuals with an identifiable etiology for stroke, suggesting paradoxical embolism as a potential underlying pathophysiological mechanism. Among subjects age 30 to 85 years enrolled in the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a PFO was detected by TEE in 33.8% of subjects; a PFO was found in 39.2% of subjects with a cryptogenic stroke vs. 29.9% of subjects with a known etiology for stroke. (Homma S S. R., 2002) It has been suggested that the presence of a PFO may play a more important role as a cause of stroke in younger compared with older patients. In the PFO-ASA Study, a PFO was identified by transesophageal echocardiography (TEE) in 45.9% of 581 young subjects with cryptogenic stroke. (Lamy C, 2002) Handke et al. reported a PFO prevalence rate of 43.9% in younger patients (age ≤55 years) with cryptogenic stroke compared with a 14.3% incidence in younger patients with stroke due to a known cause (odds ratio 4.70, 95% confidence interval [CI] 1.89 to 11.68, P<0.001). The prevalence of PFO in older patients (age >55 years) with cryptogenic stroke was 28.3% compared with 11.9% in older patients with stroke with a known cause (odds ratio 2.92, 95% CI 1.70 to 5.01, P<0.001). (Handke M, 2007) However, stroke subjects with PFO did not have a

significantly increased risk of recurrent stroke or death at 2 years compared to stroke subjects without a PFO in the PICSS trial. (Homma S S. R., 2002)

Current standard of medical care to prevent recurrent stroke in cryptogenic stroke patients with PFO

The 2014 American Heart Association and American Stroke Association stroke guidelines (affirmed by the American Academy of Neurology) recommend antiplatelet agents for patients with an ischemic stroke or transient ischemic attack (TIA) and a PFO who are not otherwise being treated with anticoagulation therapy (Class I; Level of Evidence B). (Kernan WN, 2014) These guidelines note that there are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with a PFO (Class IIb; Level of Evidence B). Regarding transcatheter device closure of a PFO in patients with a cryptogenic ischemic stroke or TIA, the guidelines state that available data do not support a benefit for PFO closure (Class III; Level of Evidence A). However, PMA-approved transcatheter atrial septal occlusion devices intended to close hemodynamically significant atrial septal defects have been widely used off-label to prevent recurrent stroke in patients with a PFO.

Clinical trials to evaluate the safety and effectiveness of PFO closure to prevent recurrent stroke in patients with PFO and a prior cryptogenic stroke

FDA has required sponsors to perform randomized controlled trials (RCTs) to conclusively demonstrate the safety and effectiveness of PFO occlusion devices to prevent recurrent stroke. FDA's requirement for RCTs has been supported by the Circulatory System Devices Advisory Panel on three occasions (October 24, 1997, September 10, 2002, and March 2, 2007). The American Heart Association/American Stroke Association, the American College of Cardiology, and the American Academy of Neurology have also endorsed the need for randomized trials of PFO closure in this patient population. (O'Gara PT, 2009)

There have been multiple challenges to executing and completing RCTs of PFO closure to prevent recurrent stroke. Despite efforts to develop trials that have feasible sample sizes, broader patient populations, and flexibility in the choice of antiplatelet agents or anticoagulation treatment in the control group, study enrollment in these trials has been slow due to:

- Lack of clinical equipoise among physicians in favor of PFO closure combined with the availability of approved atrial septal occluders that can be used off-label;
- Patient preference (i.e., desire to have the PFO closed) rather than opting for medical therapy; and
- Preference among some physicians favoring warfarin over antiplatelet therapy, leading to off-label use of devices to close the PFO in patients unwilling to take warfarin.

The first large randomized trial of a device closure of a PFO occlusion, CLOSURE I, failed to show the superiority of the STARFlex PFO Occluder vs. medical therapy for the primary endpoint of the composite of recurrent stroke or TIA at 24 months after

randomization, all-cause mortality to 30 days, or death from neurologic causes between 31 days and 24 months. In the PC trial, PFO closure with the Amplatzer PFO Occluder was not superior to medical therapy for the primary endpoint of the composite of death, nonfatal stroke, TIA, or peripheral embolism. (Meier, 2013) A pooled meta-analysis of the CLOSURE I, PC and RESPECT randomized trials suggested that PFO closure reduced the risk of recurrent stroke. (Kent DM, 2016)

Of note, Humanitarian Device Exemptions (HDE) applications for the AMPLATZER PFO Occluder and the STARFlex PFO Occluder were previously approved for patients who had recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who had failed conventional drug therapy. The AMPLATZER PFO Occluder HDE was originally approved on April 5, 2002. The HDE applications for both PFO occluders were withdrawn on October 31, 2006 because the estimated number of eligible patients was greater than the allowable patient population limit for humanitarian use devices, rendering these devices no longer eligible for marketing under an HDE. To fill the void created by the withdrawal of the HDE, the PFO Access Registry (IDE G060145) was approved by FDA on September 21, 2006 for PFO closure with the AMPLATZER PFO Occluder in patients who have had a *recurrent* cryptogenic stroke despite a trial of standard-of-care medical therapy (see **Appendix B**).

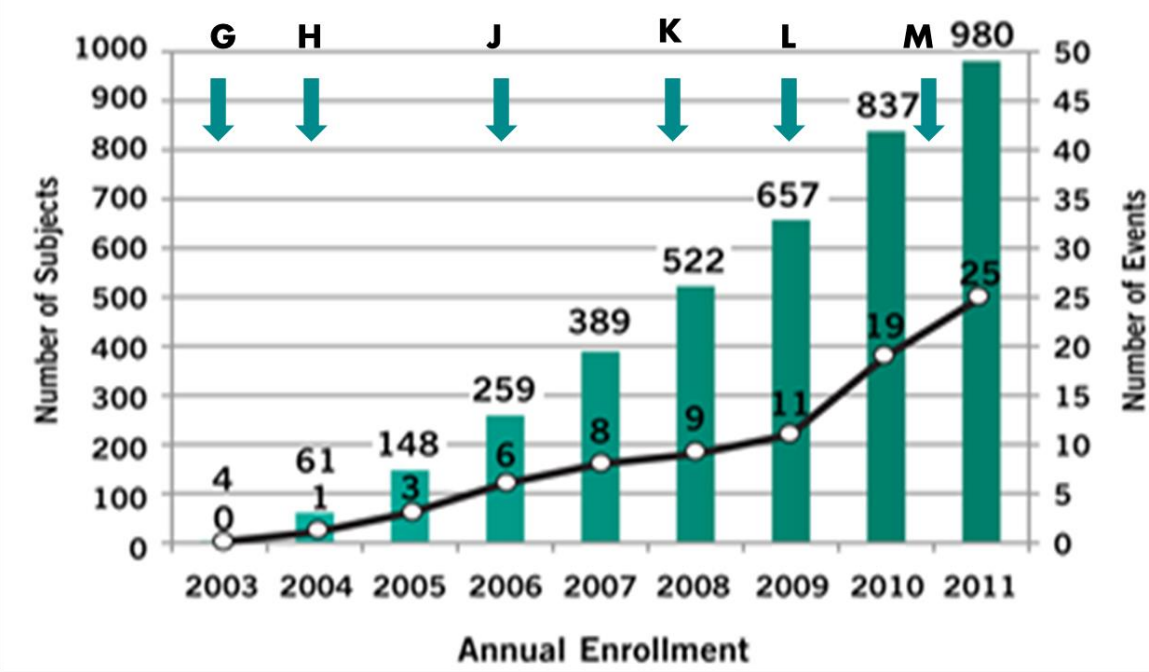
The RESPECT Trial

The pivotal RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) conducted under IDE G990318 was designed as a prospective, randomized, event-driven, multi-center clinical study to evaluate the safety and effectiveness of the AMPLATZER PFO Occluder. The objective of RESPECT was to investigate whether PFO closure with the AMPLATZER PFO Occluder is superior to the current standard of care medical treatment in the prevention of recurrent embolic stroke.

The first RESPECT subject was enrolled on August 23, 2003 under the first FDA approved protocol, Revision G. Over the course of the RESPECT trial, the clinical protocol underwent 5 revisions, many of which were intended to address slow enrollment.

Figure 4 illustrates the protocol revisions, cumulative subject enrollment, and the number of primary endpoint events over the initial 8 years of the trial.

Figure 4. RESPECT Protocol Revisions (G-M), Subject Enrollment and Total Primary Endpoint Events



An overview of the key changes made to the RESPECT protocol is as follows:

- Revision H
  - Increased the upper age limit of subjects from 55 to 60
  - Extended the duration of time between the qualifying cryptogenic stroke and enrollment from 90 days to 180 days
- Revision J
  - Further extended the duration of time between the qualifying cryptogenic stroke and enrollment from 180 days to 270 days
  - Removed aspirin combined with clopidogrel as an approved medical treatment for the Medical Management group
  - Added an exclusion criterion for subjects who are unable to discontinue the use of anticoagulation
- Revision M
  - Increased the sample size from 900 to 1000 due to the recognition of differential drop-out between treatment groups (higher in the Medical Management vs. the Device group)
  - Added Kaplan-Meier analyses for Intent to Treat and Per-Protocol populations

PMA P120021 was filed on November 30, 2012 and included the results from the RESPECT clinical study.

FDA Comment: The RESPECT trial was originally designed to test PFO closure vs. medical therapy in young patients (≤55 years old) with few comorbidities, with PFO closure occurring relatively soon (within 90 days) after a qualifying cryptogenic stroke. Because of slow enrollment, one inclusion criterion change allowed enrollment of older subjects, who may be expected to have more co-morbidities associated with stroke compared with younger individuals. Another study change extended the window between the time of the qualifying stroke and randomization from 90 to 270 days. The longer permitted time between the qualifying stroke and randomization (and a still later PFO occlusion procedure), would likely differ from how the Device would be used in practice (in which PFO closure may occur soon after the occurrence of stroke). The potential impact of these changes to the investigational plan should be considered in the interpretation of the study results.

4 NON-CLINICAL STUDIES

The sponsor conducted non-clinical bench and animal studies of the AMPLATZER PFO Occluder that included, but were not limited to, evaluations of biocompatibility, magnetic imaging compatibility, in vivo tissue responses, sterilization shelf-life/packaging, and manufacturing. The non-clinical study results provided in the PMA were reviewed by FDA and found to be acceptable.

4.1 Bench Studies

The sponsor conducted in vitro performance and material characterization studies of the AMPLATZER PFO Occluder. The bench testing was performed to ensure that the device performs as intended and meets all design requirements. The following tests were performed on the AMPLATZER PFO Occluder, and the results were found to be acceptable by FDA:

- Visual Inspection
- Dimensional Verification (pre and post- deployment)
- End Screw Attachment
- Load Force
- Handoff Force
- Advancement Force
- Simulated Deployment and Retrieval
- Simulated Device Release & Visual Inspection
- Pull Through
- Tensile Strength
- Fatigue Testing
- Particulate Testing
- Corrosion Testing

4.2 Biocompatibility

The sponsor identified all material components of the AMPLATZER PFO Occluder and conducted biocompatibility testing in accordance with *International Standard ISO-10993-1, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing*. The following tests were performed, and the results were found to be acceptable by FDA:

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity (Irritation)
- Systemic Toxicity (acute)
- Pyrogenicity
- Hemolysis
- Complement Activation
- Genotoxicity
- Implantation
- Sub-chronic toxicity

4.3 Magnetic Resonance Imaging (MRI) Compatibility

MRI Compatibility testing was conducted, and the results demonstrated that the AMPLATZER PFO Occluder is MR Conditional. The device can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla or 3.0 Tesla;
- Maximum spatial gradient field less than or equal to 30 T/m; and
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes.

4.4 Animal Studies

A GLP animal study was performed in pigs to evaluate the AMPLATZER PFO Occluder for acute deliverability and handling and chronic device implant safety and performance. The study demonstrated complete PFO closure and device stability.

4.5 Sterilization

The AMPLATZER PFO Occluder is provided sterile and for single use only. The Device is sterilized via ethylene oxide using a sterilization cycle that was validated according to FDA-recognized international standards.

4.6 Shelf-Life/Packaging

The shelf life and packaging for the AMPLATZER PFO Occluder was validated according to FDA-recognized standards.

4.7 Manufacturing

All of the manufacturing information has been reviewed and was found to be acceptable.

5 THE RESPECT TRIAL (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)

Objective: To investigate whether percutaneous PFO closure is superior to the current standard of care medical treatment for the prevention of recurrent embolic stroke in subjects who had a cryptogenic stroke due to presumed paradoxical embolism.

Study Design: Prospective, multicenter, randomized, unblinded study with an event-driven primary endpoint comparing the safety and effectiveness of the AMPLATZER PFO Occluder with medical therapy.

- Neither subjects nor health care providers were blinded to the randomization assignment.

Treatment groups:

1. *AMPLATZER PFO Occluder (the **Device**) group*
   - Timing of device implantation procedure: Subjects were required to undergo the Device implantation procedure within 21 days of randomization.
   - Medical therapy
     - Aspirin (325 mg/day) recommended at least 24 hours prior to the implant procedure.
     - Intra-procedure: Heparin to achieve an activated clotting time (ACT) >200 seconds.
     - Clopidogrel daily for 1 month and aspirin daily for 6 months after Device placement. After 6 months, medical therapy was at the physician's discretion.

2. *Medical Management (**MM**) group*
   - Subjects could be treated with any of the following regimens:
     - Aspirin alone
     - Warfarin alone
     - Clopidogrel alone
     - Aspirin plus dipyridamole
     - Aspirin plus clopidogrel
   - MM group caveats
     - Before randomization, the investigator determined the recommended medication regimen for each subject.
     - Subjects started the recommended treatment immediately.
     - Under protocol revision J, aspirin plus clopidogrel was eliminated as an acceptable medical regimen consistent with the recommendations reported in the 2006 update of the AHA/ASA guidelines. MM subjects were allowed

to change antiplatelet or anticoagulation treatment as long as the new regimen was included among the protocol-defined options.

Timing of trial enrollment: Enrollment occurred when the subject was randomized.

Randomization: 1 to 1, Device to MM

- Randomization stratified by:
  - Investigational site
  - Presence of an atrial septal aneurysm (ASA), defined as septum primum movement ≥10 mm relative to the plane of the inter-atrial septal plane, as determined by the investigator
  - Recommended medical therapy

Number of subjects randomized and investigational sites:

- 980 subjects enrolled
  - 499 randomized to the Device group
  - 481 randomized to the MM group.
- 69 investigational sites
  - 925 subjects enrolled at 62 US sites
  - 55 subjects enrolled at 7 Canadian sites

Baseline assessment and follow-up schedule:

Table 1. Baseline and Follow-up Assessment Schedule

♥ = Required testing Assessment	Baseline	Procedure	Discharge[d]	1 month (±1 week) (day 23–day 37) [f]	6 months (±1 month) (day 150–day 210) [f]	12 months (±2 months) (day 305–day 425) [f]	18 Months (±2 months) (day 485–day 605) [f]	2 years (±2 months) (day 670–day 790) [f]	3 years (±2 months) (day 1035–day 1155) [f]	Even years (±2 months) [f]	Odd years (±2 months) [f]
Office follow-up: (if required)											
History and physical exam	♥		♥	♥	♥	♥	♥	♥	♥	♥	♥
Neurologic examination											
• NIH Stroke Scale[e]	♥					♥		♥	♥	♥	♥
• Barthel Index	♥							♥		♥	
• Modified Rankin Scale	♥							♥		♥	
Stroke questionnaire + additional assessments, as necessary	♥			♥	♥	♥	♥	♥	♥	♥	♥
Pregnancy test[a]	♥										
ECG or Holter monitor	♥[b]		♥	♥[b]							
Coagulation test	♥										
MRI or CT scan	♥										
Imaging of intracranial arteries via MR angiography , CT angiography, contrast angiography, or TCD	♥										
Imaging of extracranial arteries via MRA, CT angiography, contrast angiography, or duplex sonography	♥										
Transesophageal echo with bubble study[c]	♥	♥			♥						
Telephone follow-up:											
History									♥	♥	♥
Barthel Index										♥	
Modified Rankin Scale										♥	
Stroke questionnaire									♥	♥	♥

[a] Required for pre-menopausal women and women of child bearing potential.
[b] An ECG or a Holter monitor is required for all trial subjects.
[c] The 6-month TEE is required only for subjects who receive a device. ICE may be used at procedure in place of TEE.
[d] The discharge follow-up is only required for subjects who receive a device.
[e] All personnel conducting any trial required NIHSS evaluations are required to have received training and certification per nationally accepted guidelines including, but not limited to, American Stroke Association, American Academy of Neurology, National Institute of Neurological Disorders and Stroke.
[f] For device subjects, the day of procedure is day 1. For medical management subjects, the day of randomization is day 1.

PFO shunt grade (assessed by TEE):

- Grade 0: No microbubbles in the left atrium at rest and during Valsalva within 3 cardiac cycles after right atrial opacification
- Grade I: 1 to 9 microbubbles
- Grade II: 10 to 20 microbubbles
- Grade III: More than 20 microbubbles

Maximal shunt grade was determined as the most severe grade between assessments at rest and at Valsalva. If only one assessment was available (at rest or with Valsalva), that one was used to assess shunt grade.

5.1 Enrollment Criteria

5.1.1 Inclusion Criterion

Subjects with a PFO who have had a cryptogenic stroke within the last 270 days

- Stroke was defined as an acute focal neurological deficit, presumed to be due to focal ischemia, and either 1) symptoms persisting ≥24 hours, or 2) symptoms persisting ≤24 hours but associated MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.
- Cryptogenic stroke was defined as a stroke from an unknown cause.
- A PFO was defined as visualization of microbubbles (during TEE) in the left atrium within three cardiac cycles of right atrial opacification at rest and/or during Valsalva release.

5.1.2 Key Exclusion Criteria

Patients who met any one of the following criteria were excluded from this study:

1. Age <18 years and age >60 years
2. Atherosclerosis or other arteriopathy of the intracranial or extracranial vessels with >50% lumen diameter stenosis supplying the involved lesion
3. Intracardiac thrombus or tumor
4. Acute or recent (within 6 months) MI or unstable angina
5. Left ventricular aneurysm or akinesis
6. Mitral valve stenosis or severe mitral regurgitation
7. Aortic valve stenosis (gradient >40 mmHg) or severe regurgitation
8. Mitral or aortic valve vegetation or prosthesis
9. Aortic arch plaques protruding >4 mm into the lumen
10. Left ventricular dilated cardiomyopathy with LVEF <35%
11. Another source of right to left shunts identified at baseline, including an atrial septal defect and/or fenestrated septum
12. Atrial fibrillation/atrial flutter (chronic or intermittent)
13. Active endocarditis, or other untreated infections
14. Kidney, liver or lung failure
15. Uncontrolled hypertension, defined as sustained elevated blood pressure >160/90 mm Hg on medication

16. Uncontrolled diabetes mellitus, defined as elevated glucose levels despite administration of insulin or levels >200/dl mg with glucosuria
17. Lacunar infarct probably due to intrinsic small vessel as the qualifying event, defined as an ischemic stroke in the distribution of a single, small deep penetrating vessel in a patient with any of the following:
    - A history of hypertension (except in the first week post stroke)
    - A history of diabetes mellitus
    - Age ≥50 years
    - MRI or CT with leukoaraiosis greater than symmetric, well-defined periventricular caps, or bands (European Task Force on Age-Related White Matter Changes rating scale score >0)
18. Arterial dissection as the qualifying event
19. Progressive neurological dysfunction or life expectancy is <2 years
20. A positive test with one of the following indicating a hypercoagulable state: anticardiolipin Ab (IgG or IgM), lupus anticoagulant, B2-glycoprotein-1 antibodies, or persistently elevated fasting plasma homocysteine despite medical therapy
21. Subjects contraindicated for aspirin or clopidogrel
22. Anatomy in which the Device would interfere with intracardiac or intravascular structures such as valves or pulmonary veins
23. Stroke with poor outcome at time of enrollment (modified Rankin Scale score >3)
24. Subjects not able to discontinue anticoagulation if randomized to the Device

5.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint was a composite of the following events:

- Recurrent nonfatal stroke, defined as:
  - An acute focal neurological deficit presumed to be due to focal ischemia and either:
    - Symptoms persisting ≥24 hours; or
    - Symptoms persisting <24 hours but associated with MRI or CT imaging findings of a new neuroanatomically relevant cerebral infarct
- Post-randomization all-cause mortality, defined as:
  - Death within 45 days after randomization in the MM group
  - Death within 30 days after implant or 45 days after randomization (whichever occurs latest) in the Device group
- Fatal ischemic stroke

5.2.1 Primary Effectiveness Endpoint Analysis

Statistical hypothesis: The hypothesis for the primary effectiveness endpoint was as follows:

$$H_0: r_1 \geq r_2$$
$$H_1: r_1 < r_2$$

where r_1 and r_2 are the rate of recurrent nonfatal stroke, post-randomization death or fatal ischemic stroke for the Device and MM groups, respectively.

Primary analysis cohort and analyses (pre-specified in protocol revision G prior to subject enrollment):
Intention to treat (ITT) population:

- Includes all randomized subjects
- Subjects are analyzed by the treatment group to which they were randomly assigned, regardless of the treatment that they actually received
- The primary endpoint analysis is the ITT raw count
    - A Kaplan-Meier analysis was also performed on the ITT cohort.

FDA Comment: The ITT population was the pre-specified primary analysis population (raw count analysis) in RESPECT. FDA guidance recommends that the primary statistical analysis follow the ITT principle for randomized clinical superiority trials. This potentially conservative approach avoids biases associated with patients switching treatment, selection bias, and dropout/withdrawal patterns that may confound the observed treatment effect. The ITT analysis is preferred in superiority trials because it protects against bias that might be associated with early subject withdrawal from the study.

Enrollment stopping decision rules and success criteria:
Decision rules were established for stopping trial enrollment and declaring study success based on comparing the raw counts of primary endpoint events (adjudicated by both the CEC and DSMB) in the Device and MM groups. These two decision rules would result in rejecting the null hypothesis:

- **Decision Rule 1:** Enrollment would be stopped and Device superiority would be declared if within the first 12 events, the number of primary endpoint events for the MM group equals or exceeds 10.
- **Decision Rule 2:** Enrollment would be stopped once 25 events were observed. Device superiority would be declared if within the first 25 events, the number of primary endpoint events for the MM group equals or exceeds 19.

In order to account for the differential drop-out rate observed between the Device and MM group, the protocol decision rules were revised to supplement the raw event count analysis with a Kaplan-Meier analysis and a log-rank test for the primary hypothesis.

Other analysis cohorts and analyses:
Per Protocol population (pre-specified in Revision M of the study protocol):

- Includes all subjects who received their randomly assigned treatment and complied with protocol-mandated medical treatment
- Excludes subjects who:
    - Did not receive the randomized therapy, such as:

        - Subjects who crossed over to a protocol-approved treatment prior to receiving their randomized treatment
        - Subjects who crossed over to a non-protocol approved treatment prior to receiving their randomized treatment
    - Did not comply with the protocol-mandated medical treatment, defined as <67% medication compliance during the study
    - Had a major inclusion/exclusion violation that could confound the treatment effect, including but not limited to:
        - Subjects without a PFO
        - Subjects with a multifenestrated atrial septum
        - Subjects with other (non-PFO) sources of right-to-left shunting
        - Subjects allergic to aspirin

The intent of the Per Protocol analysis was to characterize the effectiveness of the Device while accounting for protocol compliance and the duration of follow-up. Data were analyzed using the Kaplan-Meier method according to the subjects' randomization assignment.

FDA Comment: Medication non-compliance was defined as usage of <67% of protocol-mandated medical treatment during the study. However, there is no recognized standard definition for non-compliance with antiplatelet therapy.

As Treated population (agreed to by the RESPECT Steering Committee after Revision M of the study protocol in advance of the initial PMA data lock):

- Includes all subjects who received a protocol-approved treatment and complied with the protocol-mandated medical treatment
- Excludes subjects who:
    - Did not receive the randomized therapy or an alternative protocol-approved therapy
        - Subjects who crossed over to a non-protocol-approved treatment prior to receiving their randomized treatment were excluded.
        - Device group subjects who did not receive the device were excluded.
        - Device group subjects who experienced an event prior to receiving a device were excluded.
    - Did not comply with the protocol-mandated medical treatment, defined as <67% medication compliance during the study
- Subjects are analyzed per treatment groups according to the treatment received, regardless of the randomization assignment

The intent of the As Treated analysis was to characterize the effectiveness of the Device in subjects who actually received the Device compared with subjects who were compliant

with medical management, regardless of how they were randomized. Data were analyzed using the Kaplan-Meier method.

Device in Place population (a post-hoc analysis cohort recommended by the RESPECT Steering Committee):

- Includes all randomized subjects
- Subjects were analyzed per treatment groups (Device in Place or No Device in Place) according to whether or not they received the Device at the time of a primary endpoint event (i.e., subjects with a primary endpoint event prior to Device placement were included in the No Device in Place group).

The intent of the Device in Place analysis was to characterize the effectiveness of the Device in any subject who was implanted with the Device compared to subjects who were not implanted with the Device, regardless of subject compliance to protocol-required medical therapy. Data were analyzed using the Kaplan-Meier method.

5.3 Secondary Effectiveness Endpoints

- Absence of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death.
- Absence of transient ischemic attack (TIA), defined as an acute focal neurological deficit (focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit) presumed to be due to focal ischemia with symptoms persisting ≥5 minutes and <24 hours without MRI or CT findings of a new neuroanatomically relevant cerebral infarct.
- Complete PFO closure assessed by TEE with bubble study at 6 months follow-up (Device group only), defined as the absence of microbubbles in the left atrium at rest and during Valsalva within 3 cardiac cycles after right atrial opacification (adjudicated by the Echocardiography Core Lab).

There were no pre-specified hypotheses for the secondary effectiveness endpoints.

5.4 Safety

Reported adverse events were adjudicated by the Data Safety Monitoring Board (DSMB). The following were considered serious adverse events: death, a life threatening adverse event, an inpatient hospitalization or prolongation of an existing hospital stay, persistent or significant disability/incapacity, a congenital anomaly/birth defect in an offspring, or a medically significant event, including laboratory abnormalities.

FDA Comment: There was no pre-specified safety endpoint or statistical hypothesis for safety. The rates of safety events were to be presented descriptively.

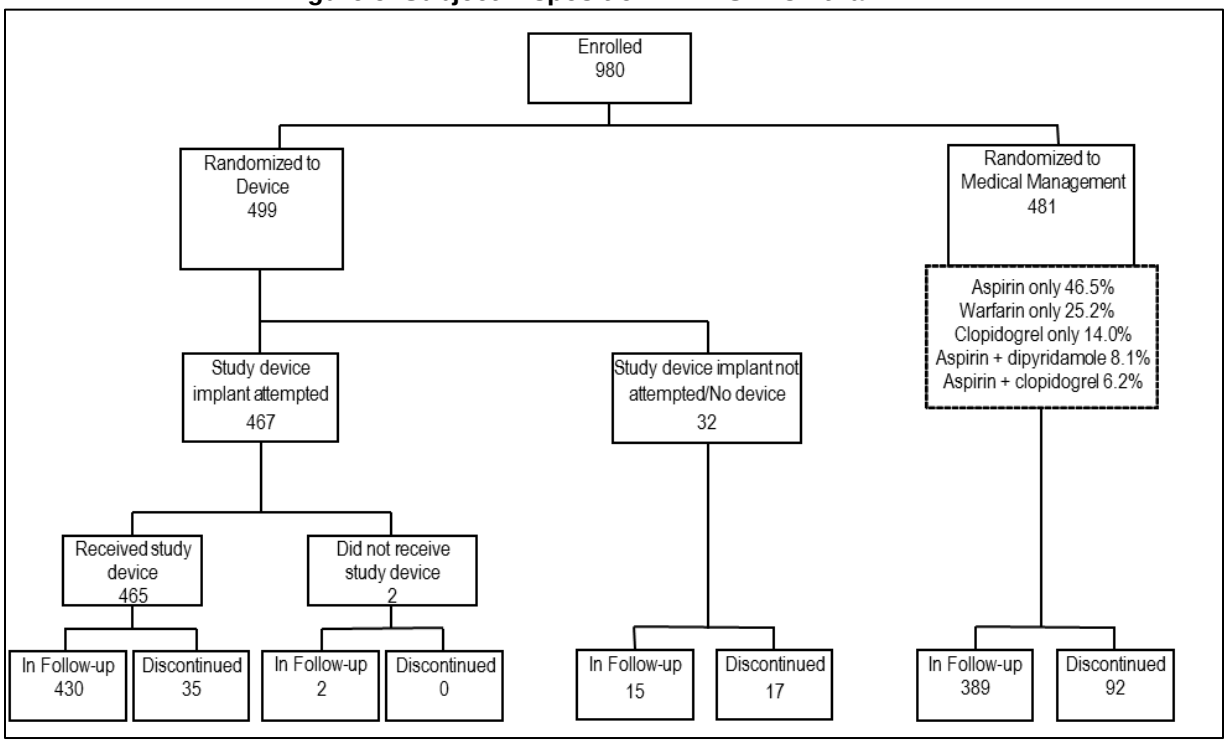
6 RESPECT TRIAL RESULTS

The initial data lock used for primary analyses of the RESPECT Trial occurred on 20 May 2012. A second data lock occurred on 14 August 2015, which includes extended follow-up results.

6.1 Subject Accountability

In the ITT population, 980 subjects were enrolled, of which 499 were randomized to the Device group and 481 to the MM group. Subject accountability as of the initial data lock (20 May 2012) is shown in **Figure 5**, which includes the distribution of the subject follow-up and discontinuation.

Figure 5. Subject Disposition in RESPECT trial



Subject follow-up for Device and MM subjects for the initial data lock (20 May 2012) and the extended follow-up data lock (14 August 2015) are shown **Table 2**. For the initial data lock (20 May 2012), the mean subject follow-up in the Device and MM groups was 3.0 and 2.7 years, respectively. For the extended follow-up data lock (14 August 2015), the mean subject follow-up in the Device and MM groups was 5.5 and 4.9 years, respectively.

Table 2. Cumulative Follow-up

Data Locks	Mean [Range] Total Patient-Years		Difference (Device – MM) Mean Total Patient-Years
	Device (N=499)	MM (N=481)	
Initial PMA: 20 May 2012	3.0 [0.0, 8.1] years 1476 patient-years	2.7 [0.0, 8.1] years 1284 patient-years	0.3 years 192 patient-years
Extended follow-up: 14 Aug 2015	5.5 [0.0, 11.4] years 2769 patient-years	4.9 [0.0, 11.3] years 2376 patient-years	0.6 years 393 patient-years

FDA Comment: RESPECT trial provides long-term follow-up data in a large number of randomized subjects. However, more data are available for the Device group vs. the MM group due to a disproportionate drop-out of MM subjects (see Section 6.3).

6.2 Study Population Demographics and Baseline Characteristics

The Device and MM groups were generally well-matched with respect to baseline subject characteristics (**Table 3**), medical history (**Table 4**), stroke risk factors (**Table 5**) and anti-thrombotic medications (**Table 6**).

Table 3. Study Population Demographics and Baseline Characteristics – ITT Population

	Device (N=499)	MM (N=481)	p-value[1]
Age, years	45.7 (9.7)	46.2 (10.0)	0.491
Time from qualifying stroke to randomization, days	130 (70)	130 (69)	0.891
Sex, male	268 (53.7%)	268 (55.7%)	0.564
NIHSS score	0.8 (1.8)	0.7 (1.6)	0.073
Barthel Index	98.9 (5.2)	99.7 (1.4)	0.046
mRS score	0.8 (0.8)	0.7 (0.8)	0.069

Continuous variables are reported as n, mean (SD), and categorical variables as n (%). [1]2-sample t-test (age), Wilcoxon-Mann-Whitney test (days from stroke to date randomized, NIHSS, Barthel, and mRS), and Fisher's Exact test (sex).

Table 4. Baseline Medical History - ITT Population

Medical History[1]	Device (N=499)	MM (N=481)	p-value[2]
Documented arrhythmias			
Heart block	13/453 (2.9%)	7/442 (1.6%)	0.258
Ventricular tachycardia	3/453 (0.7%)	2/442 (0.5%)	1.000
Atrial fibrillation	0/453 (0.0%)	1/442 (0.2%)	0.494
Atrial flutter	0/453 (0.0%)	0/442 (0.0%)	N/A
Supraventricular tachycardia	3/453 (0.7%)	6/442 (1.4%)	0.336
Other arrhythmia	14/453 (3.1%)	6/442 (1.4%)	0.112
COPD	4/499 (0.8%)	7/481 (1.5%)	0.377
Congestive heart failure	3/499 (0.6%)	0/481 (0.0%)	0.249
Coronary artery disease	19/499 (3.8%)	9/481 (1.9%)	0.084
Deep vein thrombosis	20/499 (4.0%)	15/481 (3.1%)	0.494
Migraine	195/499 (39.1%)	186/481 (38.7%)	0.948
Peripheral vascular disease	5/499 (1.0%)	1/481 (0.2%)	0.218
Previous MI	5/499 (1.0%)	2/481 (0.4%)	0.452
Previous TIA	58/499 (11.6%)	61/481 (12.7%)	0.626
Stroke prior to qualifying cryptogenic stroke	53/498 (10.6%)	51/481 (10.6%)	1.000

Different denominators across variables are due to modifications to data collection parameters over the course of the study. [1]As reported by investigator or site or recorded medical history. [2]Fisher's Exact test.

Table 5. Baseline Stroke Risk Factors - ITT Population

Risk Factors	Device (N=499)	MM (N=481)	p-value[1]
Birth control /hormone replacement therapy	41/499 (8.2%)	51/481 (10.6%)	0.228
Current Smoker	75/499 (15.0%)	55/481 (11.4%)	0.109
Diabetes mellitus	33/499 (6.6%)	41/481 (8.5%)	0.278
Family history of ischemic heart disease	161/494 (32.6%)	157/480 (32.7%)	1.000
Family history of stroke	136/495 (27.5%)	109/480 (22.7%)	0.090
Former smoker	134/499 (26.9%)	143/481 (29.7%)	0.322
Hypercholesterolemia	196/499 (39.3%)	195/481 (40.5%)	0.696
Hypertension	160/499 (32.1%)	153/481 (31.8%)	0.945
Substance Abuse	10/499 (2.0%)	5/481 (1.0%)	0.299
Other risk factor[2]	37/456 (8.1%)	40/443 (9.0%)	0.636

Different denominators across variables is due to modifications to data collection parameters over the course of the study. [1]Fisher's Exact test. [2]The most frequent other risk factors include dys/hyperlipidemia, sleep apnea, and obesity.

FDA Comment: Although balanced between treatment groups, atherosclerotic risk factors for stroke were common among enrolled subjects. A history of migraine, which has been associated with ischemic stroke, was also a relatively frequent baseline characteristic. These clinical features should be considered in: (1) categorizing the qualifying and recurrent strokes as cryptogenic, and (2) the role played by the PFO in the pathophysiology of stroke.

Table 6. Baseline Anti-thrombotic Medications - ITT Population

Medication	Device (N=499)	MM (N=481)	p-value[1]
Single antiplatelet therapy	282/499 (56.5%)	270/479 (56.4%)	0.239
Warfarin alone	117/499 (23.4%)	101/479 (21.1%)	
Dual antiplatelet therapy	72/499 (14.4%)	71/479 (14.8%)	
Anticoagulant plus single antiplatelet therapy	24/499 (4.8%)	34/479 (7.1%)	
Non- warfarin anticoagulant alone	3/499 (0.6%)	0/479 (0.0%)	
Other[2]	1/499 (0.2%)	3/479 (0.6%)	

[1] Chi-squared test. [2] Includes but is not limited to novel anticoagulant medications.

Compliance with anti-thrombotic medical therapy:
Table 7 (Device subjects) and **Table 8** (MM subjects) show subject use of protocol-directed anti-platelet therapy in the Device group and antiplatelet or anticoagulant therapy in the MM group at annual follow-up time points. Temporary medication interruptions are not shown in the tables.

In Device subjects (**Table 7**), antiplatelet therapy was per the physician's discretion after 6 months. Except for subjects at ≥8 years follow-up (in which data are limited), >90% of Device patients were using anti-thrombotic medications (the vast majority of whom were taking antiplatelet agents).

Table 7. Post-procedure medication use in Device group subjects who received a Device

Visit	Aspirin alone	Clopidogrel alone	Warfarin alone	Aspirin and dipyridamole	Aspirin and clopidogrel	Other[1]	None
Pre-Discharge	10/471 (2.1%)	3/471 (0.6%)	2/471 (0.4%)	0/471 (0.0%)	446/471 (94.7%)	9/471 (1.9%)	1/471 (0.2%)
1 Month	84/481 (17.5%)	9/481 (1.9%)	3/481 (0.6%)	0/481 (0.0%)	366/481 (76.1%)	17/481 (3.5%)	2/481 (0.4%)
6 Month	325/473 (68.7%)	13/473 (2.7%)	1/473 (0.2%)	2/473 (0.4%)	108/473 (22.8%)	8/473 (1.7%)	16/473 (3.4%)
12 Month	377/461 (81.8%)	19/461 (4.1%)	4/461 (0.9%)	2/461 (0.4%)	30/461 (6.5%)	6/461 (1.3%)	23/461 (5.0%)
18 Month	365/446 (81.8%)	22/446 (4.9%)	5/446 (1.1%)	1/446 (0.2%)	19/446 (4.3%)	6/446 (1.3%)	28/446 (6.3%)
2 Year	363/440 (82.5%)	24/440 (5.5%)	7/440 (1.6%)	1/440 (0.2%)	15/440 (3.4%)	7/440 (1.6%)	23/440 (5.2%)
3 Year	347/425 (81.6%)	28/425 (6.6%)	8/425 (1.9%)	2/425 (0.5%)	10/425 (2.4%)	5/425 (1.2%)	25/425 (5.9%)
4 Year	305/369 (82.7%)	20/369 (5.4%)	7/369 (1.9%)	1/369 (0.3%)	9/369 (2.4%)	5/369 (1.4%)	22/369 (6.0%)
5 Year	245/300 (81.7%)	17/300 (5.7%)	7/300 (2.3%)	2/300 (0.7%)	4/300 (1.3%)	5/300 (1.7%)	20/300 (6.7%)
6 Year	181/225 (80.4%)	11/225 (4.9%)	5/225 (2.2%)	2/225 (0.9%)	3/225 (1.3%)	6/225 (2.7%)	17/225 (7.6%)
7 Year	120/154 (77.9%)	5/154 (3.2%)	6/154 (3.9%)	2/154 (1.3%)	1/154 (0.6%)	6/154 (3.9%)	14/154 (9.1%)
8 Year	69/89 (77.5%)	1/89 (1.1%)	4/89 (4.5%)	3/89 (3.4%)	2/89 (2.2%)	1/89 (1.1%)	9/89 (10.1%)
9 Year	39/51 (76.5%)	0/51 (0.0%)	1/51 (2.0%)	2/51 (3.9%)	0/51 (0.0%)	2/51 (3.9%)	7/51 (13.7%)
10 Year	19/24 (79.2%)	0/24 (0.0%)	0/24 (0.0%)	0/24 (0.0%)	0/24 (0.0%)	1/24 (4.2%)	4/24 (16.7%)

Table includes subjects who received a device and had a follow-up visit; rows add to 100%
[1] The most frequent other medications were the combined use of aspirin and warfarin

In the MM group (**Table 8**), antiplatelet therapy (mostly in the form of a single agent and less commonly as combination therapy) was used in approximately 80% of subjects, with warfarin alone or on combination with an antiplatelet agent used in the remaining subjects.

Table 8. Medication use in MM group subjects

Visit	Aspirin alone	Clopidogrel alone	Warfarin alone	Aspirin and dipyridamole	Aspirin and clopidogrel[1]	Other[2]	None
Randomization	224/481 (46.6%)	67/481 (13.9%)	121/481 (25.2%)	39/481 (8.1%)	30/481 (6.2%)	0/481 (0.0%)	0/481 (0.0%)
1 Month	217/447 (48.5%)	52/447 (11.6%)	103/447 (23.0%)	38/447 (8.5%)	24/447 (5.4%)	13/447 (2.9%)	0/447 (0.0%)
6 Month	205/423 (48.5%)	55/423 (13.0%)	94/423 (22.2%)	39/423 (9.2%)	22/423 (5.2%)	6/423 (1.4%)	2/423 (0.5%)
12 Month	204/395 (51.6%)	54/395 (13.7%)	82/395 (20.8%)	34/395 (8.6%)	8/395 (2.0%)	9/395 (2.3%)	4/395 (1.0%)
18 Month	198/373 (53.1%)	44/373 (11.8%)	81/373 (21.7%)	27/373 (7.2%)	10/373 (2.7%)	8/373 (2.1%)	5/373 (1.3%)
2 Year	212/375 (56.5%)	49/375 (13.1%)	67/375 (17.9%)	26/375 (6.9%)	9/375 (2.4%)	10/375 (2.7%)	2/375 (0.5%)
3 Year	200/359 (55.7%)	51/359 (14.2%)	62/359 (17.3%)	22/359 (6.1%)	8/359 (2.2%)	11/359 (3.1%)	5/359 (1.4%)
4 Year	174/313 (55.6%)	45/313 (14.4%)	58/313 (18.5%)	19/313 (6.1%)	4/313 (1.3%)	9/313 (2.9%)	4/313 (1.3%)
5 Year	142/252 (56.3%)	33/252 (13.1%)	45/252 (17.9%)	15/252 (6.0%)	2/252 (0.8%)	8/252 (3.2%)	7/252 (2.8%)
6 Year	99/182 (54.4%)	23/182 (12.6%)	30/182 (16.5%)	15/182 (8.2%)	3/182 (1.6%)	7/182 (3.8%)	5/182 (2.7%)
7 Year	74/131 (56.5%)	10/131 (7.6%)	24/131 (18.3%)	10/131 (7.6%)	4/131 (3.1%)	4/131 (3.1%)	5/131 (3.8%)
8 Year	49/80 (61.3%)	3/80 (3.8%)	13/80 (16.3%)	7/80 (8.8%)	2/80 (2.5%)	1/80 (1.3%)	5/80 (6.3%)
9 Year	21/38 (55.3%)	1/38 (2.6%)	8/38 (21.1%)	4/38 (10.5%)	0/38 (0.0%)	0/38 (0.0%)	4/38 (10.5%)
10 Year	8/15 (53.3%)	1/15 (6.7%)	1/15 (6.7%)	3/15 (20.0%)	0/15 (0.0%)	1/15 (6.7%)	1/15 (6.7%)

Table includes MM subjects who had a follow-up visit; rows add to 100%. [1] Removed as a medication regimen option in protocol revision J. [2] The most frequent other medications were the combined use of aspirin and warfarin.

FDA Comment:

- There is no single standard-of-care anti-thrombotic medical therapy to reduce the risk of recurrent stroke in patients with cryptogenic stroke. The use of multiple acceptable combinations of anti-thrombotic agents in the MM group presents challenges in defining the probable benefits of the Device vs. medical therapy.
- In the Device group, >90% of subjects were using anti-thrombotic medications throughout the study (the vast majority of whom were taking antiplatelet agents). **Therefore, the RESPECT trial is essentially a study of the Device *plus* MM vs. MM alone**.
- In the MM group, overall compliance with protocol-directed anti-thrombotic medical therapy was high throughout the trial. Except for very late follow-up time points (in which data are limited), compliance with the use of anti-thrombotic medications was >95% at all follow-up assessments.

Neuroimaging confirmation of qualifying strokes:

Investigators at the study sites (and not a central adjudication committee) assessed the qualifying stroke in enrolled subjects. The protocol definition of stroke did not require imaging at baseline if the stroke symptoms lasted >24 hours (with imaging required if symptoms were <24 hours in duration). The rate of neuroimaging confirmation of the qualifying stroke (vs. confirmation based on symptoms alone) was significantly lower in the Device group vs. the MM group for the ITT population (**Table 9**).

Table 9. Qualifying Stroke Neuroimaging Confirmation (ITT Population, Site Investigator Assessed)

MRI/CT visualized baseline infarct of qualifying stroke	Device (N=499)	MM (N=481)	p-value[1]
Yes	447/499 (89.6%)	451/481 (93.8%)	0.021
No	52/499 (10.4%)	30/481 (6.2%)	

Categorical variables are reported as n/N (%). [1]Chi-squared test.

There were 968 subjects in whom an MRI was performed in the evaluation of their qualifying stroke. Of these, 67 (6.9%) subjects had a negative MRI for an acute infarct.

Per protocol, all subjects were required to undergo baseline imaging of the intracranial and extracranial arteries to exclude a >50% lumen diameter stenosis of a vessel supplying the involved infarct territory. **Tables 10a and 10b** show the vascular imaging modalities used in RESPECT.

Table 10a Baseline intracranial vascular imaging at the time of the qualifying stroke

Imaging Method	Device	MM[a]
Carotid ultrasound	2/499 (0.4%)	0/480 (0%)
MR angiogram	316/499 (63.3%)	282/480 (58.8%)
CT angiogram	127/499 (25.5%)	150/480 (31.3%)
Catheter angiogram	21/499 (4.2%)	21/480 (4.4%)
Transcranial Doppler	33/499 (6.6%)	27/480 (5.6%)

[a]Data missing for 1 MM subject

Table 10b. Baseline extracranial imaging at the time of the qualifying stroke

Imaging Method	Device[a]	MM
Carotid ultrasound	132/498 (26.5%)	127/481 (26.4%)
MR angiogram	226/498 (45.4%)	198/481 (41.2%)
CT angiogram	124/498 (24.9%)	137/481 (28.5%)
Catheter angiogram	15/498 (3.0%)	17/481 (3.5%)
Transcranial Doppler	0/498 (0.0%)	1/481 (0.2%)
Cerebral angiograms	1/498 (0.2%)	1/481 (0.2%)

[a]Data missing for 1 Device subject

***FDA Comment:*:**
The frequency of a lack of neuroimaging confirmation of qualifying strokes (and the differences between treatment groups) and incomplete intracranial arterial imaging should be considered in the designation of qualifying neurologic events as cryptogenic strokes.

- There were 82 of 980 (8.1%) RESPECT subjects who did not have MRI or CT confirmation of their qualifying stroke, with an observed higher rate in the Device group (10.4%) vs. the MM group (6.2%).
- Brain MRIs did not show an acute infarct in 6.9% of subjects in which an MRI was performed.

Evaluation to exclude subjects with atrial fibrillation or atrial flutter:
Exclusion for atrial fibrillation/atrial flutter was based on investigator assessment from the subjects' medical history and ECG or Holter monitor. **Table 11** shows the method of baseline cardiac rhythm assessment stratified by treatment group.

Table 11. Baseline cardiac rhythm screening to exclude atrial fibrillation or atrial flutter

Arrhythmia testing done	Device	MM
ECG	487/499 (97.6%)	467/481 (97.1%)
Holter	67/499 (13.4%)	75/481 (15.6%)

Both ECG and Holter monitor testing was performed in 55/499 (11.0%) device subjects and in 61/481 (12.7%) MM subjects

FDA Comment: Investigations intended to exclude subjects with atrial fibrillation or atrial flutter (medical history and ECG with occasional use of Holter monitoring) were limited in scope.

Baseline assessment of inter-atrial shunts:
The severity of inter-atrial shunting at baseline and the incidence of an ASA (assessed by TEE) were similar between treatment groups (**Table 12**).

Table 12. Maximal shunt and ASA assessment by TEE (ITT Population, site investigator assessed)

Variable	Device (N=499)	MM (N=481)	p-value[3]
Maximal shunt grade[1]			
Grade 0	1/499 (0.2%)	9/481 (1.9%)	0.092
Grade I	108/499 (21.6%)	114/481 (23.7%)	
Grade II	138/499 (27.7%)	121/481 (25.2%)	
Grade III	247/499 (49.5%)	231/481 (48.0%)	
Not assessed	5/499 (1.0%)	6/481 (1.2%)	
Atrial septal aneurysm[2]	180/499 (36.1%)	170/481 (35.3%)	0.812

Categorical variables are reported as n/N (%). ASA: Atrial septal aneurysm
[1] Determined as the most severe grade between assessments at rest and at Valsalva. If only 1 assessment was available, that assessment was used; if no assessments were available, it was listed as not assessed. [2] Defined as a total excursion of the septum primum ≥10 mm). [3] Chi-squared test

6.3 Discontinued Subjects

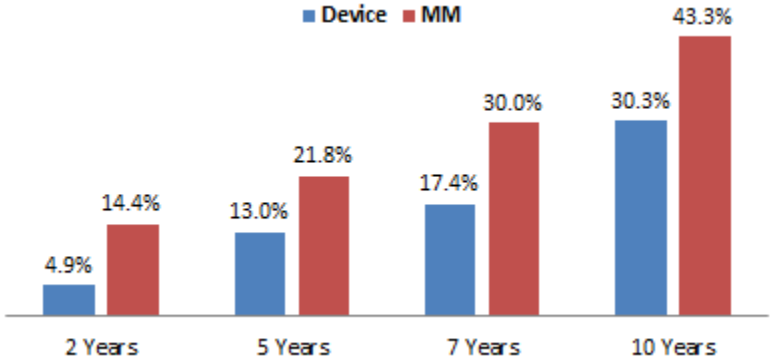
Subjects were considered to be discontinued if they withdrew consent, were lost-to-follow-up, died, or were withdrawn per investigator request. There was a higher rate of subject discontinuation in the MM group vs. the Device group for both the initial 20 May 2012 data lock (19.1% vs 10.4%, respectively) and for the extended follow-up 14 Aug 2015 data lock (30.1% vs 18.2%, respectively, **Table 13**). The difference in the overall subject discontinuation rate between treatment groups was driven by subjects deciding to withdraw from study participation.

Table 13. Discontinued Subjects

	Initial PMA Data Lock 20 May 2012		Extended Follow-up Data Lock 14 Aug 2015	
Disposition	**Device (N=499)**	**MM (N=481)**	**Device (N=499)**	**MM (N=481)**
Ongoing	447/499 (89.6%)	389/481 (80.9%)	408/499 (81.8%)	336/481 (69.9%)
Discontinued	52/499 (10.4%)	92/481 (19.1%)	91/499 (18.2%)	145/481 (30.1%)
Patient Death	3/499 (0.6%)	6/481 (1.2%)	6/499 (1.2%)	10/481 (2.1%)
Subject withdrawn	24/499 (4.8%)	55/481 (11.4%)	31/499 (6.2%)	71/481 (14.8%)
Lost to Follow-up	22/499 (4.4%)	28/481 (5.8%)	50/499 (10.0%)	59/481 (12.3%)
Investigator request	3/499 (0.6%)	3/481 (0.6%)	3/499 (0.6%)	4/481 (0.8%)
Other	0/0 (0.0%)	0/0 (0.0%)	1/499 (0.2%)	1/481 (0.2%)

Through 2 years, 5 years, 7 years and 10 years of follow-up, subject discontinuation rates excluding those who died or experienced a primary endpoint event were 4.9%, 13.0%, 17.4% and 30.3% in the Device group and 14.4%, 21.8%, 30% and 43.3% in the MM group, respectively (**Figure 6**).

Figure 6. Subject discontinuation rates
(excluding subjects who died or experienced a primary endpoint event)



PFO closure in MM subjects:

The distribution of MM subjects who underwent PFO closure was as follows:

- Initial data lock
  - 20 (4.2%) MM subjects withdrew from the trial to pursue PFO closure outside of the trial
  - 22 (4.6%) MM subjects underwent PFO closure and remained in the trial
- Extended follow-up (cumulative)
  - 23 (4.8%) MM subjects withdrew from the trial to pursue PFO closure outside of the trial
  - 28 (5.8%) MM subjects underwent PFO closure and remained in the trial

Per FDA request, the sponsor compared baseline characteristics between treatment groups for: (1) subjects who discontinued from the trial and (2) subjects who remained in the trial (ongoing). For the initial data lock (at a 5% significance level without multiple testing adjustments):

- Among subjects who discontinued from the trial, the average number of days from the qualifying stroke to randomization was lower in the MM group vs. the Device group (101 vs. 125 days, p=0.017).
- Among subjects who were ongoing in the trial, baseline NIHSS (0.8 vs 0.6, p=0.032) and mRS scores (0.8 vs. 0.7, p=0.046) were higher in Device group vs. MM group, and the frequency of coronary artery disease (3.9% vs. 1.3%, p=0.029) was higher in Device subjects vs. MM subjects.

For the extended follow-up data lock (at the 5% significance level without multiple testing adjustments):

- Among patients who discontinued from the trial, palpitations (7.0% vs 20.8%, p=0.01), current smoking at baseline (14.1% vs. 25.8%, p=0.035), and a family history of stroke (20.0% vs. 37.5 %, p=0.005) were less common among MM subjects vs. Device subjects.

FDA Comment::

- At face value, the differences in baseline characteristics between treatment groups for (1) subjects who discontinued from the trial and (2) subjects who remained in the trial would not be expected to bias the study results in favor of the Device group. These data should be interpreted with caution since the comparisons are based on post-randomization subgroups, and the p-values have not been adjusted for multiplicity. In addition to the possibility of baseline characteristics affecting the balance in discontinuation between the two study groups, unbalanced discontinuation could also impact the primary endpoint rates despite randomization.
- In the ITT analysis, the number of primary endpoint events in the Device and MM groups in the initial data lock (9 and 16, respectively, **Section 6.4.1**) were notably smaller than the number of subject withdrawals (excluding those who died or experienced a primary endpoint event) in the Device and MM groups (49 and 86, respectively). Similarly, the number of events in the Device and MM groups in the extended follow-up data lock (18 and 24, respectively) were smaller than the number of subject withdrawals (excluding those who died or experienced a primary endpoint event) in the Device and MM groups (84 and 134, respectively, **Section 6.4.1**).

6.4 Primary Endpoint Results

6.4.1 Primary Endpoint Analysis Results ITT

Initial PMA Data Lock

In accordance with the pre-specified decision rules, trial enrollment was stopped once 25 primary endpoint events occurred. **All events were recurrent nonfatal ischemic strokes**; there were 9 primary endpoint events in the device group and 16 primary endpoint events in the MM group. The raw count analysis in the ITT population was the pre-specified primary analysis for the RESPECT trial (**Table 14**). Neither of the success criteria described in **Section 5.2.1** were met, and the null hypothesis was not rejected at the 5% two-sided significance level (p=0.157). Therefore, the primary endpoint of stroke rate reduction based on the pre-specified ITT analysis was *not* met.

Table 14. Primary endpoint outcomes in the ITT Population

	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis prior to subject enrollment (Protocol Revision G)					
ITT/Count	980 (499/481)	25 (9/16)	0.534 (0.234, 1.220)	46.6%	0.157[c]

Abbreviations: ITT, intent-to-treat; KM, Kaplan-Meier; D, device; MM, medical management; RR, relative risk.
[a] The relative risk is represented by the odds ratio.
[b] 2-sided p-value using the Fisher's Exact test.
[c] This endpoint failed the raw count analysis, as less than 19 of the 25 events were in the medical management arm. The nominal *P* value from the Fisher Exact test is presented here for additional information.

FDA Comment: The primary endpoint for superiority of the Device vs. MM was not met for the primary analysis cohort (ITT, raw count). Although the estimated relative risk is 0.534, the wide 95% confidence interval (0.234, 1.220) should also be noted in considering the benefit of the Device.

Throughout the trial, a differential subject drop-out rate was observed with higher drop-out rates in the MM group (see Section 6.3). In order to account for the differential follow-up, the protocol was revised to supplement the decision rules with a Kaplan-Meier analysis and log-rank test for the primary hypothesis (protocol Revision M). The relative risk from the Cox proportional hazards model was 0.500 (95% CI: 0.221, 1.131), corresponding to a 50.0% risk reduction that also did not reach statistical significance (P=0.089, **Table 15**).

Table 15. Primary Endpoint Kaplan-Meier Analysis (ITT Analysis – Initial PMA Data Lock)

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis added in protocol Revision M					
ITT/KM	980 (499/481)	25 (9/16)	0.500 (0.221, 1.131)	50.0%	0.089

[a] The relative risk is represented by the hazard ratio
[b] 2-sided p-value using log-rank test.

The Kaplan-Meier freedom from primary endpoint analysis and plot are shown in **Figure 7** and **Table 16.** At 5 years, the Kaplan-Meier event rates in the Device and MM groups were 0.021 and 0.059, respectively.

Figure 7. Kaplan-Meier freedom from primary endpoint event (ITT Analysis - Initial PMA Data Lock)

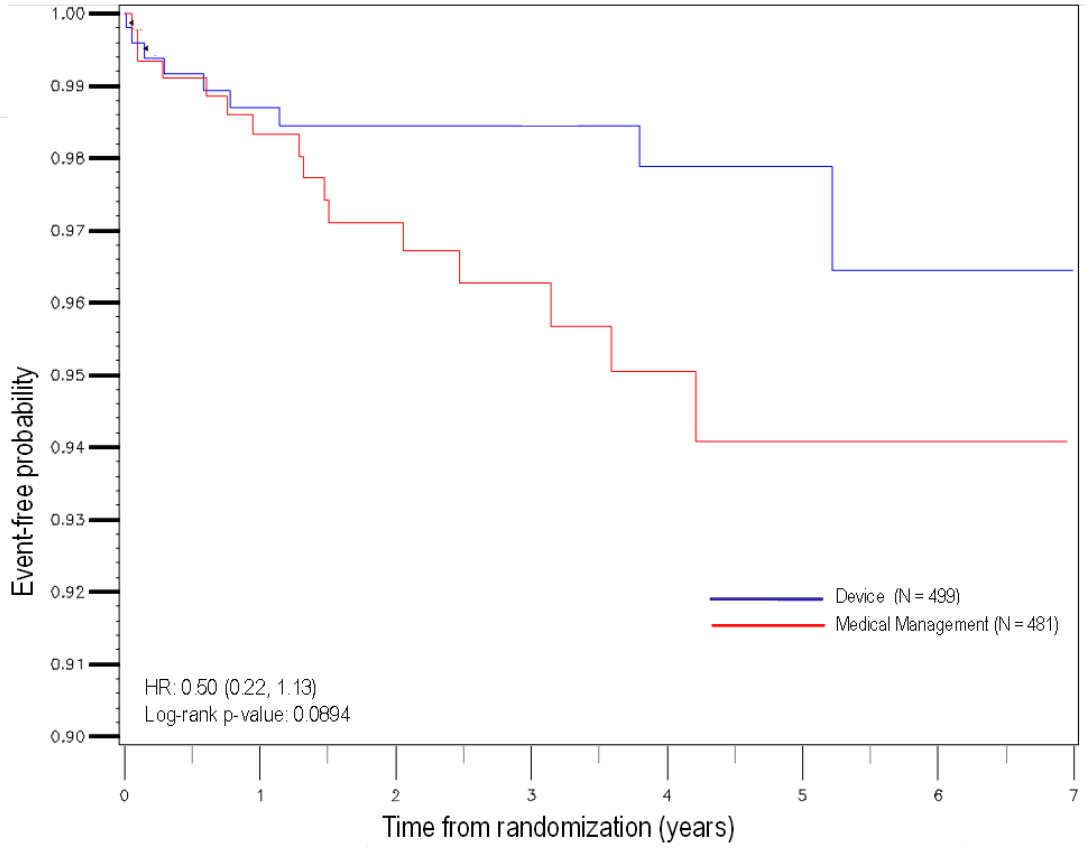


Table 16. Number at risk (ITT analysis - Initial PMA Data Lock)

	Time from randomization (years)							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Device (N=499)								
At Risk	499	408	306	224	157	105	53	19
Primary Endpoint Event	0	6	7	7	8	8	9	9
Death	0	1	2	2	3	3	3	3
Censored	0	68	161	231	290	340	388	422
Withdrawn	0	16	23	35	41	43	46	46
Primary Endpoint Event Rate	0	0.013	0.016	0.016	0.021	**0.021**	0.035	0.035
MM (N=481)								
At Risk	481	358	257	187	131	81	40	8
Primary Endpoint Event	0	7	11	13	15	16	16	16
Death	0	1	2	2	3	4	4	4
Censored	0	76	153	215	263	305	344	373
Withdrawn	0	39	58	64	69	75	77	80
Primary Endpoint Event Rate	0	0.017	0.029	0.037	0.050	**0.059**	0.059	0.059

FDA Comment: The treatment difference in the Kaplan-Meier analysis was not statistically significant (p = 0.089). Similar to the ITT raw count analysis, the 95% confidence interval around the 0.50 relative risk was notably wide (0.221, 1.131).

Extended follow-up data lock 14 Aug 2015

During extended follow-up, there were 9 additional events in the Device group and 8 additional events in the MM group resulting in a total of 18 events in the Device group and 24 events in the MM group. All events were recurrent nonfatal ischemic strokes. The primary endpoint event rates for the Device and MM groups were 0.65 and 1.01 per 100 patient-years, respectively, representing a relative risk of 0.65 (95% CI: 0.35, 1.20, **Table 17**).

Table 17. Primary endpoint events (ITT Analysis – Extended Follow-up)

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis added in protocol Revision M					
ITT/KM	980 (499/481)	42 (18/24)	0.65 (0.35, 1.20)	35.0%	0.16

[a] The relative risk is represented by the hazard ratio.
[b] 2-sided p-value using log-rank test.

The Kaplan-Meier freedom from primary endpoint analysis and plot are shown in **Figure 8** and **Table 18**. The Kaplan-Meier primary endpoint event rates at 5 years in the extended follow-up dataset were 0.028 in the Device group and 0.051 in the MM group, and at 8 years, the primary endpoint event rates were 0.06 and 0.07, respectively.

Figure 8. Kaplan-Meier time to recurrent stroke (ITT Analysis - Extended Follow-up)

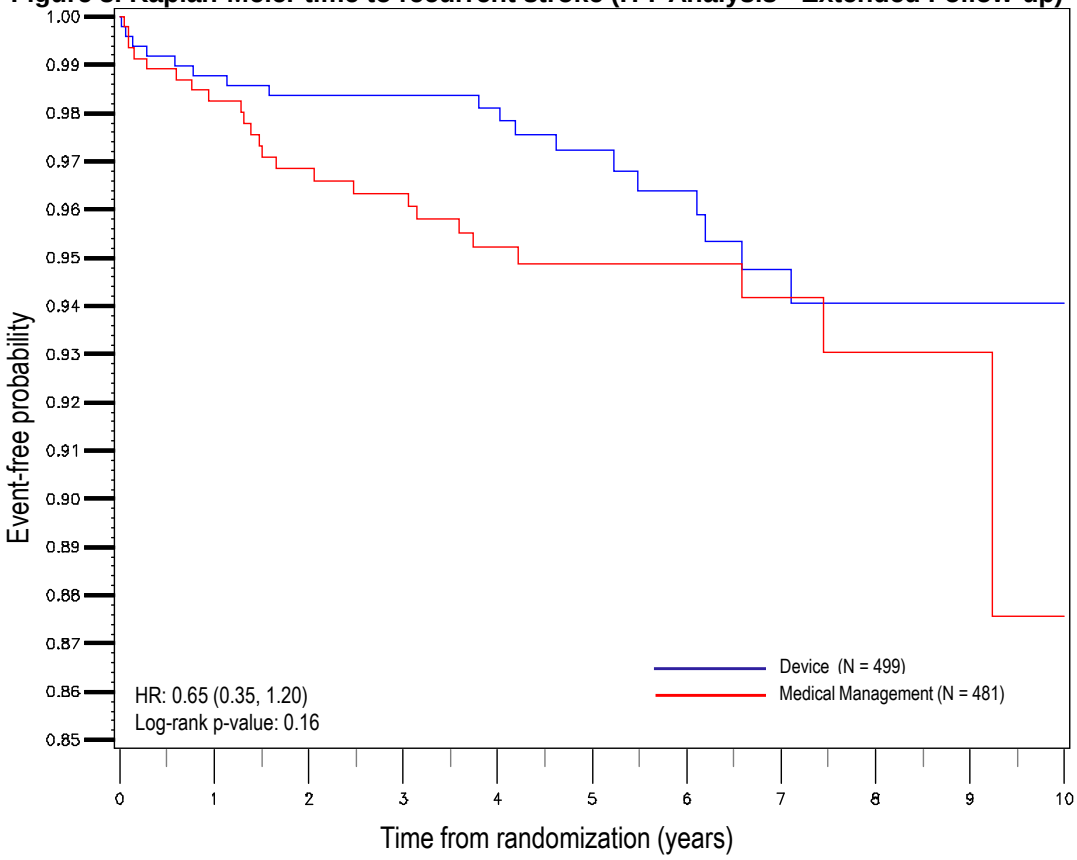


Table 18. Number at risk (ITT Analysis -Extended Follow-up)

	Time from randomization (years)										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Device (N=499)											
At Risk	499	476	463	434	369	282	212	151	86	44	20
Event	0	6	8	8	9	12	14	17	18	18	18
Death	0	1	2	3	5	5	5	6	6	6	6
Censored	0	0	2	14	68	141	202	255	312	350	373
Discontinued	0	16	24	40	48	59	66	70	77	81	82
Event Rate	0	0.014	0.016	0.016	0.019	**0.028**	0.036	0.052	**0.060**	0.060	0.060
MM (N=481)											
At Risk	481	432	394	367	307	238	168	113	71	34	10
Event	0	8	14	16	20	21	21	22	23	23	24
Death	0	1	3	3	5	7	8	8	8	8	8
Censored	0	1	2	17	62	118	176	221	258	292	313
Discontinued	0	39	68	78	87	97	108	117	121	124	126
Event Rate	0	0.018	0.032	0.037	0.048	**0.051**	0.051	0.058	**0.070**	0.070	0.124

***FDA Comment*:** In the ITT population, an event rate difference in favor of the Device group was present at 5 years. In the extended follow-up analysis (6.5 to 8 years), the curves for the two treatment groups approach each other.

Compliance with medical therapy in the week prior to the recurrent stroke – Extended follow-up:

- 42 subjects with a primary endpoint event
  - 39 subjects had medication usage information at the time of the first recurrent stroke [3 subjects without this information: 2 Device and 1 MM subject)]
    - 30 subjects were compliant with protocol required medical therapy at the time of the recurrent event
      - 16 Device subjects
      - 14 MM subjects
    - 9 subjects were not compliant with protocol required medications in the week prior to their recurrent event (**Table 19**)
      - 2 Device subjects
      - 7 MM subjects

Table 19. Medication Non-Compliance at the time of the Recurrent Stroke (ITT Analysis – Extended Follow-up)

Groups	Non- Compliance
Device	Not implanted with a Device; not taking aspirin and clopidogrel at the time of recurrent stroke
Device	Not implanted with a Device; not taking aspirin at the time of the recurrent stroke
MM	Taking both aspirin and warfarin (regimen not approved under the protocol) at the time of the recurrent stroke
MM	Missed aspirin doses during week prior to recurrent stroke
MM	Non-compliant with aspirin doses for the year prior to recurrent stroke
MM	Discontinued warfarin 11 days before the recurrent stroke (due to a pelvic hematoma)
MM	Not taking aspirin for approximately 1 week before recurrent event
MM	Discontinued aspirin/extended-release dipyridamole 1 day before recurrent stroke (due to a dental procedure)
MM	Not taking warfarin for approximately 2 months prior to recurrent stroke

FDA Comment: Among the 24 MM subjects with recurrent stroke in the extended follow-up analysis, 7 subjects (29.2%) were non-compliant with protocol-required medical therapy (with 6 of 7 subjects not taking antiplatelet or anticoagulation therapy), and medication usage was not known for one MM subject.

Status of PFO closure in the 9 ITT Device subjects who had a recurrent stroke in the initial data lock:

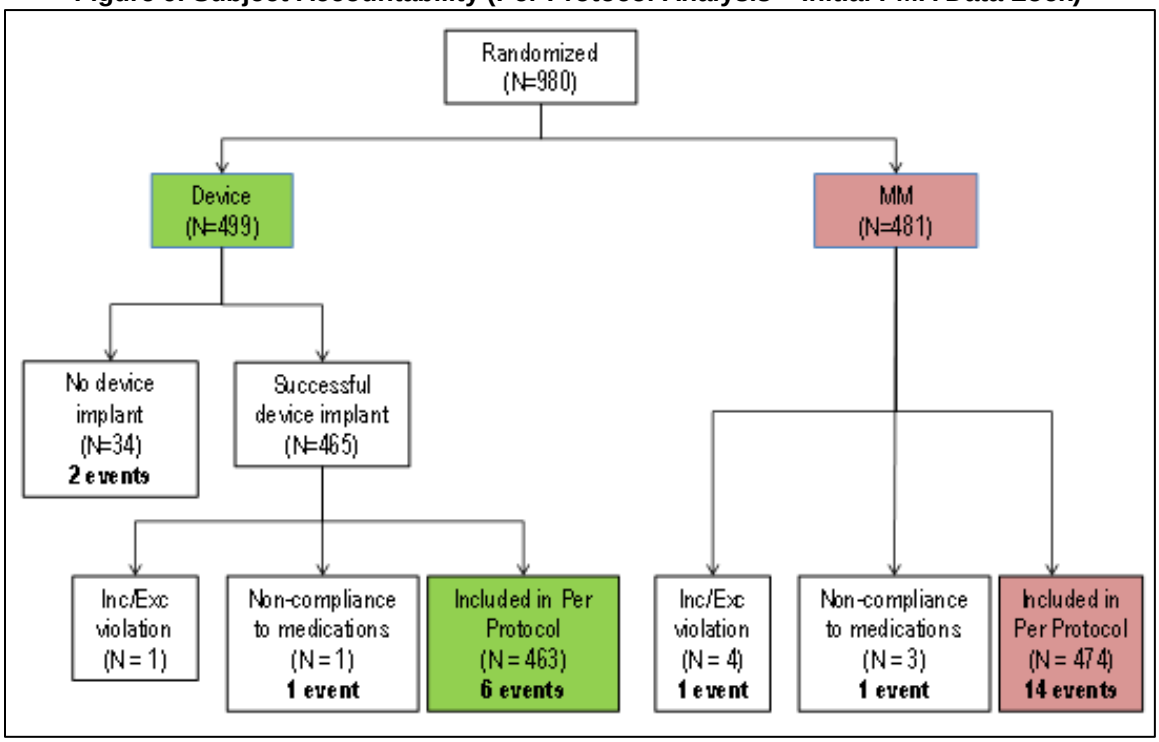
- 4 subjects had 6-month TEE assessments prior to their primary endpoint event, and there was no residual shunt.

- 2 subjects had a primary endpoint event prior to the 6-month TEE assessment.
    - 1 subject did not have a TEE/TTE reported at the time of the primary endpoint event.
    - 1 subject had grade III shunt associated with a sinus venosus atrial septal defect.
- 3 subjects did not have a device implanted at the time of the primary endpoint event (PFO closure status not applicable).

6.4.2 Primary Endpoint Analysis Results – Per Protocol

Subject accountability as of the initial data lock (20 May 2012) for the Per Protocol population is shown in **Figure 9**.

Figure 9. Subject Accountability (Per Protocol Analysis – Initial PMA Data Lock)



Per Protocol Population Caveats

Among the total of 34 Device subjects who were excluded from the Per Protocol cohort because the Device was not implanted, the following 15 patients were excluded based on evaluations or treatments performed at the time of the implant procedure:

- 8 Device subjects were excluded because a PFO was not confirmed or crossed at the implant procedure.
- 1 Device subject was excluded because atrial fibrillation was observed at time of implant procedure.
- 2 Device subjects were excluded because another source of right-to-left shunting was identified.

- 3 Device subjects were excluded because an ASD device was placed instead of PFO device.
- 1 Device subject excluded because significant coronary artery disease was identified at the time of implant procedure. The PFO was closed surgically at the time of coronary artery bypass surgery.

FDA Comment: The exclusion of some Device subjects from the Per Protocol analysis because of findings or treatments at the time of the implant procedure was consistent with the Per Protocol definition. However, MM subjects did not undergo an implant procedure during which reasons for exclusion from the Per Protocol analysis may have been found, which could lead to imbalances between treatment groups.

Initial PMA Data Lock

In the Per Protocol analysis population, there were 6 events in the Device group and 14 events in the MM group. The relative risk from a Cox proportional hazards model was 0.371 corresponding to a 62.9% relative risk reduction for stroke in the Device group vs. the MM group (**Table 20)**. The log-rank p-value was 0.034, such that the null hypothesis for the Per Protocol population can be rejected at the two-sided 5% significance level.

Table 20. Per Protocol population primary endpoint outcomes

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis added in protocol Revision M					
PP/KM	937 (463/474)	20 (6/14)	0.371 (0.14, 0.97)	62.9%	0.034

PP, per protocol; KM, Kaplan-Meier; D, device; MM, medical management; RR, relative risk.
[a] For KM analysis, the relative risk is represented by the hazard ratios.
[b] 2-sided p-value using log-rank test and not adjusted for multiplicity

The Kaplan-Meier freedom from primary endpoint analysis and plot are shown in **Figure 10** and **Table 21**. At 5 years, the Kaplan-Meier event rates in the Device and MM groups were 0.012 and 0.059.

Figure 10. Kaplan-Meier freedom from primary endpoint event (Per Protocol Analysis - Initial PMA Data Lock)

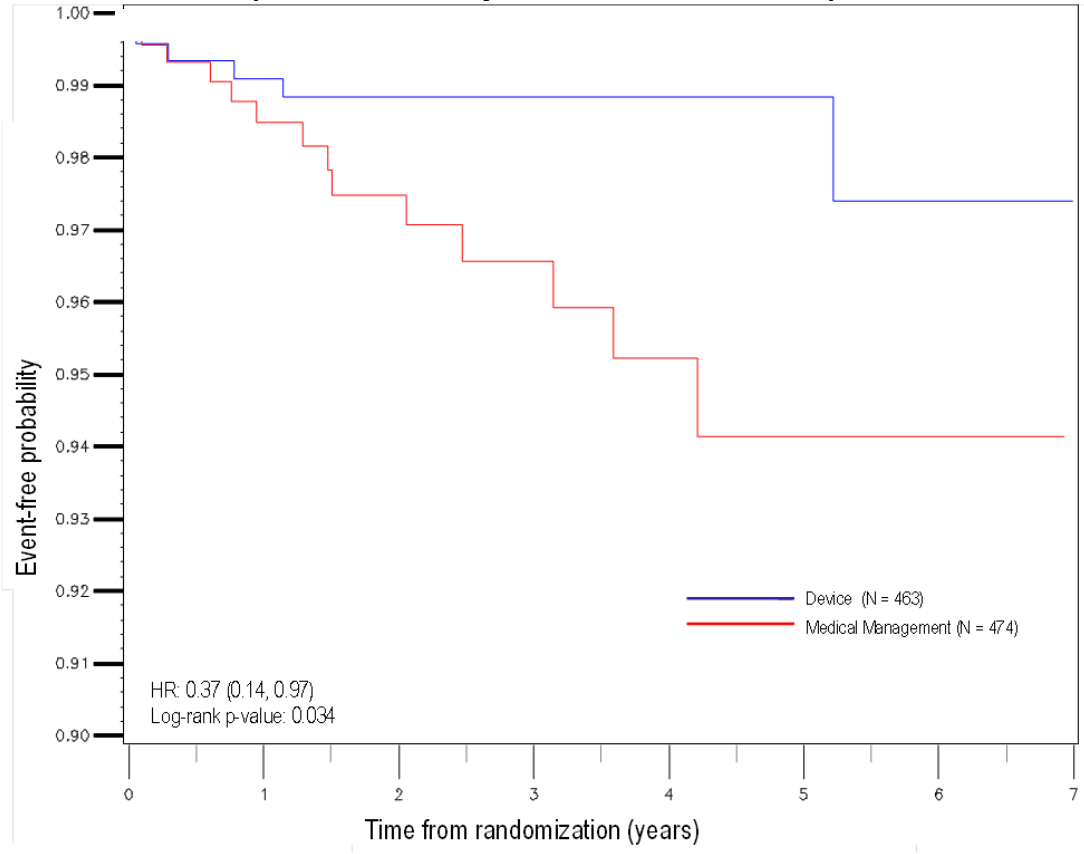


Table 21. Number at risk (Per Protocol Analysis - Initial PMA Data Lock)

	Time from randomization (years)							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Device (N=463)								
At Risk	463	390	293	215	152	102	52	19
Event	0	4	5	5	5	5	6	6
Death	0	1	2	2	3	3	3	3
Censored	0	65	155	222	278	326	372	405
Withdrawn	0	3	8	19	25	27	30	30
Event Rate	0	0.009	0.012	0.012	0.012	**0.012**	0.026	0.026
MM (N=474)								
At Risk	474	334	238	171	119	72	36	8
Event	0	6	9	11	13	14	14	14
Death	0	3	3	3	4	5	5	5
Censored	0	88	166	225	269	310	344	369
Withdrawn	0	43	58	64	69	73	75	78
Event Rate	0	0.015	0.025	0.034	0.048	**0.059**	0.059	0.059

FDA Comment: Similar to the ITT analysis, the Kaplan-Meier curves in the Per Protocol cohort begin separating approximately 1.5 years after randomization. In the Per Protocol population, the primary endpoint event rate was numerically lower in the Device group vs. the MM group.

Extended Follow-up data lock 14 Aug 2015

During extended follow-up in the Per Protocol analysis population, there were 9 additional nonfatal ischemic stroke events in the Device group and 8 additional nonfatal ischemic stroke events in the MM group for a total of 15 events in the Device group and 22 events in the MM group. The relative risk (Device vs. MM) was 0.58 (95% CI: 0.30, 1.120, **Table 22**).

Table 22. Primary endpoint events (Per Protocol Analysis – Extended Follow-up

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis added in protocol Revision M					
PP/KM	937 (463/474)	37 (15/22)	0.58 (0.30, 1.12)	42%	0.10

PP, per protocol; KM, Kaplan-Meier; D, device; MM, medical management; RR, relative risk.
[a] For KM analysis, the relative risk is represented by the hazard ratios.
[b] 2-sided p-value using log-rank test and not adjusted for multiplicity

The Kaplan-Meier freedom from primary endpoint plot and analysis are shown in **Figure 11** and **Table 23.** At 5 years, the Kaplan-Meier event rates in the Device and MM groups were 0.022 and 0.049, respectively, and at 8 years, the event rates were 0.055 and 0.069 respectively.

Figure 11. Kaplan-Meier freedom from primary endpoint event (Per Protocol Analysis - Extended Follow-up)

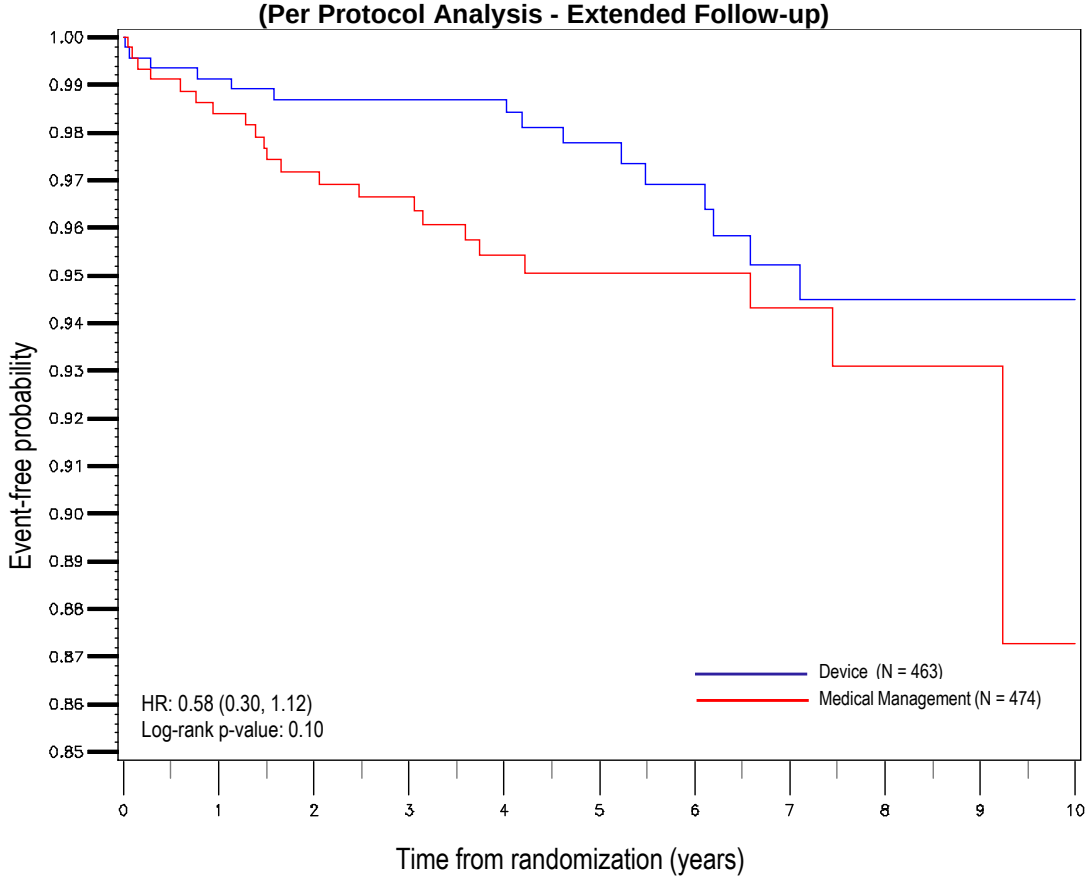


Table 23. Number at risk (Per Protocol Analysis - Extended Follow-up)

	Time from randomization (years)										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Device (N=463)											
At Risk	463	455	444	418	356	273	205	146	82	43	20
Event	0	4	6	6	6	9	11	14	15	15	15
Death	0	1	2	3	5	5	5	6	6	6	6
Censored	0	0	2	12	64	134	193	244	300	337	359
Discontinued	0	3	9	24	32	42	49	53	60	62	63
Event Rate	0	0.011	0.013	0.013	0.013	**0.022**	0.031	0.048	**0.055**	0.055	0.055
MM (N=474)											
At Risk	474	412	376	346	285	221	154	106	66	31	10
Event	0	7	12	14	18	19	19	20	21	21	22
Death	0	3	4	4	6	8	9	9	9	9	9
Censored	0	8	11	28	74	128	184	222	258	291	309
Discontinued	0	44	71	82	91	98	108	117	120	122	124
Event Rate	0	0.016	0.028	0.034	0.046	**0.049**	0.049	0.057	**0.069**	0.069	0.127

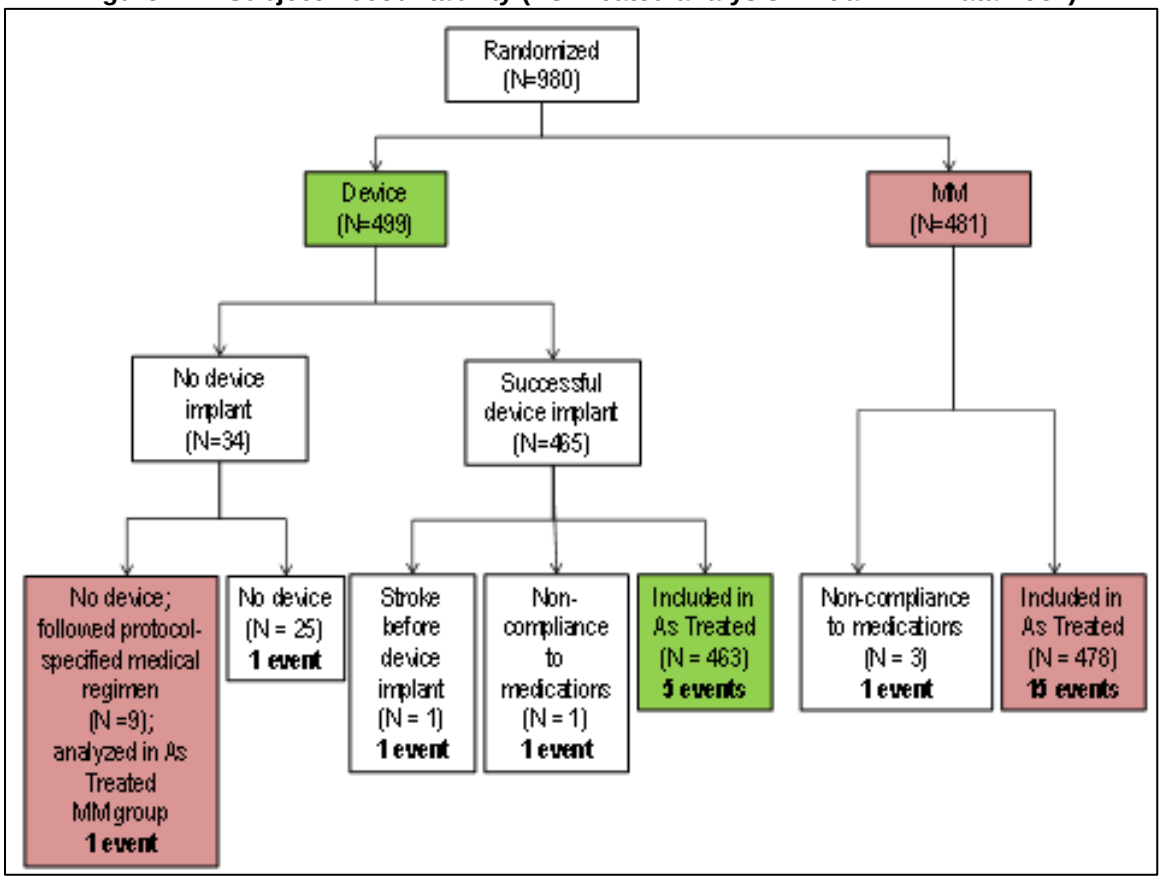
***FDA Comment*:** In the Kaplan-Meier analysis of the Per Protocol population for extended follow-up, the curves for the two treatment groups approach each other (at 6.5 to 8 years).

6.4.3 Primary Endpoint Analysis Results – Additional Analyses

6.4.3.1 As Treated Analysis

Subject accountability as of the initial data lock (20 May 2012) for the As Treated population is shown in **Figure 12**.

Figure 12. Subject Accountability (As Treated analysis- Initial PMA Data Lock)



As Treated Population Caveats

Among the total of 34 Device subjects who were excluded from the As Treated cohort, the following 9 patients were excluded based on evaluations or treatments performed at the time of the implant procedure:

- 4 Device subjects were excluded because a PFO was not confirmed or crossed at the implant procedure.
- 1 Device subject was excluded because atrial fibrillation was observed at time of the implant procedure.
- 3 Device subjects were excluded because an ASD device was placed instead of PFO device.
- 1 Device subject was excluded because significant coronary artery disease was identified at the time of implant procedure. The PFO was closed surgically at the time of coronary artery bypass surgery.

In addition, 9 Device subjects (one of whom had a primary endpoint) were added to the MM arm in the as treated analysis. These subjects did not have device implantation and agreed to follow protocol-specified medical regimen.

FDA Comment: The exclusion of some Device subjects from the As Treated analysis because of findings or treatments at the time of the implant procedure was consistent with the As Treated definition. However, MM subjects did not undergo an implant procedure, during which reasons for exclusion from the As Treated analysis may have been found, which could lead to imbalances between treatment groups.

Initial PMA Data Lock

In the As Treated analysis population, there were 5 events in the Device group and 16 events in the MM group. The relative risk from a Cox proportional hazards model was 0.280 corresponding to a 72.0% relative risk reduction for stroke in the Device group vs. the MM group (**Table 24**).

Table 24. As Treated population primary endpoint outcomes

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis added after protocol Revision M					
AT/KM	950 (463/487)	21 (5/16)	0.280 (0.101, 0.77)	72.0%	0.008

AT, As Treated; KM, Kaplan-Meier; D, device; MM, medical management; RR, relative risk.
[a] For KM analysis, the relative risk is represented by the hazard ratios.
[b] 2-sided p-value using log-rank test and not adjusted for multiplicity

The Kaplan-Meier freedom from primary endpoint plot and analysis are shown in **Figure 13** and **Table 25**. At 5 years, the Kaplan-Meier event rates for device and MM were 0.010 and 0.066.

Figure 13. Kaplan-Meier freedom from primary endpoint event (As Treated analysis -initial PMA data lock)

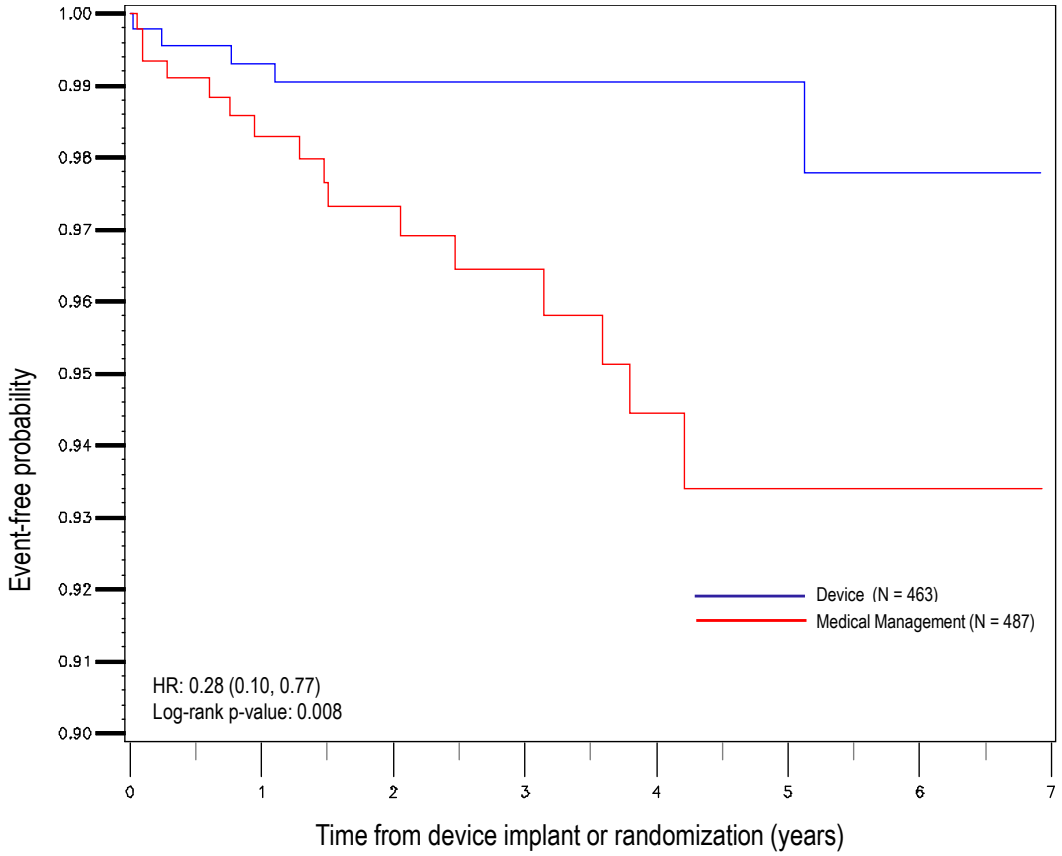


Table 25. Number at risk (As Treated analysis - initial PMA data lock)

	Time to Event (years) Device							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Device (N=463)								
At Risk	463	389	289	211	146	95	46	19
Event	0	3	4	4	4	4	5	5
Death	0	1	2	2	3	3	3	3
Censored	0	67	160	227	285	334	379	406
Withdrawn	0	3	8	19	25	27	30	30
Event Rate	0	0.007	0.010	0.010	0.010	**0.010**	0.022	0.022
MM (N=487)								
At Risk	487	344	245	176	121	73	36	8
Event	0	7	10	12	15	16	16	16
Death	0	3	3	3	4	5	5	5
Censored	0	89	169	230	276	318	353	378
Withdrawn	0	44	60	66	71	75	77	80
Event Rate	0	0.017	0.027	0.036	0.056	**0.066**	0.066	0.066

Extended Follow-up data lock 14 Aug 2015

During extended follow-up in the As Treated population, there were 9 additional nonfatal ischemic stroke events in the Device group and 8 additional nonfatal ischemic stroke events in the MM group resulting in a total of 14 Device group and 24 MM group events (**Table 26)**. The relative risk (Device vs. MM) was 0.51 (95% CI: 0.26, 0.99).

Table 26. Primary endpoint events (As Treated analysis – extended follow-up)

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Pre-specified analysis added after protocol Revision M					
AT/KM	950 (463/487)	21 (14/24)	0.51 (0.26, 0.99)	49.0%	0.04

AT, As Treated; KM, Kaplan-Meier; D, device; MM, medical management; RR, relative risk.
[a] For KM analysis, the relative risk is represented by the hazard ratios.
[b] 2-sided p-value using log-rank test and not adjusted for multiplicity

The Kaplan-Meier freedom from primary endpoint analysis and plot are shown in **Figure 14** and **Table 27**. At 5 years, the KM event rates in the device and MM groups were 0.020 and 0.053, respectively, and at 8 years, the rates were 0.053 and 0.073 respectively.

Figure 14. Kaplan -Meier freedom from primary endpoint event (As Treated Analysis - Extended Follow-up)

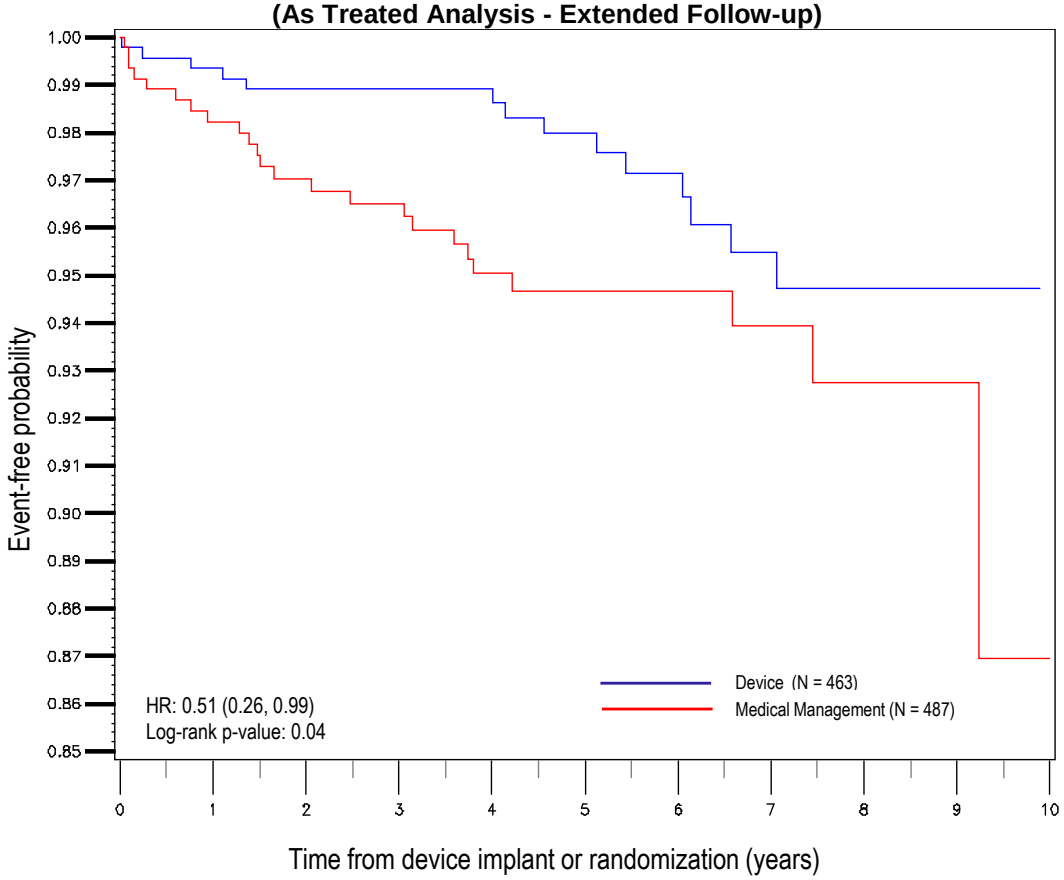


Table 27. Number at risk (As Treated Analysis - Extended Follow-up)

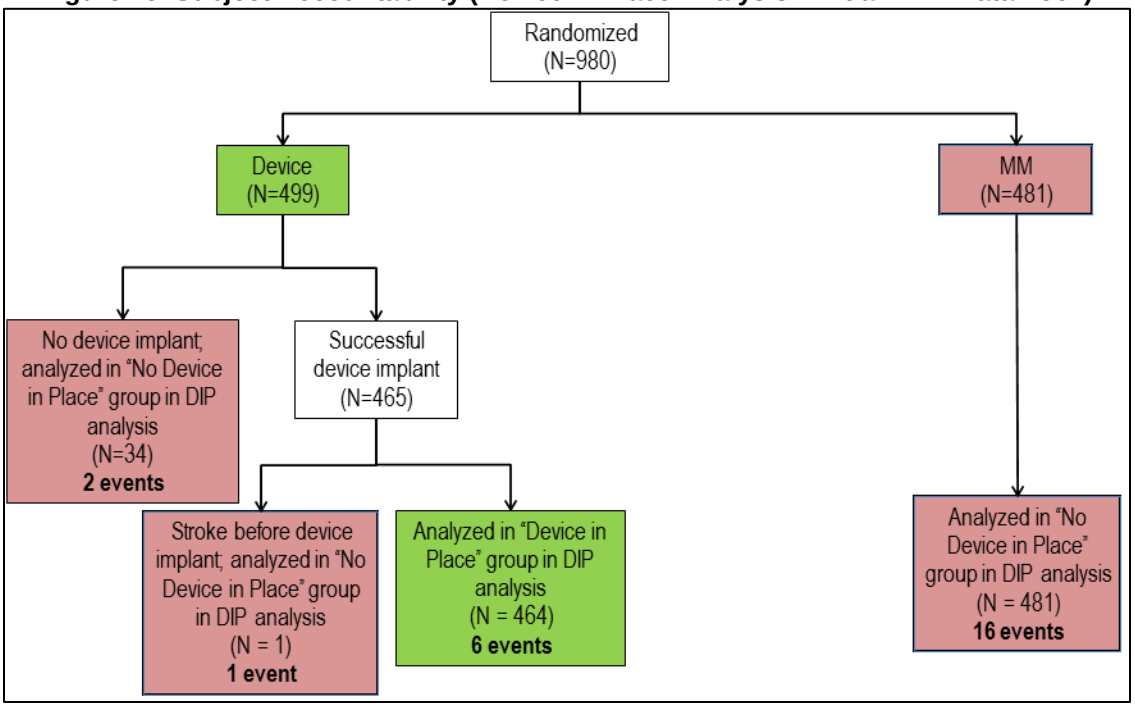
	Time from device implant or randomization (years)										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Device (N=463)											
At Risk	463	456	445	418	348	269	205	140	78	43	20
Event	0	3	5	5	5	8	10	13	14	14	14
Death	0	1	2	3	5	5	5	6	6	6	6
Censored	0	0	2	13	73	139	194	251	305	338	360
Discontinued	0	3	9	24	32	42	49	53	60	62	63
Event Rate	0	0.009	0.011	0.011	0.011	0.020	0.029	0.045	0.053	0.053	0.053
MM (N=487)											
At Risk	487	423	386	356	293	226	158	107	67	31	10
Event	0	8	13	15	20	21	21	22	23	23	24
Death	0	3	4	4	6	8	9	9	9	9	9
Censored	0	8	11	28	75	131	188	229	265	298	316
Discontinued	0	45	73	84	93	101	111	120	123	126	128
Event Rate	0	0.018	0.030	0.035	0.050	0.053	0.053	0.061	0.073	0.073	0.131

FDA Comment: In the Kaplan-Meier analysis of the extended follow-up of the As Treated population, the curves for the two treatment groups approach each other (at 6.5 to 8 years).

6.4.3.2 Device in Place Analysis

Subject accountability as of the initial data lock (20 May 2012) for the "Device in Place" population is shown in **Figure 15**.

Figure 15. Subject Accountability (Device in Place Analysis - Initial PMA Data Lock)



The Device in Place analysis was intended to characterize the effect of the Device vs. no Device (regardless of compliance to protocol-recommended medical therapy). In this analysis, subjects are analyzed according to whether or not they received the study Device, and follow-up for all subjects begins at randomization (see Section **5.2.1** for a complete description of the Device in Place population).

There were 6 events in 464 Device in Place subjects and 19 events in 516 No Device in Place subjects (**Figure 28**). The relative risk from the Cox proportional hazards model was 0.304 (95% CI: 0.122, 0.763), corresponding to a 69.6% relative risk reduction for stroke in favor of the Device in Place group.

Table 28. Primary endpoint outcomes (Device in Place Analysis - Initial PMA Data Lock)

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Post hoc analysis added after enrollment stopped					
DIP/KM[c]	980 (464/516)	25 (6/19)	0.304 (0.122, 0.763)	69.6%	0.007

Abbreviations: DIP, Device in Place; KM, Kaplan-Meier; D, Device; MM, Medical Management; RR, relative risk.
[a]For KM analysis, the relative risk is represented by the hazard ratios.
[b] 2-sided p-value using log-rank test and not adjusted for multiplicity
[c] The Device in Place analysis was based on device vs no device instead of device vs medical management.

The Kaplan-Meier freedom from primary endpoint analysis and plot are shown in **Table 29** and **Figure 16.** At 5 years, the Kaplan-Meier event rates for the Device in Place and No Device in Place groups were 0.012 and 0.067, respectively.

Figure 16. Kaplan - Meier freedom from primary endpoint event (Device in Place analysis -Initial PMA data lock)

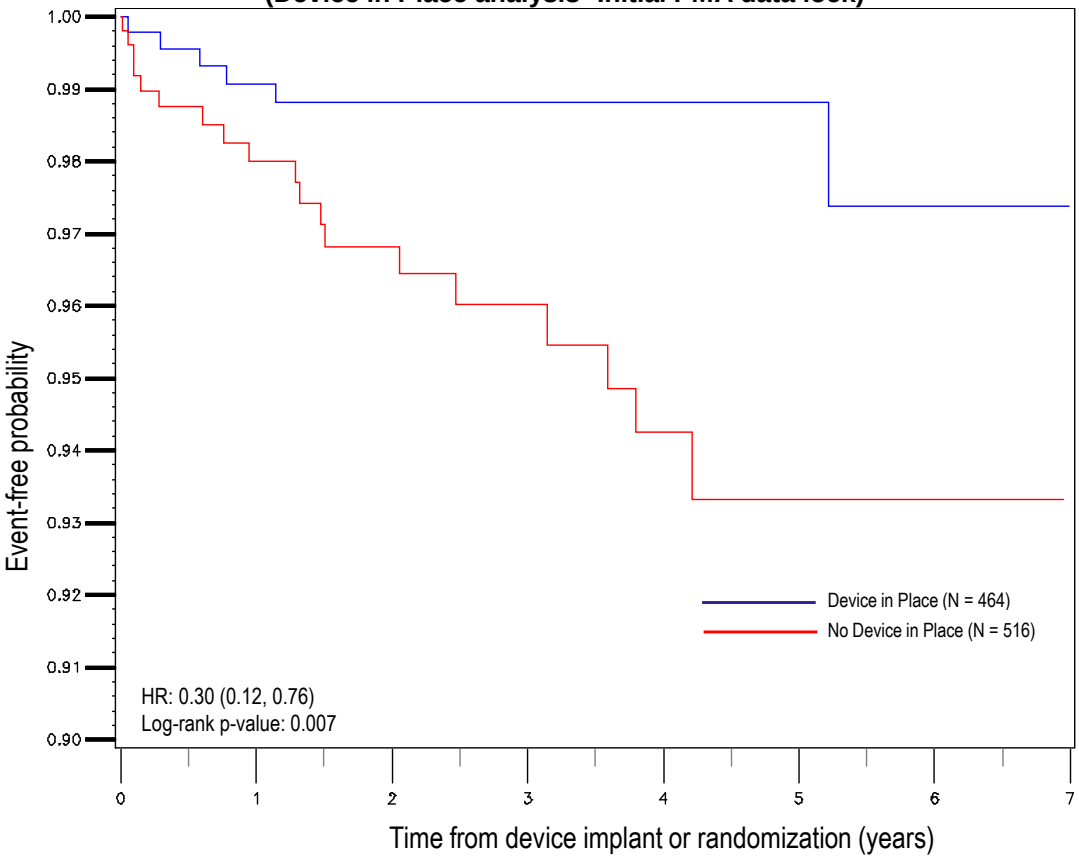


Table 29. Number at risk (Device in Place Analysis - Initial PMA Data Lock)

	Time to event (years)							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Device in Place (N=464)								
At Risk	464	393	295	216	153	102	53	19
Primary Endpoint Event	0	4	5	5	5	5	6	6
Death	0	1	2	2	3	3	3	3
Censored	0	64	154	222	278	327	372	406
Withdrawn	0	2	8	19	25	27	30	30
Primary Endpoint Event Rate	0	0.009	0.012	0.012	0.012	**0.012**	0.026	0.026
No Device n Place (N=516)								
At Risk	516	373	268	195	135	84	40	8
Primary Endpoint Event	0	9	13	15	18	19	19	19
Death	0	1	2	2	3	4	4	4
Censored	0	80	160	224	275	318	360	389
Withdrawn	0	53	73	80	85	91	93	96
Primary Endpoint Event Rate	0	0.020	0.032	0.040	0.057	**0.067**	0.067	0.067

Extended Follow-up

During extended follow-up, in the Device in Place population there were 9 additional events in the Device in Place group and 8 additional events in the No Device in Place group resulting in a total of 15 events in the Device group and 27 events in the MM group. The primary endpoint event rates for the Device in Place and No Device in Place groups were 0.61 and 1.24 per 100 patient-years, respectively, representing a relative risk of 0.51 (95% CI: 0.28, 0.94, **Table 30**).

Table 30. Primary endpoint event (Device in Place Analysis - Extended Follow-up)

Cohort Analysis	Subjects N total (N_D/N_{MM})	Primary Endpoint Events N total (N_D/N_{MM})	Relative Risk (D vs MM)[a] RR (95% CI)	Risk Reduction (1 - RR)	*P* value[b]
Post hoc analysis added after enrollment stop					
DIP/KM[c]	980 (464/516)	42 (15/27)	0.51 (0.28, 0.94)	49.0%	0.04

Abbreviations: DIP, Device in Place; KM, Kaplan-Meier; D, device; MM, medical management; RR, relative risk.

[a] For KM analysis, the relative risk is represented by the hazard ratios.

[b] 2-sided p-value using log-rank test and not adjusted for multiplicity

[c] The DIP analysis was based on device vs no device instead of device vs medical management.

The Kaplan-Meier freedom from primary endpoint plot and analysis are shown in **Figure 17** and **Table 31**. In the extended follow up Device in Place analysis, the event rates at 5 years are 0.022 in the Device in Place group and 0.056 in the No Device in Place group, and at 8 years, the primary endpoint event rates were 0.055 and 0.073, respectively.

Figure 17. Kaplan -Meier freedom from primary endpoint event (Device in Place Analysis - Extended Follow-up)

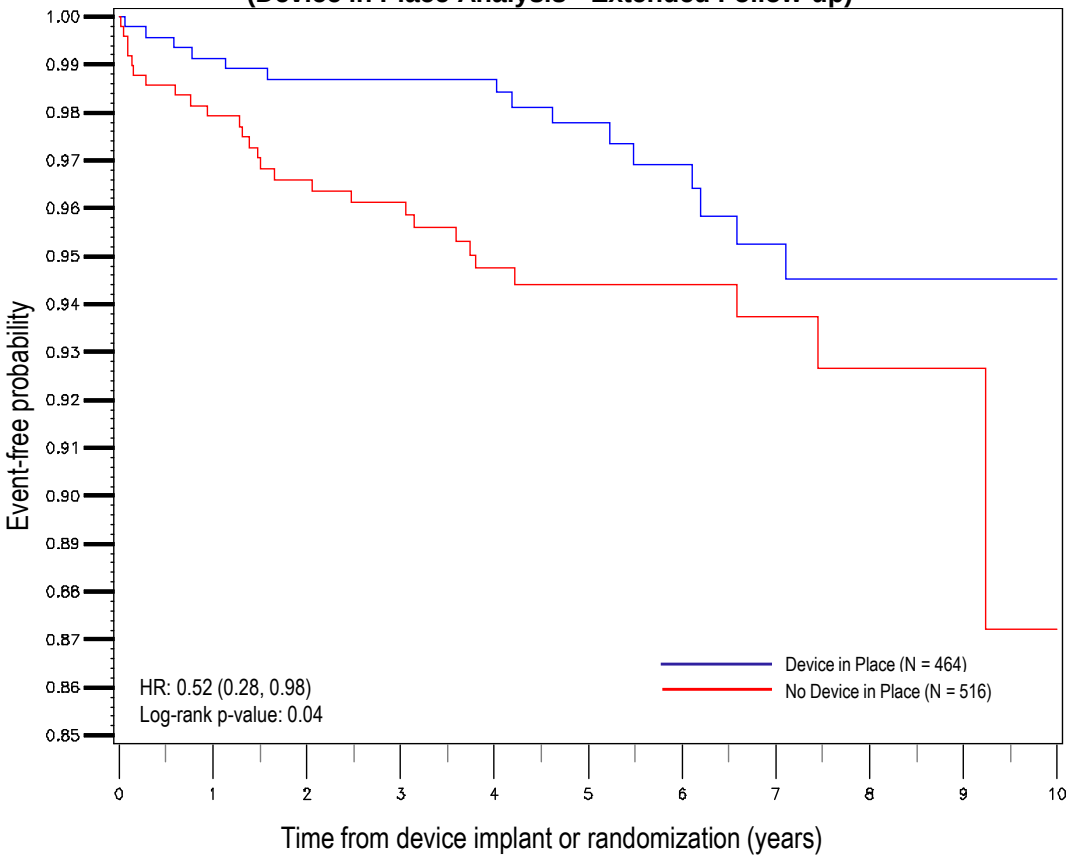


Table 31. Number at risk table (Device in Place Analysis - Extended follow-up)

	Time from randomization (years)										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Device in Place (N=464)											
At Risk	464	457	445	419	357	274	206	147	82	43	20
Event	0	4	6	6	6	9	11	14	15	15	15
Death	0	1	2	3	5	5	5	6	6	6	6
Censored	0	0	2	12	64	134	193	244	301	338	360
Discontinued	0	2	9	24	32	42	49	53	60	62	63
Event Rate	0	0.011	0.013	0.013	0.013	**0.022**	0.031	0.048	**0.055**	0.055	0.055
No Device in Place (N=516)											
At Risk	516	451	412	382	319	246	174	117	75	35	10
Event	0	10	16	18	23	24	24	25	26	26	27
Death	0	1	3	3	5	7	8	8	8	8	8
Censored	0	1	2	19	66	125	185	232	269	304	326
Discontinued	0	53	83	94	103	114	125	134	138	143	145
Event Rate	0	0.021	0.034	0.039	0.052	**0.056**	0.056	0.063	**0.073**	0.073	0.128

6.4.4 Primary Endpoint Analysis Results – Stroke Characteristics by ASCOD Phenotype

The ASCOD phenotyping evaluates the etiology of the ischemic stroke and assigns a degree of likelihood that the ischemic stroke can be attributed to an underlying disease state. The five phenotypes are (**Table 32**):

Table 32. ASCOD Phenotypes

Phenotype	Disease State
A	Atherosclerosis
S	Small vessel disease
C	Cardiac pathology
O	Other cause
D	Dissection

Each phenotype is assigned a Grade (**Table 33**):

Table 33. ASCOD Phenotype Grades

Grade	
1	Disease is present and potentially causal
2	Disease is present and causal link is uncertain
3	Disease is present and causal link is unlikely
0	Disease is absent
9	Workup is insufficient for grading

A post-hoc ASCOD phenotyping of each primary endpoint stoke event was conducted by a blinded committee consisting of two Steering Committee Neurologists and one Neuroradiologist from the CEC. The ASCOD grading for the ITT and Device in Place cohorts in the initial data lock is shown in **Table 34**. In the initial PMA data lock, the ASCOD Committee graded 7 of the 9 recurrent strokes in the Device group and 12 of the 16 recurrent strokes in the MM group in the ITT population as not having a Grade 1 cause (disease is present and potentially causal). In the Device in Place population, 4 of the 6 recurrent strokes in the Device Implanted and 15 of the 19 recurrent strokes in the No Device Implanted group in the Device in Place population were assessed as not having a Grade 1 cause (potentially cryptogenic).

Table 34. ASCOD coding for primary endpoint stroke events (Initial PMA Data Lock)

	ITT Events		Device in Place Events	
ASCOD code	Device 9 Events	MM 16 Events	Device Implanted 6 Events	No Device Implanted 19 events
Grade 1 cause	2 (22.2%)	4 (25.0%)	2 (33.3%)	4 (21.1%)
No Grade 1 cause	7 (77.8%)	12 (75.0%)	4 (66.7%)	15 (78.9%)

The ASCOD coding for the ITT and Device in Place cohorts in the extended follow-up analysis is shown in **Table 35**. In the ITT cohort, 10 of the 18 recurrent strokes in the Device group and 19 of the 24 recurrent strokes in the MM group were adjudicated as not having a Grade 1 cause. In the Device in Place cohort, 7 of the 15 recurrent strokes in the

Device Implanted group and 22 of the 27 recurrent strokes in the No Device Implanted group were adjudicated as not having a Grade 1 cause.

Table 35. ASCOD coding for primary endpoint stroke events (Extended Follow-up)

	ITT Events		Device in Place Events	
ASCOD code	Device 18 Events	MM 24 Events	Device Implanted 15 Events	No Device Implanted 27 Events
Grade 1 cause	8 (44.4%)	5 (20.8%)	8 (53.3%)	5 (18.5%)
No Grade 1 cause	10 (55.6%)	19 (79.2%)	7 (46.7%)	22 (81.5%)

FDA Comment: Although the ASCOD coding analysis suggests that the Device was associated with a reduction in the rate of recurrent stroke with no Grade 1 cause (i.e., fewer possible cryptogenic strokes), the scientific robustness of this analysis is limited, because there was no systematic uniform evaluation of subjects to determine the etiology of the recurrent stroke. The ASCOD algorithm was not designed to evaluate recurrent strokes. The ASCOD evaluation was reported as incomplete for 11 events, and in 6 additional events, it was noted that disease was present but the link to the event was uncertain.

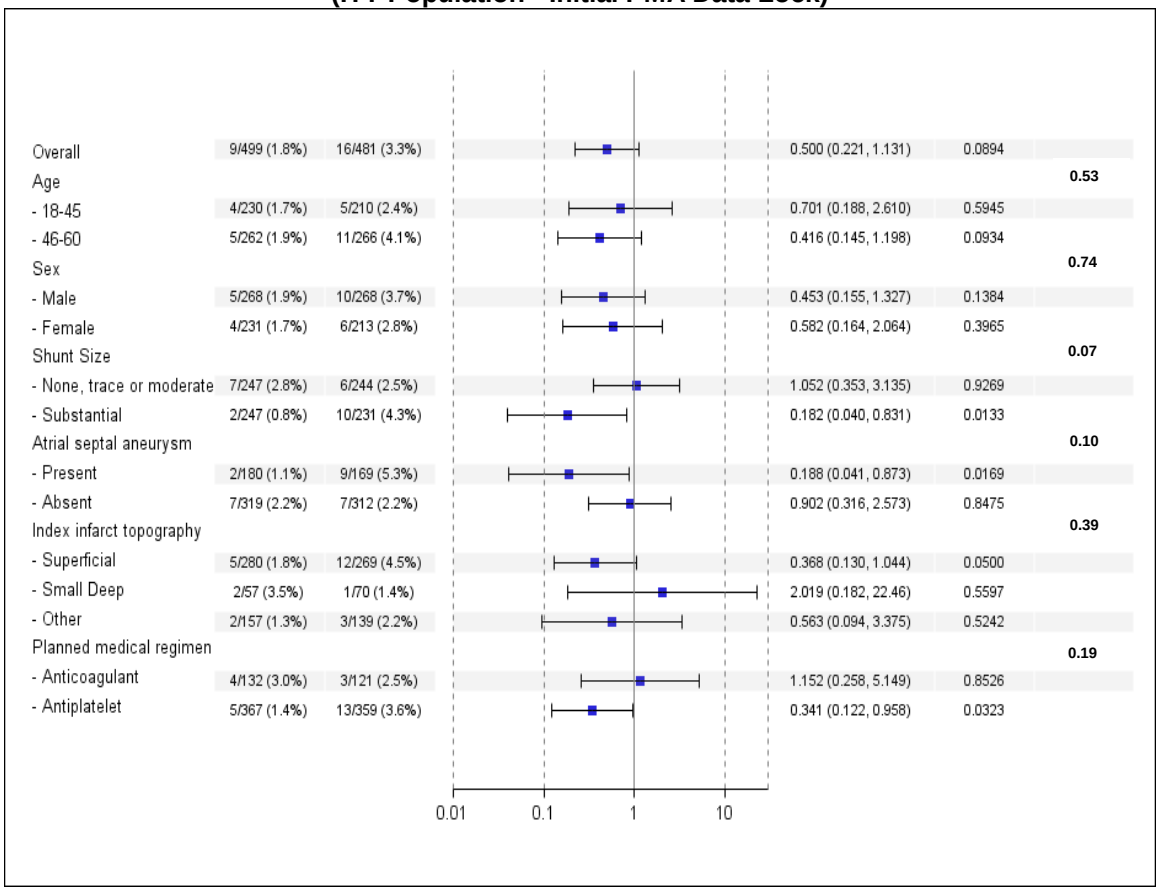
6.4.5 Primary Endpoint Analyses – Post-hoc Subgroups

Post-hoc analyses were performed on the following subgroups:

- Age (18-45 and 46-60 years)
- Sex (Male and Female)
- Shunt size (None/Trace/Moderate/ Substantial)
- Index infarct topography (Superficial, Small, Deep, and Other)
- Planned medical regimen (Anticoagulant and Antiplatelet)

A forest plot for the subgroups listed above for the primary endpoint is shown in **Figure 18** for the ITT population. At a *10% significance level*, there was a suggestion that the subgroup of patients with a substantial inter-atrial shunt or an ASA derive a benefit from the Device.

Figure 18. Subgroup analysis of the primary endpoint (ITT Population - Initial PMA Data Lock)



FDA Comment: The subgroup analysis suggests that the Device may provide an increased benefit in subjects with substantial shunt or an ASA. However, because the primary endpoint was not met, the subgroup analyses should be considered as hypothesis-generating for future studies.

6.4.6 Summary of Primary Endpoint Analysis Results

The number of primary endpoint events and Kaplan-Meier event rates at 5 and 8 years for each analysis population and dataset are summarized below in **Table 36**.

Table 36. Kaplan-Meier event rates at 5 and 8 years for each analysis population

Analysis Population	Subjects (Subjects with Events)		Kaplan-Meier Estimate at 5 years		Kaplan-Meier Estimate at 8 years		Hazard Ratio (95% CI)
	Device	MM	Device	MM	Device	MM	
ITT Initial Data Lock	499 (9)	481 (16)	0.021	0.059	N/A[1]	N/A[1]	0.50 (0.22, 1.13)
ITT Extended Follow-up	499 (18)	481 (24)	.028	0.051	0.060	0.070	0.64 (0.36, 1.16)
Per Protocol Initial Data Lock	463 (6)	474 (14)	0.012	0.059	N/A[1]	N/A[1]	0.37 (0.14, 0.97)
Per Protocol Extended Follow-up	463 (15)	474 (22)	0.022	0.049	0.055	0.069	0.58 (0.03, 1.12)
As Treated Initial Data Lock	463 (5)	487 (16)	0.010	0.066	N/A[1]	N/A[1]	0.28 (0.10, 0.77)
As Treated Extended Follow-up	463 (14)	487 (24)	0.020	0.053	0.053	0.073	0.51 (0.26, 0.99)
Device in Place Initial Data Lock	464 (6)	516 (19)	0.012	0.067	N/A[1]	N/A[1]	0.30 (0.12, 0.76)
Device in Place Extended Follow-up	464(15)	516 (27)	0.022	0.056	0.055	0.073	0.51 (0.28, 0.94)

[1]Not applicable: Initial data lock follow-up duration was 7 years

FDA Comment: Although there were numerical trends in favor of the Device, statistical significance for the primary endpoint in the ITT population (the primary analysis cohort) was not met. In the initial data lock analyses of three supplementary populations, event rates were more favorable to the Device group. In the extended follow-up analyses, the upper bound of the 95% CI for the hazard ratio was >1 for the ITT and Per Protocol populations. The Panel will be asked to comment on the clinical significance of the primary endpoint results.

6.5 Secondary Endpoint Results

6.5.1 Recurrent Symptomatic Cryptogenic, Nonfatal Stroke or Cardiovascular Death

The secondary composite endpoint of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death in the ITT population using the initial data lock was evaluated with the Kaplan-Meier method and Cox proportional hazards model. The hazard ratio was 0.174 (Device vs. MM).

FDA Comment: The clinical importance of this analysis is limited by causes of cardiovascular death, which in most cases were not associated with the presence of an untreated PFO, device-closure of the PFO, or medical therapy post-randomization.

6.5.2 TIA

The secondary endpoint of CEC-adjudicated TIA in the ITT population for the initial data lock was evaluated with the Kaplan-Meier method (**Figure 19** and **Table 37**) and Cox proportional hazards model. The hazard ratio was 0.901.

Figure 19. Kaplan-Meier freedom from TIA (ITT Analysis - Initial PMA Data Lock)

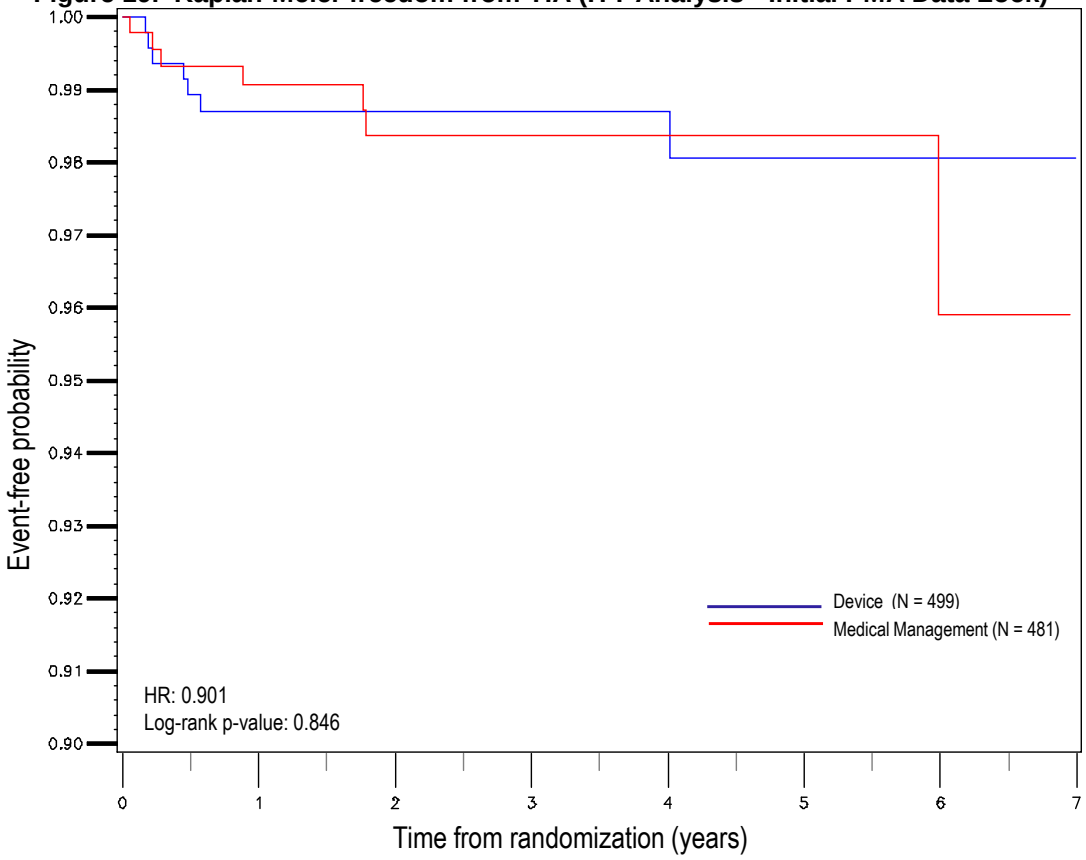


Table 37. Number at risk table (ITT Analysis - Initial PMA Data Lock)

	Time to event (years)							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Device (N=499)								
At Risk	499	407	305	225	158	106	54	20
TIA Event	0	6	6	6	6	7	7	7
Death	0	1	2	2	3	3	3	3
Censored	0	68	162	230	290	339	388	422
Withdrawn	0	17	24	36	42	44	47	47
TIA Rate	0	0.013	0.013	0.013	0.013	0.019	0.019	0.019
MM (N=481)								
At Risk	481	361	258	188	131	79	38	8
TIA Event	0	4	6	6	6	6	7	7
Death	0	1	3	3	5	6	6	6
Censored	0	76	153	216	265	310	348	376
Withdrawn	0	39	61	68	74	80	82	84
TIA Rate	0	0.009	0.016	0.016	0.016	0.016	0.041	0.041

FDA Comment: Although the diagnosis of TIA may be less definitive than stroke (since TIA's lack imaging confirmation), the absence of any signal suggesting that the TIA rate was lower in the Device group vs. MM (HR 0.901) is notable.

6.5.3 PFO Closure Assessment

PFO closure was assessed by TEE and bubble study at the 6-month follow-up in Device subjects and was adjudicated by the Echocardiography Core Laboratory. *Complete* PFO closure was the pre-specified secondary endpoint, which was defined as the absence of microbubbles (i.e., grade 0 shunt) in the left atrium at rest and with Valsalva within 3 cardiac cycles after right atrial opacification.

There were the 465 Device subjects who were eligible for complete PFO closure analysis by 6 month TEE. Of these:

- 338 subjects had a shunt grade assessment both at rest and with Valsalva; these subjects were included in the closure analysis.
- 11 subjects had a shunt grade assessed as Grade 1 or higher either at rest or with Valsalva; these subjects were included in the closure analysis as complete closure failures.
- 58 subjects had a missing shunt grade assessment either at rest or with Valsalva; these subjects were omitted from the closure analysis since complete closure could not be confirmed.
- 58 subjects were not assessed by Echo Core Lab (25 subjects did not undergo TEE, and the TEE in 33 subjects had neither rest nor Valsalva results); these subjects were omitted from the closure analysis.

There were 249 of 349 subjects with a grade 0 shunt both at rest and Valsalva at 6 months, corresponding to a complete closure rate of 71.3% (**Table 38**). Therefore,

incomplete PFO was common, occurring in 28.7% of assessed subjects. An additional analysis of the proportion of subjects with "effective closure" (defined as *either a grade 0 or a grade I* shunt at rest and Valsalva) showed a 94.2% PFO effective closure rate at 6 months (**Table 38**).

Table 38. 6-month PFO closure data, Device group subjects who received a Device

Closure	Shunt grade	n/N (%)
Complete	Grade 0 Rest AND Grade 0 Valsalva	249/349[1] (71.3%)
Effective	Grade 0/I Rest AND Grade 0/I Valsalva	323/343 (94.2%)

[1]349 subjects includes 338 subjects with a shunt grade assessed both at rest and Valsalva plus 11 subjects with a shunt grade assessed as Grade 1 or higher either at rest or with Valsalva (included in the closure analysis as complete closure failures).

Of the 6 subjects in the device group who had a stroke after device implant, two subjects experienced a recurrent stroke after device implant but prior to their 6-month shunt assessment (one had a grade I shunt both at rest and with Valsalva at the 6-month TEE, and the other had sinus venous ASD in addition to the PFO). No residual shunt was detected in the remaining 4 Device subjects with recurrent strokes.

FDA Comment: Complete PFO closure (defined as a Grade 0 shunt at rest and with Valsalva) was a pre-specified secondary endpoint, and there were 465 subjects with a successful Device implant. Six month TEE-assessed PFO shunt data were available on 349 Device subjects. Therefore, PFO closure data was incomplete or missing for 116 subjects. Complete PFO closure was achieved 71.3% of assessed Device subjects. Thus, despite Device implantation, residual right-to-left shunting was relatively common (28.7% of subjects).

6.6 Safety Evaluation

All adverse events were adjudicated by the DSMB to specify their seriousness and their relation to the procedure, Device or study protocol. Serious adverse events of interest through extended follow-up are presented below. Of note, there were no device erosion events or unanticipated adverse effects.

6.6.1 Deaths

There were 16 deaths: 6 in the Device group (6/499, 1.2%) and 10 in the MM group (10/ 481, 2.1%, **Table 39**) with 15 of 16 deaths occurring >6 months post-randomization, and one Device group death within 6 months due to coronary artery disease. None of the deaths were adjudicated by the DSMB as being related to the Device, procedure, delivery system, or study protocol. One Device subject and one MM subject died following a non-primary endpoint hemorrhagic stroke. There were four cases that could be considered cardiovascular deaths (1 Device and 3 MM subjects). One Device subject had a fatal pulmonary embolism (see **Section 6.6.2**).

Table 39. Deaths (extended follow-up)

Cause of Death	Subjects
Device Subjects (n=6)[1]	
Cancer	2
Respiratory failure as a result of acute stroke/intracerebral hemorrhage	1
Pulmonary embolism	1
Drug overdose (non-study medication)	1
Asystole as a result of coronary artery disease	1
MM Subjects (N=10)	
Cancer[2]	3
Trauma	2
Intracerebral hemorrhage[2]	1
Cardiac arrest/dysrhythmia	3
Sepsis	1

[1]All device group subjects received a Device. [2]One subject with cancer and one subject with an Intracerebral hemorrhage were adjudicated as having experienced a primary endpoint nonfatal ischemic stroke.

6.6.2 Serious Adverse Events (SAEs) and Clinically Relevant Non-SAEs

There were 25 SAEs related to the Device or implantation procedure in 21 Device group subjects. The proportion of Device group subjects with SAEs related to the Device or implantation procedure was 4.5% (21 of 467 subjects with a Device implantation attempt). Selected Device group SAEs are shown in **Table 40**. There were no device- or procedure-related acute ischemic strokes resulting from air or observed thromboemboli from the device. There were 2 cases of pericardial tamponade, 1 cardiac perforation, 3 cases of major vascular access site complications, and two Device explantation procedures.

Table 40. Selected SAEs related to the Device or implantation procedure – Device group only

Event	Subjects with Event	Subjects in Denominator	Event Rate
Ischemic stroke	2	467	0.4%
Pericardial tamponade	2	467	0.4%
Cardiac perforation	1	467	0.2%
Major vascular access site complication (bleeding or hematoma)	3	467	0.6%
Device explantation[1]	2	465[2]	0.4%

[1]Subject (b) had an ischemic stroke post PFO-implant and was found to have septal communication near the IVC; the Device was surgically removed. Subject (b) had endocarditis approximately 2 years after PFO implant and had the Device surgically explanted.
[2]Two subjects did not have a successful implant.

No Device subject had an SAE associated with a Device thrombus. However, in one Device subject, a TEE showed a thrombus attached to the right atrial wall inferior to the device; the patient was treated with anticoagulation, and thrombus resolution was confirmed by TEE at 2 months.

Table 41 shows SAEs adjudicated as protocol-related in the MM group (excluding 1 MM subject who had an SAE associated with off-label PFO closure and 1 subject with a cerebral aneurysm that was detected incidentally). The overall rate for these SAEs was 1.0%, and these events were adjudicated as related to the anti-thrombotic therapy.

Table 41. SAEs related to the protocol - MM group only

Event	Event Rate
Abnormal Lab Value	0.2% (1/481)
Hematoma	0.2% (1/481)
Menorrhagia	0.2% (1/481)
Subdural Hemorrhage	0.4% (2/481)
Total	1.0% (5/481)

Table 42 shows the rate of major bleeding, stratified by treatment group. The major bleeding rates were similar between the Device and MM group.

Table 42. Rate of major bleeding

Device (N=499 subjects, 2769 patient-years)			MM (N=481 subjects, 2376 patient-years)		
Subjects	**Events[1]**	**Event Rate (per 100 pt-yrs)**	**Subjects**	**Events[1]**	**Event Rate (per 100 pt-yrs)**
13	17	0.61	14	14	0.59

[1]Multiple events may occur in a single subject.

Table 43 shows the rates of atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia adjudicated as either SAEs or non-SAEs, stratified by treatment group.

Table 43. Rates of atrial arrhythmias (SAES and non-SAEs)

Event	Device (N=499 subjects, 2769 patient-years)				MM (N=481 subjects, 2376 patient-years)			
	Subjects	Percent	Events	Rate (per 100 pt years)	Subjects	Percent	Events	Rate (per 100 pt years)
Atrial Fibrillation	18	3.6%	20	0.72	9	1.9%	12	0.51
Paroxysmal Atrial Fibrillation	3	0.6%	3	0.11	0	0.0%	0	0.00
Atrial Flutter	2	0.4%	2	0.07	0	0.0%	0	0.00
PSVT[1]	5	1.0%	5	0.18	0	0.0%	0	0.00

[1]Paroxysmal supraventricular tachycardia (all were non-serious adverse events)

The observed rates of atrial fibrillation and paroxysmal supraventricular tachycardia were numerically higher in the Device vs. the MM group. On a per-subject basis, the atrial fibrillation rate was 4.2% (21/499) in the Device group subjects (1.9% 9/481) in the MM group.

Table 44 shows the rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) adjudicated as either SAEs or non-SAEs, stratified by treatment group.

Table 44. Rates of DVT and PE (SAEs and non-SAEs)

Event	Device (N=499 subjects, 2769 patient-years)				MM (N=481 subjects, 2376 patient-years)			
	Subjects	Percent	Events	Rate (per 100 pt years)	Subjects	Percent	Events	Rate (per 100 pt years)
DVT[1] or PE[2]	18	3.6%	24	0.87	3	0.6%	5	0.21
DVT	11	2.2%	11	0.40	3	0.6%	3	0.13
PE	12	2.4%	13	0.47	2	0.4%	2	0.08

[1]Deep venous thrombosis. [2]Pulmonary embolism (all pulmonary embolism events were SAEs).

There were 18 subjects (3.6%) in the Device group and 3 subjects (0.6%) in the MM group who had a DVT or PE. The reasons for the higher observed rates of DVT or PE in the Device group are not clear. One possible explanation is that some PFO patients are at increased risk for venous thrombosis, and the more frequent use of warfarin in the MM group (in approximately 20% of subjects, **Table 8**) reduced their risk of DVT and PE compared warfarin use in the Device group (<4% of subjects, **Table 7**). Additional

studies would be needed to help identify patients who are at particularly high risk of venous thrombosis and to determine whether PFO closure plus anticoagulation is superior to anticoagulation alone to prevent ischemic stroke.

FDA Comment::

- Subject deaths were uncommon, and there was no signal of increased mortality in either treatment group.
- The proportion of Device group subjects with SAEs related to the Device or implantation procedure was 4.5%.
- Major bleeding rates were similar between treatment groups.
- The total observed atrial fibrillation rate was numerically higher in the Device group (4.2%) compared with the MM group (1.9%).
- There was a signal for a higher rate of deep venous thrombosis and pulmonary embolism in the Device vs. the MM group (3.6% vs. 0.6%, respectively).

The panel will be asked to comment on the significance of the safety data.

7 POST-APPROVAL STUDY

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing a reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has made the recommendation that if the AMPLATZER PFO Occluder is approved, a post-approval study (PAS) should be required as a condition of approval for this first-of-a-kind device. Through our review of the premarket data, FDA recommends a post-approval study of newly enrolled subjects to address short and long-term performance of the AMPLATZER PFO Occluder. The FDA and the sponsor have begun to discuss the design a potential study. An overview of the proposed new-enrollment PAS outline is provided below, and the FDA will be requesting Panel input on the PAS investigational plan.

7.1 Overview of Proposed Post-Approval Study

Objective:

- To assess long-term safety of the Device by assessing the rate of device- or procedure-related serious adverse events

- To provide additional assurance of Device effectiveness by assessing the rate of recurrent ischemic stroke

Study design: Single arm, multi-center study.

Study population: Patients who are intended for percutaneous, transcatheter closure of a PFO who have had a cryptogenic ischemic stroke due to a presumed paradoxical embolism.

Inclusion criteria: Subjects with PFO who have had a cryptogenic stroke within the last 270 days, with stroke defined as an acute focal neurological deficit, presumed to be due to focal ischemia, and either 1) symptoms persisting ≥24 hours, or 2) symptoms persisting <24 hours but associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.

Exclusion criteria:

1. Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels of >50% of lumen diameter supplying the involved lesion
2. Intracardiac thrombus or tumor
3. Acute or recent (within 6 months) MI or unstable angina
4. Left ventricular aneurysm or akinesis
5. Mitral valve stenosis or severe mitral regurgitation irrespective of etiology
6. Aortic valve stenosis (gradient >40 mmHg) or severe aortic valve regurgitation
7. Mitral or aortic valve vegetation or prosthesis
8. Aortic arch plaques protruding >4 mm into the lumen
9. Left ventricular dilated cardiomyopathy with LVEF <35%
10. Subjects with other source of right to left shunts identified at baseline, including an atrial septal defect and/or a fenestrated septum
11. Atrial fibrillation/atrial flutter (chronic or intermittent)
12. Pregnant or desire to become pregnant within the next year
13. Age <18 years and age >60 years
14. Active endocarditis or other untreated infections
15. Kidney, liver, or lung failure
16. Uncontrolled hypertension: Sustained elevated systemic BP >160/90 with medications.
17. Uncontrolled diabetes: Elevated glucose levels despite administration of insulin with levels >200 mg/dl with presence of glucose in the urine.
18. Ischemic stroke in the distribution of a single, small deep penetrating vessel in a patient with any of the following: 1) a history of hypertension (except in the first week post stroke); 2) history of diabetes mellitus; 3) Age ≥50; or 4) MRI or CT shows leukoaraiosis greater than symmetric, well-defined periventricular caps or bands (European Task Force on Age-Related White Matter Changes rating scale score >0)
19. Arterial dissection as qualifying event
20. Signs of progressive neurological dysfunction or malignancy or other illness

where life expectancy is less than 2 years

21. Subjects who test positive with one of the following hypercoagulable states: Anticardiolipin Ab of the IgG or IgM, Lupus anticoagulant, B2-glycoprotein-1 antibodies or persistently elevated fasting plasma homocysteine despite medical therapy
22. Subjects with contraindication to aspirin or clopidogrel therapy
23. Anatomy in which the AMPLATZER PFO Occluder would interfere with intracardiac or intravascular structures such as valves or pulmonary veins
24. Stroke with poor outcome at time of enrollment (Modified Rankin score >3)

Study endpoints:

1. *Effectiveness endpoint:* The 5-year rate of the composite of:
    - recurrent non-fatal ischemic stroke
    - fatal ischemic stroke

    where ischemic stroke is defined as acute focal neurological deficit presumed to be due to focal ischemia, and either 1) symptoms persisting ≥24 hours, or 2) symptoms persisting <24 hours but associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.

Hypothesis: The endpoint event rate at 5-years is less than the pre-specified performance goal (PG) of 4.4%.

The hypothesis is based on the proportion of subjects experiencing a primary effectiveness endpoint event (π), and is as follows:

H_0: $\pi \geq 4.4\%$

$H_{1:}$ $\pi < 4.4\%$

The primary effectiveness endpoint event rate at 5 years is assumed to be 2.2% based on the 5-year Kaplan-Meier rate of ischemic stroke for subjects who received a Device in the Device group of the RESPECT trial (using the extended follow-up dataset, cutoff date 14 Aug 2015). The PG is twice the expected event rate.

2. *Safety endpoint:* The 5-year rate of the composite of device- or procedure-related serious adverse events, including:
    - New onset atrial fibrillation
    - Pulmonary embolism
    - Device thrombus
    - Device erosion/embolization
    - Major bleeding requiring transfusion
    - Vascular access site complications requiring surgical intervention
    - Device- or procedure-related serious adverse event leading to death

Hypothesis: The event rate at 5-years is less than the pre-specified PG of 4.0%.

The hypothesis is based on the proportion of subjects experiencing a primary safety endpoint event is as follows:

H_0: p ≥4.0%

H_1: p <4.0%

The primary safety endpoint event rate at 5 years is assumed to be 2.0% based on the adverse event data in the RESPECT trial (using the extended follow-up dataset, cutoff date 14 Aug 2015). The PG is twice the expected event rate.

Descriptive endpoints

- Components of primary effectiveness endpoint
- All-cause mortality
- TIA
- Effective PFO closure: Grade 0 or 1 shunt through the PFO at rest and/or Valsalva as assessed by TTE at 1 year
- Technical success: Successful delivery and release of the Device in subjects in whom delivery system entered the body
- Procedural success: Successful implantation of the Device with no reported in-hospital SAEs for subjects in whom delivery system entered the body

Follow-up: Subjects will be followed for 5 years post-Device implant at pre-hospital discharge, 1-month, 6-months, and 12-months with telephone follow-up annually thereafter. The total duration of the study is expected to be 8 years.

Study Flow Chart

♥ = Required testing

	Baseline	Procedure	Discharge	1 month (± 1 week)	6 months (± 1 month)	12 months (± 3 months)	2 years (± 3 months)	3 years (+3 months)	4 years (+3 months)	5 years (+3 months)
Exam	♥		♥	♥	♥	♥				
Modified Rankin	♥									
Stroke Questionnaire + additional assessments, as necessary	♥			♥	♥	♥	♥	♥	♥	♥
Telephone Follow-up							♥	♥	♥	♥
Transesophageal Echo with bubble study	♥	♥				♥				

Projected sample size: Approximately 806 subjects will be enrolled in this study and the study will be conducted in approximately 80 centers in the US.

Sample size calculation

Effectiveness endpoint

- Expected event rate at 5 years: 2.2% (5-year Kaplan-Meier rate of ischemic stroke for subjects who received a device in the device group)
- Performance goal = 4.4%
- Significance level = 5%
- Sample size = 604 subjects
- Power = 93%

Safety endpoint

- Expected event rate at 5 years: 2.0% (10/499)
- Performance goal = 4.0%
- Significance level = 5%
- Sample size = 604 subjects
- Power = 90%

Table 40 in **Section 6.6.2** provides the number of events for the components of the safety endpoint from the RESPECT trial. There were 10 subjects who experienced at least one safety endpoint event, corresponding to a rate of 2.0% (10/499).
The sample size was calculated by simulation of the primary effectiveness and safety endpoints. Events for the primary effectiveness and safety endpoints were simulated from a binomial distribution. The primary effectiveness and safety endpoints will be analyzed when all subjects reach 5-year of follow-up. Assuming a 5-year attrition rate of 25%, 806 subjects are required to be enrolled.

Statistical Analysis

Analysis of the primary effectiveness endpoint will include subjects successfully implanted with the Device. The analysis will be carried out by estimating the 5-year using the Kaplan-Meier method. The null hypothesis will be rejected if the 95% upper confidence bound (UCB) for π is less than 4.4%. The UCB will be calculated by the Greenwood method.

Analysis of the primary safety endpoint will include subjects who undergo Device implant attempts. An implant attempt is defined as the Device delivery system entering the body. The null hypothesis will be rejected if the 95% UCB for π is less than 4.0%. The UCB will be calculated by the Greenwood method.

FDA Comment:

- In RESPECT, there was a signal for a higher rate of deep venous thrombosis and pulmonary embolism in the Device vs. the MM group. It would be appropriate to explore this issue further in a post-approval study.
- The rate of *complete* PFO closure is an endpoint of interest for a post-approval study.
- Evaluation of the training program for new operators is a common objective of post-approval studies.

FDA will ask the Panel to provide recommendations on whether the proposed post-approval study is acceptable or whether additional elements or objectives should be considered to provide surveillance on the safety and effectiveness of the Device (if approved).

8 FDA CONSIDERATIONS AND CONCLUSIONS

The RESPECT trial was designed to assess whether the AMPLATZER PFO Occluder is superior to the standard of care medical treatment for the prevention of recurrent embolic stroke in subjects who had a cryptogenic stroke due to presumed paradoxical embolism.

When evaluating whether the results of the RESPECT study provide reasonable assurance of safety and effectiveness of the Device for the proposed indications, the following points should be considered:

1. The primary effectiveness endpoint of a significantly reduced rate of recurrent ischemic stroke in Device vs. MM subjects was not met in the ITT analysis. In the initial data lock, there were 25 total events in the ITT population (9 in the Device and 16 in the MM group); the P-value for the primary raw count analysis was 0.157. The P-value for the Kaplan-Meier analysis (performed to help address the higher rate of subject dropout in the MM group) was also not statistically significant (0.089).

2. There were relatively few primary endpoint events (42 in total) in a trial of that enrolled 980 subjects with the vast majority of subjects followed for at least 4 to 5 years. The low number of recurrent strokes and the small event rate differences between treatment groups (0.65 per 100 patient years in the Device group vs. 1.01 per 100 years in the MM group in the extended follow-up analysis) suggests that many patients could be potential candidates for an invasive cardiac procedure to implant a permanent device to prevent a relatively uncommon event. Unfortunately, there was no particular patient subgroup for whom there is

compelling evidence for an enhanced benefit associated with implantation of the Device.

3. The primary endpoint was evaluated in additional patient cohorts: Per Protocol, As Treated and Device in Place (post-hoc). While these analyses suggest a Device benefit of a reduced observed rate of recurrent ischemic stroke, it should be noted that since the primary endpoint was not met, the results of supplementary analyses are typically used to generate hypotheses for future studies.

4. Analyses conducted on the extended follow-up data lock demonstrate a smaller difference in recurrent ischemic stroke rates in the Device vs. MM groups compared to the difference observed in the original PMA dataset, reducing the likelihood that PFO closure with the Device provides a durable benefit.

5. The rate of subject discontinuation was relatively high for the entire enrolled population and was higher in the MM vs the Device group (30.1% vs. 18.2%, respectively, in the extended follow-up data lock). The unbalanced rate of subject withdrawal limits the robustness of the trial results.

6. Atherosclerotic risk factors for stroke were common among enrolled subjects in both groups, and 8.1% of subjects did not have imaging confirmation of their qualifying stroke, raising the possibility that the event that was considered the qualifying stroke in some subjects was not a cryptogenic and in which the pathophysiologic role of the PFO is uncertain.

7. PFO closure assessment of the 6-month TEE by the Echo Core lab was missing in approximately 25% of subjects implanted with the Device. In addition, residual right-to-left shunting was relatively common, occurring in 28.7% of subjects who had PFO closure assessed at 6 months. .

8. With respect to Device safety, the proportion of Device group subjects with serious adverse events related to the Device or implantation procedure was 4.5%. There was a signal for an increased risk of atrial fibrillation and deep venous thrombosis/pulmonary embolism in subjects treated with the Device.

9. Over the course of 8 years, there were a number of key changes to the RESPECT clinical protocol in an effort to increase enrollment. These changes included, but were not limited to, an increased age of study-eligible patients,, extension of the number days from the qualifying stroke to study enrollment, and the provision for additional statistical analyses.

The data presented in the PMA describe the safety and effectiveness of the AMPLATZER PFO Occluder for reducing the risk of recurrent ischemic stroke when used in patients who have had a cryptogenic stoke due to presumed paradoxical embolism. The Advisory Panel will be asked to review and assess whether the totality of the data provides a reasonable assurance of safety and effectiveness and address the benefit-risk profile of the AMPLATZER PFO Occluder when used in accordance with the proposed indications.

9 Appendices

Appendix A – Key Study Protocol Definitions

Acute focal neurological deficit	Focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit.
Adverse event	Any undesirable health occurrence or untoward deviation in health away from baseline, whether or not device- or procedure-related.
As Treated population	Population includes subjects who received a protocol-approved treatment and complied with the protocol-mandated medical treatment. The population excludes subjects who were non-compliant to the prescribed medication regimen in the protocol in either group at least 67% of the time, device group subjects who did not receive the device, and device group subjects who experienced an event prior to receiving a device.
Atrial septal aneurysm	Movement of the septum primum greater than or equal to 10 mm relative to the place of the inter-atrial septum.
Cryptogenic stroke	Stroke from unknown causes.
Delivery system-related adverse event	An adverse event related to the delivery system.
Device in Place population	Population includes all randomized subjects and analyzed per treatment groups according to whether or not the subject received the Device at the time of a primary endpoint event.
Device-related AE	An adverse event specifically related to the study device.
Other adverse event	Events that do not meet the definition of a serious adverse event or adverse event. These events may be changes from baseline health, but not untoward medical occurrences. This category includes events that are determined by the DSMB to be unrelated to the procedure, device, delivery system, or protocol. These types of events are listed separate from events related to the trial.
Intent to Treat population	Population includes all randomized subjects and analyzed by the treatment group to which subject was randomly assigned, regardless of treatment actually received.
Ischemic stroke	Acute, focal neurological deficit presumed to be due to focal ischemia and either 1) symptoms persisting 24 hours or longer, or 2) symptoms persisting less than 24 hours but associated with MR or CT findings of a new, neuroanatomically relevant cerebral infarct.

Major bleed	Serious adverse events of either an intracranial hemorrhage or bleeding that led to hemodynamic compromise requiring intervention (e.g., pericardiocentesis, blood transfusion) or death. Bleeding events include intraparenchymal hemorrhage, hemorrhagic stroke, hematoma, pericardial effusion, pericardial tamponade, gastrointestinal bleeding, and menorrhagia.
Major vascular access site complication	Serious adverse events of vascular access site complications (VASC) including VASC bleeding, VASC hematoma, and cardiac perforation.
Patent foramen ovale	Visualization of microbubbles per TEE in the left atrium within 3 cycles from right atrial opacification at rest and/or at Valsalva release.
Per protocol population	Population includes subjects who received their randomly assigned treatment and complied with the protocol-mandated medical treatment. The population excludes subjects who did not meet key eligibility criteria, subjects who were non-compliant to the prescribed medication regimen in the protocol in either group 67% of the time, and device group subjects who did not receive the device.
PFO closure	Absence of microbubbles in the left atrium at rest and during Valsalva within 3 cycles from right atrial opacification.
Procedure-related AE	An adverse event related to the implant procedure and not the study device or delivery system.
Protocol-related adverse event	An adverse event related to either a study procedure (e.g., sore throat as a consequence of a TEE) or a side effect of medication that was prescribed as part of the protocol. This category does not include adverse events attributable to the device, delivery system, or implant procedure.
Serious adverse event	Any untoward medical occurrence resulting in at least 1 of the following impacts: death, life-threatening, inpatient hospitalization or prolongation of existing hospital stay, persistent or significant disability/incapacity, congenital anomaly/birth defect, or medically significant event (including laboratory abnormalities).
Transient ischemic attack	Acute focal neurological deficit presumed to be due to focal ischemia with symptoms persisting greater than or equal to 5 minutes and less than 24 hours that are not associated with MR or CT findings of a new neuroanatomically relevant cerebral infarct.
Unanticipated adverse device effects	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application including a supplementary plan or

	application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unrelated adverse event	An event not thought to be related to the device, procedure, delivery system, or protocol. These events, provided they are not determined to be serious adverse events, may be considered "other" events.

Appendix B – PFO Access Registry

Name: Patent Foramen Ovale Closure with the AMPLATZER PFO OCCLUDER in Patients with Recurrent Cryptogenic Stroke due to Presumed Paradoxical EmboliSm through a Patent Foramen Ovale who have Failed Conventional Drug Therapy

Objective: To allow access to the AMPLATZER PFO Occluder in subjects with a PFO who have already experienced at least two cryptogenic strokes due to presumed paradoxical embolism through PFO and who have failed conventional drug therapy. The registry objectives, data collection and registry management are not intended to support formal statistical hypothesis testing.

Duration: The PFO ACCESS Registry will include a maximum of 2000 subjects per year at a maximum of 100 institutions.

All subjects will be followed up to 1 year from the date of implant until registry closure. Once the PMA for the AMPLATZER PFO Occluder device is approved, the ACCESS PFO Registry will be closed.

Subject Selection:
Inclusion Criteria
A documented PFO and recurrent cryptogenic stroke on anticoagulant or antiplatelet therapy. Anticoagulant/antiplatelet therapy is defined as therapeutic dose of warfarin at an INR range 2-3; adequate dosage of aspirin; or adequate dosage of a combination of aspirin and Plavix or Ticlid.

Exclusion Criteria

- Subjects with INR outside the 2-3 range
- Intracardiac Thrombus (subjects may be enrolled after medical treatment and resolution of the thrombus)

If a subject has a hypercoagulable state, or cannot take antiplatelet medications, careful consideration must be taken if the subject should be enrolled into the PFO Access study.

Treatment: Post-catheterization treatment includes antiplatelet/anticoagulation therapy, such as aspirin for 6 months post implant. The decision to continue antiplatelet/anticoagulation therapy beyond 6 months is at the discretion of the physician. Endocarditis prophylaxis will be carried out for six months in all subjects according to the recommendations of the American Heart Association.

Follow-up Schedule:

Table 45. Follow-up Assessment Schedule

Required Test	6 months (± 3 months)	1 year (± 3 months)
Echo Doppler and closure assessment by cardiologist	√	X
Recurrent stroke assessment by neurologist	Y	√
Serious Adverse Events assessment	√	√

√ Required
X Required only if residual shunt at 6 months
Y Required if neurological symptoms present at 6 month visit with cardiologist

Summary of Results: Adverse events were adjudicated by the same independent DSMB as the RESPECT trial. **Table 46** summarizes the serious adverse events of interests in subjects with the Device as of 25 Jun 2015.

Table 46. Serious adverse events of interest in subjects with the Device

	Subjects with implanted Device (N=584)	
	Events N	Subjects N (%)
Acute ischemic stroke due to air or thromboemboli [1]	0	0 (0%)
Atrial fibrillation	4	4 (0.68%)
Death from any cause	16	16 (2.7%)
Device explantation	0	0 (0%)
Device embolization	0	0 (0%)
Incomplete device closure at 6-Months [2]	40	40/522 (7.7%)
Major bleeding	11	9 (1.5%)
Major vascular complications	0	0 (0%)
Surgical intervention possibly related to device	0	0 (0%)
Thrombus on device	0	0 (0%)
Ischemic stroke	23	21 (3.6%)
Transient ischemic attack	23	18 (3.1%)

[1] Defined as procedure or device related stroke resulting from air emboli or thromboemboli on the device. Events were identified by manual review of subject CRFs and source documentation
[2] Denominator is only implanted subjects with a TEE assessment at 6 months (site reported)

10 REFERENCES

Albers GW, A. P. (2004). Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *CHEST*, 126:483S-512S.

Di Tullio MR, S. R. (2007). Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardio*, 49: 797– 802.

Hagen PT, S. D. (1984). Incidence and size of patent foramen during the first 10 decades of life: an autopsy study of 965 normmal hearts. *Mayo Clinic Proc*, 59: 17–20.

Handke M, H. A. (2007). Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med*, 357:2262– 8.

Homma S, S. R. (2002). Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale In Cryptogenic Stroke Study. *Circulation*, 105:2625–31.

Homma S, S. R. (2005). Contemporary reviews in cardiovascular medicine: Patent foramen ovale and stroke. *Circulation*, 112:1063–72.

Kent DM, D. I. (2016). Device closure of patent foramen ovale: Pooled analysis of completed randomized trials. *J Am Coll Cardiol* , 67: 907-17.

Kernan WN, e. a. (2014). Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. . *Stroke* , 45: 2160–2236.

Lamy C, G. C. (2002). Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. *Stroke* , 33:706–11.

Mas JL, A. C. (2001). Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. . *N Engl J Med*, 345:1740–6.

Meier, B. K. (2013). Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Eng J Med*, 368: 1083-91.

Meissner I, K. B. (2006). Patent foramen ovale: Innocent or guilty? Evidence from a prospective population-based study. . *J Am Coll Cardiol*, 47:440 –5.

O'Gara PT, M. S. (2009). Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention: A Call for Completion of Randomized Clinical Trials. *Circulation*, 119: 2743-7.

Roger VL, G. A.-J. (2012). Americal Heart Association Statistics Committee and Stroke Statistics Subcommittee . Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*, 125:e2-e220.

Sacco RL, A. R. (2006). *Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke.* 113:e409-e449: Circulation.

Sacco RL, E. J. (1989). Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol.* , 25:382-390.

Salem DN, O. P. (2008). Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* , 133(suppl): 593S– 629S.

Srivastava TN, P. M. (1997). Images in clinical medicine: paradoxical embolism–thrombus in transit through a patent foramen ovale. *N Engl J Med* , 337: 681.
Wöhrle, J. (2006). Closure of patent foramen ovale after cryptogenic stroke. *Lancet*, 368:350 –2.