

# **SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

## **I. GENERAL INFORMATION**

Device Generic Name: Patent Foramen Ovale (PFO) Occluder

Device Trade Name: AMPLATZER™ PFO Occluder

Device Procode: MLV

Applicant's Name and Address: St. Jude Medical  
5050 Nathan Lane North  
Plymouth, MN 55442

Date of Panel Recommendation: May 24, 2016

Premarket Approval Application (PMA) Number: P120021

Date of FDA Notice of Approval: October 28, 2016

## **II. INDICATIONS FOR USE**

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

## **III. CONTRAINDICATIONS**

The AMPLATZER PFO Occluder is contraindicated for use in:

- Patients with intra-cardiac mass, vegetation, tumor or thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the PFO is gained;
- Patients whose vasculature, through which access to the PFO is gained, is inadequate to accommodate the appropriate sheath size;
- Patients with anatomy in which the AMPLATZER PFO device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins;
- Patients with other source of right-to-left shunts, including an atrial septal defect and/or a fenestrated atrial septum; and/or
- Patients with active endocarditis or other untreated infections.

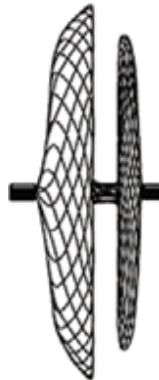
#### IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the AMPLATZER PFO Occluder labeling (Instructions for Use).

#### V. **DEVICE DESCRIPTION**

The AMPLATZER PFO Occluder (Figure 1) is a self-expanding, double disc device made from a Nitinol wire mesh. The wire mesh is formed into a device containing two discs linked together by a short connecting waist. The waist allows each disc to articulate in relationship to the defect and conform to the septal wall. In order to increase its closing ability, the discs contain thin polyester fabric. The polyester fabric is securely sewn to each disc by a polyester thread. The device is delivered percutaneously via a delivery cable attached to the end screw at the proximal disc of the device. This end screw allows the device to be attached to a delivery cable and loaded into a transcatheter delivery system for percutaneous implantation as well as for recapture if required.

**Figure 1: AMPLATZER PFO Occluder**



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.

The PFO occluder is available in sizes 18mm, 25mm and 35mm. The device size is determined by the right atrial disc diameter.

#### VI. **ALTERNATIVE PRACTICES AND PROCEDURES**

There are several other alternatives for reducing the risk of recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

The 2014 American Heart Association and American Stroke Association stroke guidelines<sup>1</sup> (affirmed by the American Academy of Neurology<sup>2</sup>) 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). 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). Open surgery to close a PFO is another treatment option but is rarely performed.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## **VII. MARKETING HISTORY**

The AMPLATZER PFO Occluder is commercially available in the following countries:

- Algeria
- Argentina
- Armenia
- Australia
- Austria
- Azerbaijan
- Bahrain
- Bangladesh
- Belarus
- Belgium
- Brazil
- Bulgaria
- Canada
- Chile
- China
- Colombia
- Costa Rica
- Croatia
- Cuba
- Republic of Cyprus
- Czech Republic
- Denmark
- Egypt
- El Salvador
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- India
- Indonesia
- Iraq
- Ireland
- Israel
- Italy
- Jordan
- Kazakhstan
- Kenya
- Korea
- Kuwait
- Kyrgyzstan
- Latvia
- Lebanon
- Liechtenstein
- Lithuania
- Luxembourg
- Malaysia
- Malta
- Mexico
- Moldova
- Monaco
- Mongolia
- Morocco
- Nepal
- Netherlands
- New Zealand
- Oman
- Pakistan
- Panama
- Paraguay
- Peru
- Philippines
- Poland
- Portugal
- Qatar
- Romania
- Russia
- Saudi Arabia
- Singapore
- Slovakia
- Slovenia
- South Africa
- Spain
- Sri Lanka
- Sweden
- Syria
- Tunisia
- Turkey
- Ukraine
- United Arab Emirates
- United Kingdom
- Uruguay
- Uzbekistan
- Venezuela
- Yemen

The device has not been withdrawn from marketing for any reason related to its safety and effectiveness.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the AMPLATZER PFO Occluder or the device implantation procedure:

- Air embolus
- Allergic dye reaction
- Allergic drug reaction
- Allergic metal reaction: Nitinol (nickel, titanium), platinum/iridium, stainless steel (chromium, iron, manganese, molybdenum, nickel)
- Anesthesia reactions
- Apnea
- Arrhythmia
- Bacterial endocarditis
- Bleeding
- Brachial plexus injury
- Cardiac perforation
- Cardiac tamponade
- Cardiac thrombus
- Chest pain
- Device embolization
- Device erosion
- Deep vein thrombosis
- Death
- Endocarditis
- Esophagus injury
- Fever
- Headache/migraine
- Hypertension/hypotension
- Myocardial infarction
- Pacemaker placement secondary to device placement
- Palpitations
- Pericardial effusion
- Pericardial tamponade
- Pericarditis
- Peripheral embolism
- Pleural effusion
- Pulmonary embolism
- Reintervention for residual shunt/device removal
- Sepsis
- Stroke
- Transient ischemic attack
- Thrombus
- Valvular regurgitation
- Vascular access site injury
- Vessel perforation

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

## **IX. SUMMARY OF NONCLINICAL STUDIES**

### **A. Laboratory Studies**

A series of non-clinical studies were performed to evaluate the AMPLATZER PFO Occluder.

#### **1. Biocompatibility Studies on the Implant**

Biocompatibility testing for the AMPLATZER PFO Occluder was conducted. In addition, chemical characterization and nickel leach studies were conducted to support the overall biocompatibility of the device.

All biocompatibility testing was conducted in accordance with:

- ISO 10993-1: 2002, “Biological evaluation of medical devices – Part 1: Evaluation and testing” (2002); and
- Good Laboratory Practices Regulations (21 CFR § 58).

A summary of the biocompatibility data provided to support this PMA can be found in Table 1. “Pass” denotes that the test results met the product specifications or acceptance criteria.

**Table 1: Biocompatibility Test Summary**

<b>Biological Study</b>	<b>Test Description</b>	<b>Results</b>
<b>Cytotoxicity</b>	ISO Minimum Essential Medium Elution (1X MEM) Assay with Mouse fibroblast cells L929	<b>Pass</b> Non-cytotoxic
<b>Sensitization</b>	ISO Guinea Pig Maximization	<b>Pass</b> Non-sensitizer
<b>Irritation</b>	ISO Intracutaneous Reactivity	<b>Pass</b> Non-irritant
<b>Acute Systemic Toxicity</b>	ISO Systemic Toxicity	<b>Pass</b> Non-toxic
<b>Pyrogenicity</b>	USP Material-mediated pyrogenicity	<b>Pass</b> Non-pyrogenic
<b>Hemocompatibility</b>	Hemolysis - direct and indirect contact	<b>Pass</b> Non-hemolytic
	Complement Activation - C3a and SC5b-9	<b>Pass</b> Not a complement activator
<b>Genotoxicity</b>	ISO Bacterial reverse mutation assay	<b>Pass</b> Non-mutagenic
	ISO Mouse Lymphoma Assay (4 and 24 hour)	<b>Pass</b> Non-mutagenic
	Mouse Micronucleus Assay	<b>Pass</b> Non-genotoxic
<b>Implantation</b>	1 and 4 week implant Rabbit (New Zealand White)	<b>Pass</b> Non-irritant at 1 week Slight irritant at 4 weeks <sup>1</sup>
<b>Sub chronic toxicity</b>	13 Week Implant Rat	<b>Pass</b> Slight irritant <sup>1</sup>
<b>Chemical Characterization</b>	Gas Chromatography - Mass Spectroscopy (GC/MS) for volatile and semi-volatile, organic compounds	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns

<b>Chemical Characterization</b>	Inductively Coupled Plasma (ICP) Spectroscopy for metallic compounds	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
<b>Chemical Characterization</b>	Liquid Chromatography - Mass Spectroscopy (LC/MS) for semi-volatile and non-volatile organic compounds	Compounds consistent with manufacturing materials, and amounts do not raise toxicity concerns
<b>Nickel Leaching</b>	60 day immersion study	Peak release on day 1 with very low release for remainder of study (levels relevant for sensitization, but no concerns for cancer or other non-cancer toxicity endpoints)

Also evaluated as part of the animal studies outlined in Section B below.

Irritation, sub-chronic and chronic toxicity, and thrombogenicity studies were performed as part of the *in vivo* studies conducted to evaluate the safety and effectiveness of the device in a vascular implant location, as described in Section B, below. These additional animal studies demonstrated a lack of tissue irritation or chronic toxicity, with acceptable thrombus formation when the occluder was implanted in a clinically-relevant vascular location.

The omission of carcinogenicity testing was supported by information regarding the starting materials and processing of the finished device, in conjunction with chemical characterization data, nickel leaching studies, and toxicity information from the literature.

The information provided demonstrated that the AMPLATZER PFO Occluder is biocompatible.

## **2. In Vitro Engineering Testing**

The *in vitro* engineering studies performed are summarized in Table 2. “Pass” denotes that the test results met the product specifications or acceptance criteria.

**Table 2: Engineering Testing**

<b>Test</b>	<b>Purpose</b>	<b>Acceptance Criteria</b>	<b>Results</b>
<b>Visual Inspection</b>	To visually assess the device is free from damage and defects.	Meet design requirements	Pass
<b>Proximal and Distal Disc Diameter, Waist Length (Pre Deployment)</b>	To quantitatively assess that the device meets all dimensional requirements.	Waist length 3±0.5 mm Proximal and distal disc 18 +0.5/-1.5	Pass

		25 +0.5/-1.5 35 +0.5/-1.5	
<b>End Screw Attachment</b>	To verify that the TorqVue Delivery Systems' delivery cable correctly connects to the end screw on the PFO device.	Minimum 4 Full Turns of Thread	Pass
<b>Load Force</b>	To determine that the force required to pull the device into the Loader meets the requirement in the product specification matrix.	Less than 8.0 Lbs.	Pass
<b>Handoff Force</b>	To determine the maximum force needed to handoff the device from the loader into the delivery sheath.	Less than 5.0 Lbs.	Pass
<b>Advancement Force</b>	To determine the force needed to advance the device through the correct sized sheath.	Less than 5.0 Lbs.	Pass
<b>Recapture Force</b>	To determine the force needed to recapture the device once it has been deployed from the sheath.	Less than 8.0 lbs.	Pass
<b>Deployment and Retrieval</b>	To ensure that the device can be recaptured into the sheath and redelivered without damage or deformities to the device.	Minimum 3 times	Pass
<b>Device release</b>	To verify that the device can be successfully detached from the delivery cable while in a simulated use model.	Minimum four turns of thread and no rotation while in the simulated model	Pass
<b>Visual Inspection of Device while in Simulated PFO Model</b>	To visually assess that the device maintains its intended shape and form while deployed in a simulated model.	Device apposes model septal wall, device maintains intended shape, device fits in simulated model with no sharp edges	Pass
<b>Pull Through</b>	To determine the force required to pull the device through the PFO defect once it has been deployed.	Greater than 1.0 lbs.	Pass
<b>Proximal and Distal Disc Diameter, Waist Length (Post Deployment)</b>	To ensure that the device meets all dimensional requirements set forth in the Product Specification Matrix after interaction testing.	Waist length 3±0.5 mm Proximal and distal disc 18 +0.5/-1.5	Pass

		25 +0.5/-1.5 35 +0.5/-1.5	
<b>Tensile Strength</b>	To determine the minimum force that is required to cause a failure of the marker bands that are attached to the device body and the end screw that is attached to the marker band.	Greater than 12 lbs.	Pass
<b>Particulate Testing</b>	To quantify and characterize particulate matter introduced to the body when implanting the Amplatzer® Patent Foramen Ovale Occluder with the TorqVue Delivery System	USP<788>	Pass
<b>Galvanic Corrosion</b>	To assess the susceptibility to galvanic corrosion due to galvanic coupling of dissimilar metals in the device	ASTM G71	Pass Time to corrode: Nitinol: 7532 years 316LSS: 110 years
<b>Potentiodynamic Corrosion</b>	To assess the corrosion susceptibility of the device	ASTM F2129	Minimal localized pitting observed through SEM analysis

Magnetic Resonance Imaging (MRI) Compatibility

Non-clinical testing has demonstrated the AMPLATZER PFO Occluder is MR Conditional. It 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 of scanning.

In non-clinical testing, the AMPLATZER PFO Occluder device produced a temperature rise of less than or equal to 1.79°C at a maximum whole-body averaged specific absorption rate (SAR) of 3.4 W/kg for 15 minutes of MR scanning in a 3.0 Tesla MR system (Siemens Trio, SYNGO MR A35 4VA35A software, Erlangen, Germany).

In non-clinical testing the AMPLATZER PFO Occluder device produced a temperature rise of less than or equal to 1.61°C at a maximum whole-body averaged specific absorption rate (SAR) of 2.9 W/kg for 15 minutes of MR scanning in a 1.5

Tesla MR system (Siemens Espree, SYNGO MR B17 software, Erlangen, Germany).

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the device. Therefore, it may be necessary to optimize MR imaging parameters for the presence of this implant.

### **3. Sterilization**

The AMPLATZER PFO Occluder is sterilized via ethylene oxide. The sterilization cycle was validated to meet a minimum Sterility Assurance Level (SAL) of  $10^{-6}$ .

### **4. Shelf Life/ Packaging**

The shelf life and packaging for the AMPLATZER PFO Occluder was validated to ensure that both device performance and package integrity were maintained for 5 years. The testing to support the product shelf life included functional performance testing and packaging integrity of test samples accelerated aged to an equivalent of 5 years. A summary of the functional testing was presented above in Table 2 and a summary of packaging integrity testing can be found below in Table 3.

**Table 3: Packaging Integrity Testing Summary**

<b>Test</b>	<b>Samples</b>	<b>Specification</b>	<b>Results</b>
<b>Bubble Leak</b>	Inner and outer pouch	No leaks	Pass
<b>Seal Strength</b>	Inner and outer pouch	Equal to or greater than 0.5 lbs	Pass

### **B. Animal Studies**

Three chronic GLP studies were performed to evaluate the AMPLATZER PFO Occluder for delivery, handling, and device implant safety and performance. The studies are summarized in Table 4.

**Table 4: Summary of Animal Studies**

<b>Study</b>	<b>No. of Animals and Study Duration; Species</b>	<b>Objective</b>	<b>Results</b>
Chronic GLP study of the AMPLATZER PFO device	6 animals 180 days; Porcine	To evaluate the AMPLATZER PFO Occluder for delivery, handling and device implant safety and performance.	The AMPLATZER PFO Occluder met the requirements for establishing pre-clinical safety and performance. Complete PFO closure and device stability were demonstrated in all cases as confirmed by follow-up echocardiography and fluoroscopy at designated time points.
GLP Study to evaluate Nitinol surface change	2 animals, 30 days; Canine	To evaluate and compare devices built with different surface finishes.	The occlusion times were similar for the devices built with 2 different surface finishes.
GLP study to evaluate systemic Nickel content	8 animals, 60 days; Porcine	To evaluate systemic (serum) nickel content from test animals as compared to sham animals.	There was no difference in nickel levels between the test animals and sham animals.

**X. SUMMARY OF PRIMARY CLINICAL STUDY**

The applicant performed a clinical study in the US under IDE G990318 (the RESPECT trial) to establish a reasonable assurance of safety and effectiveness of transcatheter PFO closure with the AMPLATZER PFO Occluder to reduce the risk of recurrent ischemic stroke in subjects who have had a cryptogenic stroke due to presumed paradoxical embolism. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

**A. Study Design**

The RESPECT trial was a prospective, multi-center, randomized (1:1), event driven, unblinded clinical study designed to evaluate whether PFO closure with the AMPLATZER PFO Occluder (the Device) is superior to standard of care medical management (MM) in reducing the risk of recurrent embolic stroke.

Patients were enrolled at 69 investigational sites between August 23, 2003 and December 28, 2011. The database for this PMA reflected data collected through August 14, 2015 and included 980 randomized patients.

There was an independent Data Safety Monitoring Board (DSMB) to oversee study progress and review clinical data and safety, an independent Clinical Events Committee (CEC) to adjudicate neurologic events to determine if the event met primary or secondary neurologic endpoint definitions, and an independent Echocardiography Core Lab that reviewed 6-month echocardiograms to assess PFO closure status (in subjects implanted with the Device).

#### 1. Clinical Inclusion and Exclusion Criteria

Enrollment in the RESPECT trial was limited to patients who met the following inclusion criteria:

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  $\geq 24$  hours, or
  - 2) symptoms persisting  $\leq 24$  hours with 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.

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

- Age  $< 18$  years and age  $> 60$  years
- Atherosclerosis or other arteriopathy of the intracranial or extracranial vessels with  $> 50\%$  lumen diameter stenosis supplying the involved lesion
- Intracardiac thrombus or tumor
- Acute or recent (within 6 months) MI or unstable angina
- Left ventricular aneurysm or akinesis
- Mitral valve stenosis or severe mitral regurgitation
- Aortic valve stenosis (gradient  $> 40$  mmHg) or severe regurgitation
- Mitral or aortic valve vegetation or prosthesis
- Aortic arch plaques protruding  $> 4$  mm into the lumen
- Left ventricular dilated cardiomyopathy with LVEF  $< 35\%$
- Another source of right to left shunts identified at baseline, including an atrial septal defect and/or fenestrated septum
- Atrial fibrillation/atrial flutter (chronic or intermittent)
- Active endocarditis, or other untreated infections
- Kidney, liver or lung failure
- Uncontrolled hypertension, defined as sustained elevated blood pressure  $> 160/90$  mm Hg on medication
- Uncontrolled diabetes mellitus, defined as elevated glucose levels despite administration of insulin or levels  $> 200$ /dl mg with glucosuria

- 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  $\geq$ 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  $>0$ )
- Arterial dissection as the qualifying event
- Progressive neurological dysfunction or life expectancy is  $<2$  years
- 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
- Subjects contraindicated for aspirin or clopidogrel
- Anatomy in which the Device would interfere with intracardiac or intravascular structures such as valves or pulmonary veins
- Stroke with poor outcome at time of enrollment (modified Rankin Scale score  $>3$ )
- Subjects not able to discontinue anticoagulation if randomized to the Device

Screening to establish the diagnosis of cryptogenic stroke included:

- Work-up of qualifying stroke evaluated by a neurologist
- TEE
- ECG or Holter monitor. [Both ECG and Holter monitor testing was performed in 55/499 (11.0%) device subjects and in 61/481 (12.7%) MM subjects.]
- Brain MRI or CT scan
- Imaging of intracranial arteries with MR angiography, CT angiography, contrast arterial angiography, or transcranial Doppler
- Imaging of extracranial arteries with MRA, CTA, contrast arterial angiography, or duplex ultrasound
- Hypercoagulable state screening

## 2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 1 month, 6 months, 12 months, 18 months, 2 years, and annually until study termination. The key time points and evaluations conducted in the study are shown in Table 5.

**Table 5: Follow-up Schedule**

♥ = Required testing	Baseline	Procedure	Discharge <sup>4</sup>	1 month (± 1 week) (day 23 – day 37) <sup>6</sup>	6 months (± 1 month) (day 150 – day 210) <sup>6</sup>	12 months (± 2 months) (day 305 – day 425) <sup>6</sup>	18 Months (± 2 months) (day 485 – day 605) <sup>6</sup>	2 years (± 2 months) (day 670 – day 790) <sup>6</sup>	3 years (± 2 months) (day 1035 – day 1155) <sup>6</sup>	4 years (± 2 months) (day 1400 – day 1520) <sup>6</sup>	Annual Visit until Study Closure (± 2 months)
Office Follow-up: (if required)											
History and Physical Exam	♥		♥	♥	♥	♥	♥	♥	♥	♥	♥
Neurologic examination											
• NIH Stroke Scale <sup>5</sup>	♥					♥		♥	♥	♥	♥
• Barthel Index	♥							♥	♥	♥	♥ <sup>7</sup>
• Modified Rankin	♥							♥	♥	♥	♥ <sup>7</sup>
• Stroke Questionnaire + additional assessments, as necessary	♥			♥	♥	♥	♥	♥	♥	♥	♥
Telephone Follow-up:									♥	♥	♥
History									♥	♥	♥
• Barthel Index										♥	♥ <sup>7</sup>
• Modified Rankin										♥	♥ <sup>7</sup>
• Stroke Questionnaire									♥	♥	♥
Pregnancy test <sup>1</sup>	♥										
ECG or Holter monitor	♥ <sup>2</sup>		♥	♥ <sup>2</sup>							
Coagulation test	♥										
MRI or CT											
• Submit report(s) and film(s) to AGA	♥										
Imaging of Intracranial Arteries via MRA, CT angiography, Contrast Angiography or TCD	♥										
Imaging of Extracranial Arteries via MRA, CT angiography, Contrast Angiography or Duplex sonography	♥										
Transesophageal Echo with bubble study <sup>3</sup>											
• Submit Report and Videotape or DICOM CD to AGA Medical Corporation	♥	♥			♥						

<sup>1</sup> Required for pre-menopausal women and women of child bearing potential.

<sup>2</sup> An ECG or a Holter monitor required for all study subjects

<sup>3</sup> 6 month TEE required only for subjects who receive a device. ICE may be used at procedure in place of TEE.

<sup>4</sup> Discharge follow-up only required for subjects who receive a device.

<sup>5</sup> Personnel conducting any study-required NIHSS evaluations required to have received training and certification per national guidelines including but not limited to American Stroke Association, American Academy of Neurology, National Institute of Neurological Disorders and Stroke

<sup>6</sup> For device subjects, the day of procedure is day 1. For medical management subjects, the day of randomization is day 1

<sup>7</sup> These tests are conducted at every other year (even year) visits.

### 3. Clinical Endpoints

The primary effectiveness endpoint was the composite of the following:

- Recurrent nonfatal stroke, defined as:
  - An acute focal neurological deficit presumed to be due to focal ischemia and either:
    - Symptoms persisting  $\geq 24$  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

The secondary effectiveness endpoints included the absence of transient ischemic attack (TIA) and the rate of complete PFO closure (assessed by TEE bubble study) at 6 months follow-up (in the Device group only).

Statistical analysis plan: The primary analysis population was the intent-to-treat (ITT) population. Although a raw event count analysis was pre-specified as the primary analysis, a Kaplan-Meier analysis was deemed more informative than the raw count analysis because of an unbalanced rate of subject withdrawals between treatment groups. 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. A decision rule was established that 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.

Analyses were also performed on the Per Protocol population, which consisted of subjects who received their randomly assigned treatment and complied with protocol-mandated medical treatment and excluded subjects who did not receive their randomized therapy, did not comply with the protocol-mandated medical treatment, or had a major inclusion/exclusion criteria violation.

There was no pre-specified safety endpoint or a statistical hypothesis for safety. The following events were considered serious adverse events as determined by the DSMB and were adjudicated for severity and relatedness to the device, procedure, delivery system, or clinical protocol: 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.

Number of subjects randomized and investigational sites:

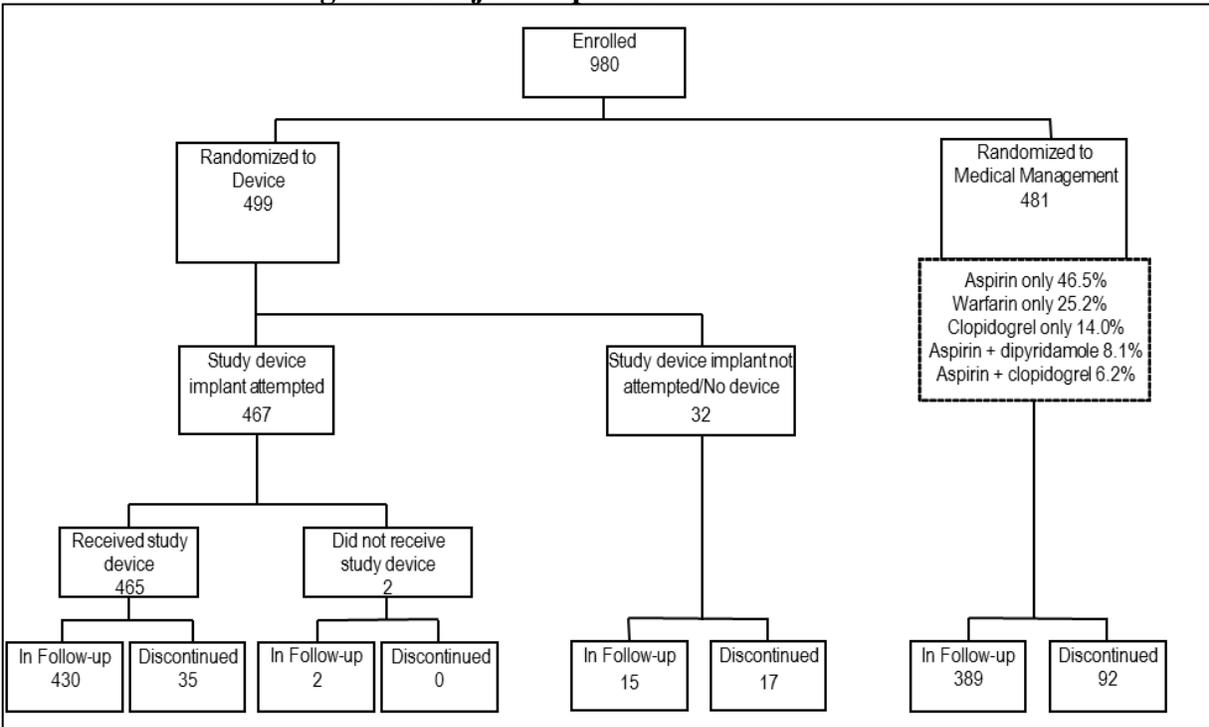
- 980 subjects enrolled
  - 499 randomized to the Device group
  - 481 randomized to the MM group.
- 69 investigational sites
  - 925 subjects enrolled at 62 US sites
  - 55 subjects enrolled at 7 Canadian sites
- Randomization was stratified by:
  - Investigational site
  - Presence of an atrial septal aneurysm (ASA), defined as septum primum movement  $\geq 10$  mm relative to the plane of the inter-atrial septal plane, as determined by the investigator
  - Recommended medical therapy

The four medical therapy regimens allowed per protocol in the MM group were: (a) aspirin alone, (b) warfarin alone, (c) clopidogrel alone or (d) aspirin combined with dipyridamole. Patients implanted with the Device were to take clopidogrel for 30 days and aspirin for 6 months. Additional medical therapy beyond six months was at the discretion of the treating physician. Device group subjects were evaluated by transesophageal echocardiogram (TEE) at approximately 6 months post implant to assess PFO closure. Approximately 90% of Device group subjects were taking anti-platelet medications throughout the study (predominately aspirin alone beginning 6-months post-Device implantation).

#### **B. Accountability of PMA Cohort**

There were two data locks for the analyses of the RESPECT trial: a May 20, 2012 initial data lock and an August 14, 2015 extended follow-up data lock. Subject accountability as of the initial data lock (20 May 2012) is shown in Figure 2, which includes the distribution of the subject follow-up and discontinuation.

**Figure 2: Subject Disposition in RESPECT trial**



In the initial data lock analysis, the average duration of subject follow-up was 3.0 years in the Device group and 2.7 years in the MM group; total accumulated follow-up was 1476 patient-years and 1284 patient-years in the Device and MM groups, respectively.

In the extended follow-up data lock analysis, the average duration of subject follow-up was 5.5 years and 4.9 years in the Device and MM groups, respectively; total accumulated follow-up was 2769 patient-years and 2376 patient-years in the Device and MM groups, respectively.

There was a higher rate of subject discontinuation in the MM group vs. the Device group for both the initial data lock (19.1% vs 10.4%, respectively) and for the extended follow-up data lock (30.1% vs 18.2%, respectively). The difference in the overall subject discontinuation rate between treatment groups was driven by subjects deciding to withdraw from study participation.

**C. Study Population Demographics and Baseline Parameters**

The demographics of the study population are typical for a recurrent stroke study performed in the US. Patient demographics and risk factors are summarized in Table 6 and 7.

**Table 6: Study Population Demographics and Baseline Characteristics – ITT Population**

Variable	Device Group	MM Group	p-value <sup>a</sup>
Age, years <sup>b</sup>	N=492 45.7 (9.7) 46.7 [18.1, 61.0]	N=476 46.2 (10.0) 47.6 [18.4, 60.9]	0.491
Time from stroke to randomization, days	N=499 130 (70) 117 [10, 277]	N=481 130 (69) 121 [10, 286]	0.891
Sex, male	268/499 (53.7%)	268/481 (55.7%)	0.564
Previous myocardial infarction	5/499 (1.0%)	2/481 (0.4%)	0.452
Previous transient ischemic attack	58/499 (11.6%)	61/481 (12.7%)	0.626
Stroke prior to qualifying cryptogenic stroke	53/499 (10.6%)	51/481 (10.6%)	1.000
Substantial Shunt at Rest or Valsalva <sup>c</sup>	247/499 (49.5%)	231/481 (48.0%)	0.655
Atrial septal aneurysm <sup>d</sup>	180/499 (36.1%)	170/481 (35.3%)	0.842

Continuous variables are reported as n, mean (SD), median [min, max] and categorical variables as n (%).

MM = Medical Management

a. 2-sample t-test (age), Wilcoxon-Mann-Whitney test (days from stroke to date randomized) or Fisher's Exact test.

b. The IRB at one site did not allow recording of subject birthdates on the case report forms (12 subjects).

c. Substantial shunt defined as Grade III at rest or Valsalva by TEE.

d. Defined as total excursion of the septum primum relative to the plane of the interatrial septum  $\geq$  10 mm.

**Table 7: Baseline Stroke Risk Factors - ITT Population**

Variable	Device Group	MM Group	p-value <sup>a</sup>
Current Smoker	75/499 (15.0%)	55/481 (11.4%)	0.109
Former smoker	134/499 (26.9%)	143/481 (29.7%)	0.322
Diabetes mellitus	33/499 (6.6%)	41/481 (8.5%)	0.278
Hypercholesterolemia	196/499 (39.3%)	195/481 (40.5%)	0.696
Hypertension	160/499 (32.1%)	153/481 (31.8%)	0.945
Atrial fibrillation	0/453 (0.0%)	1/442 (0.2%)	0.494
Birth control/HRT	41/499 (8.2%)	51/481 (10.6%)	0.228
Migraine	195/499 (39.1%)	186/481 (38.7%)	0.948
Other risk factor	37/456 (8.1%)	40/443 (9.0%)	0.636

MM = Medical Management

<sup>a</sup> Fisher's Exact test.**D. Safety and Effectiveness Results****1. Safety Results**

There were 16 deaths: 6 in the Device group (6/499, 1.2%) and 10 in the MM group (10/481, 2.1%, Table 8) 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.

**Table 8: Deaths (extended follow-up)**

Cause of Death	Subjects
<b>Device Subjects (n=6)<sup>1</sup></b>	
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
<b>MM Subjects (N=10)</b>	

Cause of Death	Subjects
Cancer <sup>2</sup>	3
Trauma	2
Intracerebral hemorrhage <sup>2</sup>	1
Cardiac arrest/dysrhythmia	3
Sepsis	1

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

There were 386 serious adverse events (SAEs) in 189 patients in the Device group and 298 SAEs in 168 patients in the MM group. The proportions of patients experiencing an SAE in the two groups were similar (37.9% in the Device group and 34.9% in the MM group; Table 9).

In the Device group, there were 25 SAEs related to the Device or implantation procedure in 21 subjects. The proportion of patients experiencing an SAE related to the procedure was 2.4% and the proportion of patients experiencing an SAE related to the device was 2.0%. No unanticipated adverse device effects were reported in the trial.

**Table 9: Overall rate of SAEs through the extended follow-up data lock**

	Device Group (N=499, 2769 patient-years)		MM Group (N=481, 2376 patient-years)	
	n <sup>a</sup> (%)	Events (Rate per 100 Pt-Yrs)	n (%)	Events (Rate per 100 Pt-Yrs)
Any SAE	189 (37.9%)	386 (13.9)	168 (34.9%)	298 (12.5)
Deaths related to procedure or device	0 (0.0%)	0 (0.0%)	N/A	N/A
Related to procedure	12 (2.4%)	12 (0.4)	N/A	N/A
Related to device	10 (2.0%)	13 (0.5)	N/A	N/A

MM = Medical Management; Pt-Yrs = Patient-years

<sup>a</sup> Subjects could have more than one event

Twelve (12) procedure-related SAEs occurred in 12 patients (2.4%), and are summarized in Table 10.

**Table 10: Procedure-related SAEs in the Device group through the extended follow-up data lock (N = 467)**

Event	n (%)
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Cardiac perforation ( <i>required pericardiocentesis</i> )	2 (0.4%)
Cardiac perforation ( <i>no treatment required</i> )	2 (0.4%)
Access site bleeding ( <i>1 required sutures, 1 required transfusion, 1 required no treatment</i> )	3 (0.6%)
Right atrial thrombus ( <i>detected during procedure - procedure abandoned</i> )	1 (0.2%)
Deep vein thrombus	1 (0.2%)
Atrial fibrillation	1 (0.2%)
Other ( <i>allergic drug reaction - vasovagal response</i> )	2 (0.4%)

Thirteen (13) device-related SAEs occurred in 10 patients (2.0%) and are summarized in Table 11.

**Table 11: Device-related SAEs in the Device group through the extended follow-up data lock (N = 467)**

<b>Event</b>	<b>n (%)</b>
Ischemic stroke ( <i>included in the primary endpoint</i> )	2 (0.4%)
Pulmonary embolism	2 (0.4%)
Thrombus in right atrium ( <i>not attached to device</i> )	1 (0.2%)
Explant/surgical intervention	2 (0.4%)
Atrial fibrillation	1 (0.2%)
Residual shunt ( <i>requiring closure with septal occluder device</i> )	1 (0.2%)
Other ( <i>chest tightness, atrial flutter, non-sustained ventricular tachycardia, sepsis</i> )	4 (0.8%)

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 12 shows SAEs adjudicated as protocol-related in the MM group. The overall rate for these SAEs was 1.0%, and these events were adjudicated as related to the anti-thrombotic therapy.

**Table 12: SAEs related to the protocol – MM group**

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)
<b>Total</b>	<b>1.0% (5/481)</b>

There were a total of 29 reported venous thromboembolism (VTE) events (serious or non-serious events) in 21 subjects: 18 events in 24 Device group subjects, and 5 events in 3 MM group subjects. These events are summarized in Table 13.

**Table 13: Venous thromboembolic events through the extended follow-up data lock**

	Device Group (N=499)			MM Group (N=481)		
	# Patients	# Events	Rate Per 100 Pt-Yrs	# Patients	# Events	Rate Per 100 Pt-Yrs
All VTEs	18	24	0.87	3	5	0.21
Deep Vein Thrombosis	11	11	0.40	3	3	0.13
Pulmonary Embolism	12	13	0.47	2	2	0.08

MM = Medical Management; Pt-Yrs = Patient-years

There were a total of 30 supraventricular arrhythmia events (serious or non-serious events) reported in the Device group subjects and 12 events in MM group subjects. Most events were atrial fibrillation. These events are summarized in Table 14.

**Table 14: Supraventricular arrhythmia events through the extended follow-up data lock**

	Device Group (N=499)			MM Group (N=481)		
	# Patients	# Events	Rate Per 100 Pt-Yrs	# Patients	# Events	Rate Per 100 Pt-Yrs
Atrial fibrillation	20	23	0.83	9	12	0.51
Peri-procedural	7	7	0.25	NA	NA	NA
Post-procedural	13	16	0.58	NA	NA	NA

Atrial Flutter	2	2	0.07	0	0	0
Paroxysmal Supraventricular Tachycardia	5	5	0.18	0	0	0

MM = Medical Management; Pt-Yrs = Patient-years

## 2. Effectiveness Results

ITT population. All primary endpoint events were non-fatal ischemic strokes. The primary endpoint analysis of the initial (20 May 2012) and extended follow-up (14 August 2015) data locks are shown in Table 15. In the initial data lock analysis, there were 25 total primary endpoint events: 9 in the Device group (rate of 0.61 per 100 patient-years) vs. 16 in the MM group (rate of 1.25 per 100 patient-years), corresponding to a 50% relative risk reduction in favor of the Device group which did not achieve statistical significance (p=0.089). In the extended follow-up data lock analysis, there were 42 total primary endpoint events (18 in the Device group and 24 in the MM group) and a numerically smaller relative risk reduction (35%) compared with the initial data lock analysis in favor of the Device group.

**Table 15: Summary of primary endpoint analyses results (ITT population)**

Data Lock	# Events (Rate per 100 Pt-Yrs) <sup>a</sup>		Hazard Ratio <sup>b</sup> (95% CI)	Relative Risk Reduction	p-value <sup>c</sup>
	Device group (N=499)	MM Group (N=481)			
20 May 2012	9 (0.61)	16 (1.25)	0.50 (0.22, 1.13)	50%	0.089
14 August 2015	18 (0.65)	24 (1.01)	0.65 (0.35, 1.2)	35%	–

a. 100 x (Total number of events / total patient years follow-up)

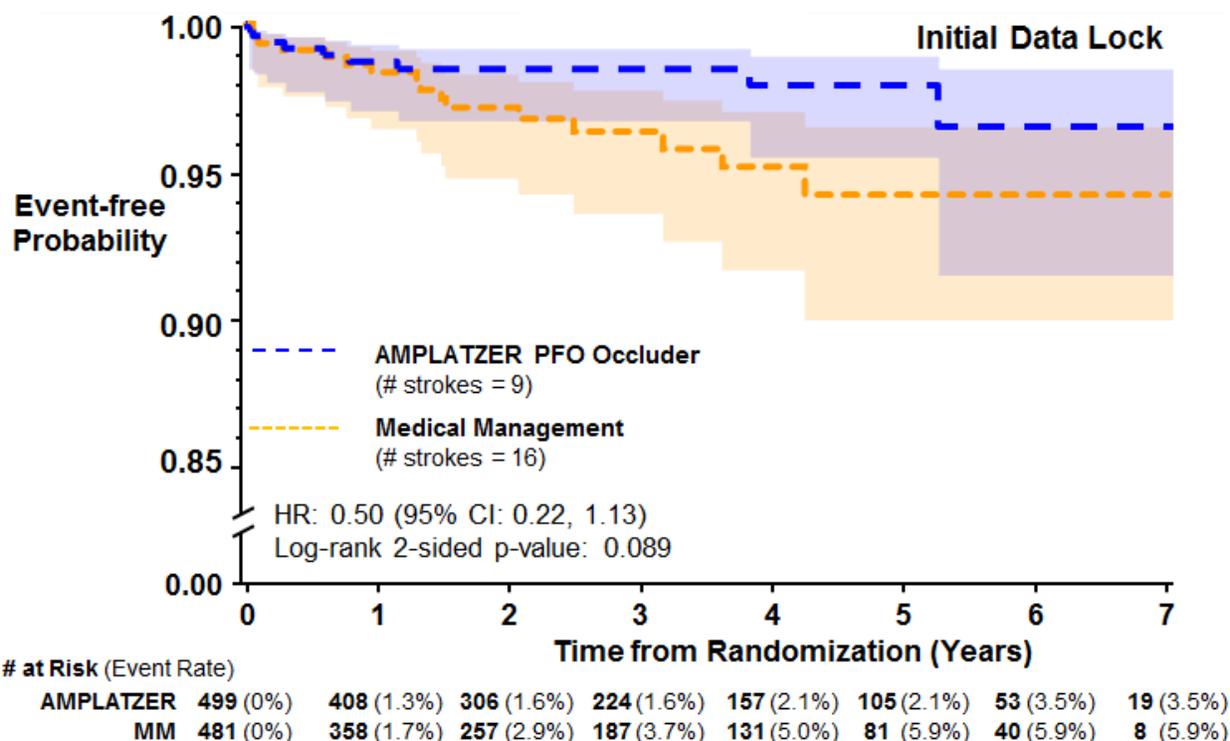
b. Based on a Cox proportional hazards model

c. Based on a log-rank test

MM = Medical Management; Pt-Yrs = Patient-years

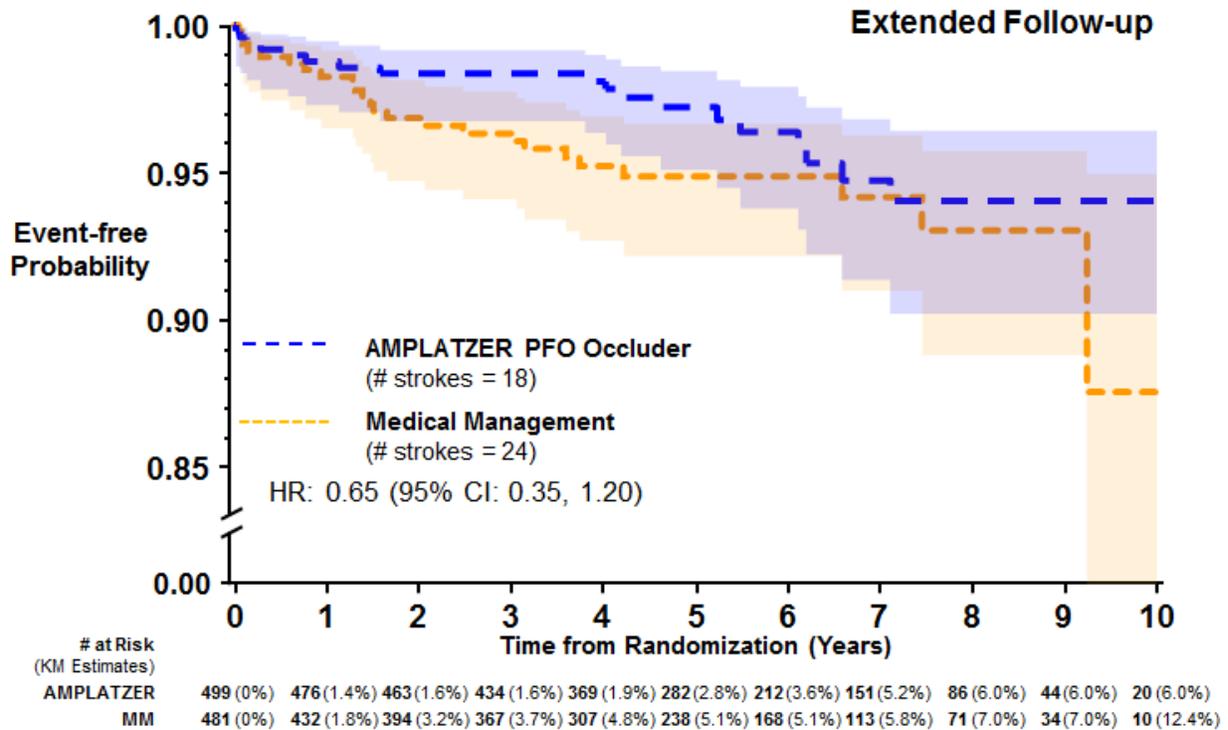
For the initial data lock, the Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 years were 0.021 in the Device group vs. 0.059 in the MM group (Figure 3). For the extended follow-up data lock, the Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 and 8 years were 0.028 in the Device group vs. 0.051 in the MM group, and 0.060 in the Device group vs. 0.070 in the MM group, respectively (Figure 4).

**Figure 3: Kaplan-Meier Freedom from Primary Endpoint Event, ITT Analysis - Initial Data Lock**



Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

**Figure 4: Kaplan-Meier Freedom from Primary Endpoint Event, ITT Analysis - Extended Follow-Up**



Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

The number needed to treat with the AMPLATZER PFO Occluder to prevent one recurrent stroke at 5 years was 27 in the initial data lock analysis and 43 in the extended follow-up data lock analysis.

Per-Protocol population. The primary endpoint results for the initial (20 May 2012) and extended follow-up (14 August 2015) data locks for the Per-Protocol population (463 Device subjects and 474 MM subjects) are shown in Table 16. In the initial data lock analysis, there were 20 total primary endpoint events: 6 in the Device group (rate of 0.42 per 100 patient-years) and 14 in the MM group (rate of 1.19 per 100 patient-years), corresponding to a 63% relative risk reduction in favor of the Device group which reached statistical significance ( $p=0.034$ , unadjusted for multiple testing). In the extended follow-up data lock analysis, there were 37 total primary endpoint events (15 in the Device group and 22 in the MM group) and a numerically smaller relative risk reduction (42%) compared with the initial data lock analysis in favor of the Device group.

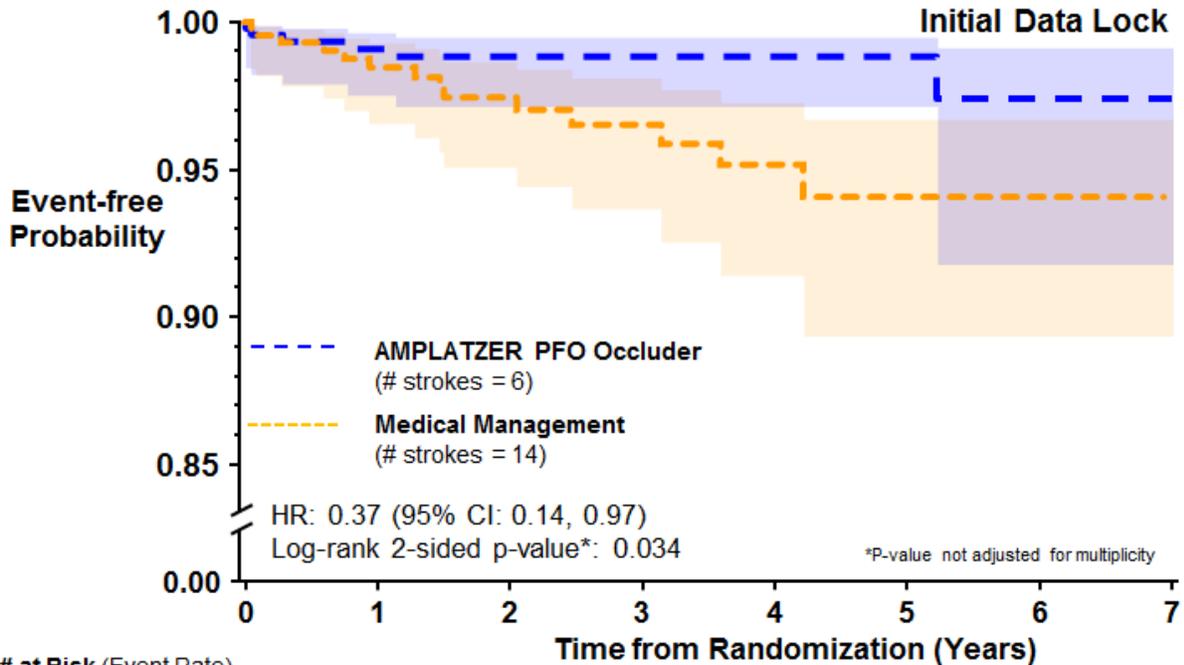
**Table 16: Summary of primary endpoint analyses results (Per-Protocol population)**

Data Lock	# Events (Rate per 100 Pt-Yrs)		Hazard Ratio <sup>a</sup> (95% CI)	Relative Risk Reduction	p-value <sup>b</sup>
	Device group (N=463)	MM Group (N=474)			
20 May 2012	6 (0.42)	14 (1.19)	0.37 (0.14, 0.97)	63%	0.034
14 August 2015	15 (0.57)	22 (0.99)	0.58 (0.30, 1.12)	42%	–

<sup>a</sup> Based on a Cox proportional hazards model  
<sup>b</sup> Based on a log-rank test, unadjusted for multiple testing  
 MM = Medical Management; Pt-Yrs = Patient-years

For the initial data lock, the Per Protocol Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 years were 0.012 in the Device group vs. 0.059 in the MM group (Figure 5). For the extended follow-up data lock, the Per Protocol Kaplan-Meier rates of recurrent non-fatal ischemic stroke at 5 and 8 years were 0.022 in the Device group vs. 0.049 in the MM group, and 0.055 in the Device group vs. 0.069 in the MM group, respectively (Figure 6).

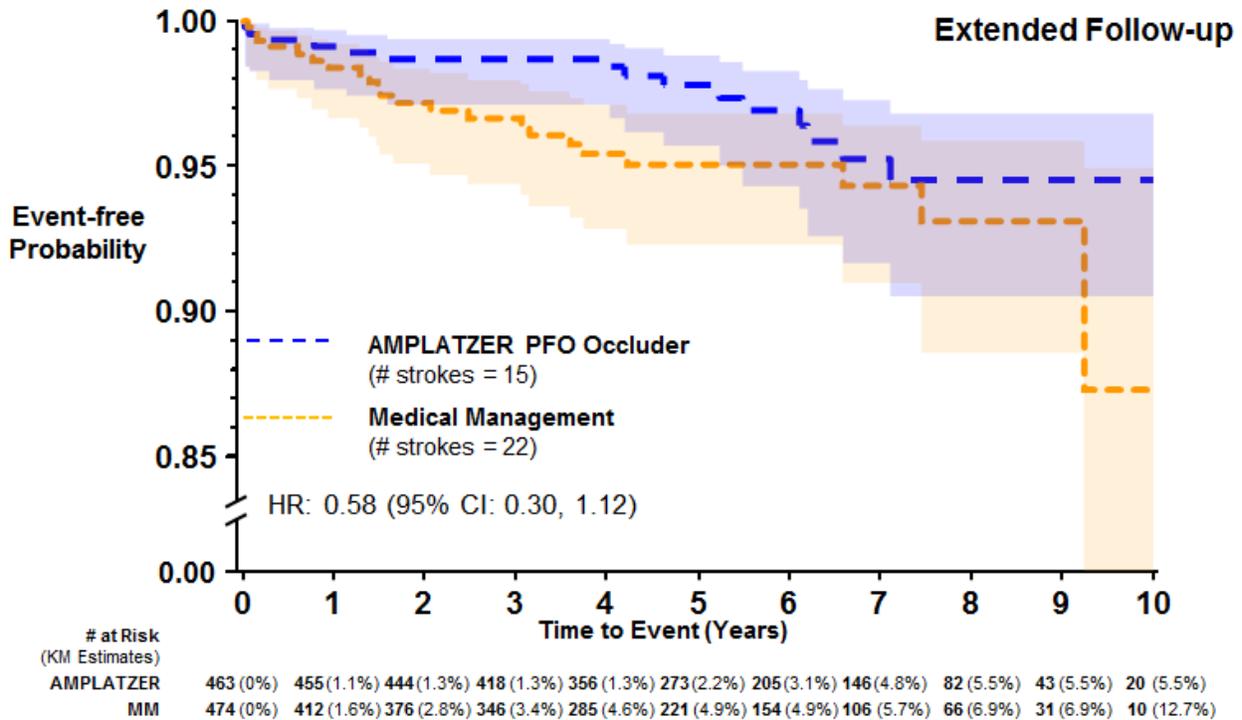
**Figure 5: Kaplan-Meier Freedom from Primary Endpoint Event, Per Protocol Analysis - Initial Data Lock**



# at Risk (Event Rate)	0	1	2	3	4	5	6	7
AMPLATZER	463 (0%)	390 (0.9%)	293 (1.2%)	215 (1.2%)	152 (1.2%)	102 (1.2%)	52 (2.6%)	19 (2.6%)
MM	474 (0%)	334 (1.5%)	238 (2.5%)	171 (3.4%)	119 (4.8%)	72 (5.9%)	36 (5.9%)	8 (5.9%)

Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

**Figure 6: Kaplan-Meier Freedom from Primary Endpoint Event, Per Protocol Analysis - Extended Follow-Up**



Confidence intervals are calculated without multiplicity adjustment. 95% confidence intervals are provided to illustrate the variability of estimates and should not be used to draw any statistical conclusions.

For the secondary endpoint of the rate of PFO closure at 6 months in subjects implanted with the Device, 249 of 349 subjects had grade 0 shunt both at rest and post-Valsalva at 6 months, corresponding to a complete closure rate of 71.3% (Table 17). The rate of effective closure (Grade 0 or I at Rest and Grade 0 or I at Valsalva) was 94.2%.

**Table 17: 6-month PFO closure data, Device group subjects who received a Device**

Closure	Shunt grade	n/N (%)
<b>Complete</b>	Grade 0 Rest AND Grade 0 Valsalva	249/349 <sup>a</sup> (71.3%)
<b>Effective</b>	Grade 0/I Rest AND Grade 0/I Valsalva	323/343 (94.2%)

<sup>a</sup>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). PFO closure data were incomplete or missing in 33.2% of subjects

For the secondary endpoint of freedom from TIA, the Kaplan-Meier rate per 100 patient years in the initial data lock analysis was 0.47 in the Device group vs. 0.55 in the MM group.

### 3. Pediatric Extrapolation

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

#### **E. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 342 investigators of which none were full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0;
- Significant payment of other sorts: 4;
- Proprietary interest in the product tested held by the investigator: 0; and
- Significant equity interest held by investigator in sponsor of covered study: 0.

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

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

#### **A. Panel Meeting Recommendation**

On May 24, 2016, the Circulatory System Devices Advisory Panel voted 15-1 that there is reasonable assurance the AMPLATZER PFO Occluder is safe, 9-7 that there is reasonable assurance that the device is effective, and 11-5 that the benefits of the device outweigh the risks in patients who meet the criteria specified in the proposed indication.

Information from this advisory meeting can be found on FDA's website at the following:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm485091.htm>

#### **B. FDA's Post-Panel Action**

The panel members recommended that the labeling include language describing the clinical evaluation of a cryptogenic stroke in patients who might be candidates for the PFO Occluder. Following the panel, the FDA worked with the applicant interactively

to revise the Instructions for Use (including expanded *Patient Selection for Treatment* and *Patient Counseling Information* sections) as well as a Patient Guide to help physicians and patients make informed treatment decisions regarding the use of the AMPLATZER PFO Occluder.

## **XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

Although the difference in the rate of recurrent ischemic stroke was lower in the Device group vs. the MM group in the ITT population (the pre-specified primary analysis cohort), the difference did not achieve statistical significance. Nonetheless, there was a clinically meaningful 50% relative risk reduction in the rate of new ischemic strokes in favor of the Device group. In the Per Protocol analysis, the rate of recurrent ischemic stroke in the Device group was significantly lower compared to the MM group.

### **B. Safety Conclusions**

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the RESPECT clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory and animal studies performed on the AMPLATZER PFO Occluder demonstrate that the device is suitable for long-term implantation. The risks associated with the device include pulmonary embolism, thrombus in the right atrium, need for device explantation by open surgery, atrial fibrillation, and residual shunting across the PFO requiring additional closure attempts. Additionally, procedure-related risks include but are not limited to cardiac perforation, access site bleeding, and deep vein thrombus. The safety evaluation performed during the RESPECT study showed an acceptable rate of adverse events. The risk of device- or implantation procedure-related serious adverse events (SAEs) in patients undergoing an AMPLATZER PFO Occluder implantation procedure was 4.2% in the Device group in the RESPECT trial. There were no device- or implantation procedure-related deaths. However, it should be noted that the Device group experienced a numerically higher rate of atrial fibrillation, deep venous thrombosis, and pulmonary embolism compared to the MM group.

### **C. Benefit-Risk Determination**

The probable risks of the AMPLATZER PFO Occluder include device- and procedure-related serious adverse events such as cardiac perforation and access site bleeding. There was a small increased risk of atrial fibrillation and venous thromboembolic events (pulmonary embolism and deep venous thrombosis) in patients treated with the Device compared with medical therapy.

The probable benefits of the device are also based on data collected in the RESPECT trial. There was a 50% relative risk reduction in the rate of recurrent ischemic stroke

in subjects randomized to the Device vs. MM. Additionally, effective PFO closure with the device at 6 months was observed in 94.2% (323/343) of evaluated patients.

#### Patient Perspectives

An intervention that reduces the risk of recurrent stroke would be highly valued by patients and would improve the quality of life. The Sponsor administered a patient satisfaction questionnaire to 744 RESPECT trial subjects who remained in active follow-up as of August 2015 (408 in the Device group and 336 in the MM group). A total of 491 surveys were returned (278 in Device group and 213 in MM group). The Sponsor reported that among subjects who responded to the survey, 97.5% of Device patients were satisfied with their treatment compared with 74.6% of MM patients. With regard to the benefit-risk profile of the subjects' treatment assignment, 90.7% of Device patients responded that the benefits outweighed the risks vs. 49.2% of MM patients.

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

#### **D. Overall Conclusions**

The information provided in this PMA support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use (i.e., the AMPLATZER PFO Occluder reduces the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke).

### **XIII. CDRH DECISION**

CDRH issued an approval order on October 28, 2016. The final conditions of approval cited in the approval order are described below.

- 1. OSB Lead PMA Post-Approval Study – AMPLATZER PFO Occluder New Enrollment PAS:** The study will evaluate the long-term safety and effectiveness of the AMPLATZER PFO Occluder and the effectiveness of a training program for new operators. This will be a prospective, open-label, multi-center evaluation of the AMPLATZER PFO Occluder consisting of at least 1,214 US participants that receive the device post-approval.

The primary effectiveness endpoint, which is the rate of recurrent ischemic stroke through 5 years, will be compared to a performance goal (PG) of 3.9%. The primary safety endpoint, which is the cumulative incidence of device- or procedure-related serious adverse events through 30 days includes the following events: atrial fibrillation, pulmonary embolism, deep vein thrombosis, device thrombus, device erosion, device embolization, ischemic stroke (if subject was not successfully implanted with a

device), hemorrhagic stroke, major bleeding requiring transfusion or surgical or endovascular intervention, vascular access site complication requiring surgical intervention, and device- or procedure-related serious adverse event leading to death. The primary safety endpoint will be compared to a PG of 4.14%. The study will enroll 1,214 subjects who will provide 84.5% and 98.5% power at a significance level of 2.5% to reject the null hypothesis for effectiveness and safety, respectively.

Office visits for all subjects will be performed at baseline, 1, 6, and 12 months post-implant. Beginning at the 2-year visit and annually thereafter through the 5-year visit, study visits will be completed via telephone. SF-12 quality of life physical and mental component score and the health state utility values from EQ-5D will be assessed at baseline, 1 month, 6 months and 1 year. Effective closure and complete closure will be assessed at 1 year post-implant. A transthoracic echocardiogram or transesophageal echocardiogram will be performed at 12 months and post-suspected stroke to determine if there is a residual shunt. A 90-day office follow-up will be conducted post-confirmed stroke. Descriptive endpoints to be assessed through each follow-up include: (1) rate of stroke of unknown cause, (2) rate of transient ischemic attack, (3) rate of atrial fibrillation, (4) rate of pulmonary embolism (PE), (5) rate of deep vein thrombosis (DVT), (6) rate of venous thrombosis events (DVT or PE), (7) rate of device thrombus, (8) rate of device erosion, (9) rate of device embolization, (10) rate of ischemic stroke, (11) rate of hemorrhagic stroke, (12) rate of atrial flutter, (13) rate of paroxysmal supraventricular tachycardia requiring treatment, and (14) antithrombotic medication use. This study will also assess technical success and procedural success.

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

#### **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

#### **XV. REFERENCES**

<sup>1</sup> Kernan WN, et. al. (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.

<sup>2</sup> Messé SR, et al. (2016). Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*, 87 (8): 815 -821.