SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name	PFO Occluder
Device Trade Name	AMPLATZER™ PFO Occluder
Applicant's Name and Address	St. Jude Medical 5050 Nathan Lane North Plymouth, MN 55442
PMA Number	P120021
Date of Panel Recommendation	To be determined
Date of Notice of Approval to the Applicant	To be determined

II. Indications for Use

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.

III. Device Description

The AMPLATZER PFO Occluder 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. Radiopaque marker bands are on the distal and proximal ends of the device. The device is delivered percutaneously via the femoral vein using 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.

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

IV. Contraindications, Warnings, and Precautions

Contraindications, warnings, and precautions are provided in the device labeling for the AMPLATZER PFO Occluder.

V. Alternative Practices and Procedures

The AMPLATZER PFO Occluder is a percutaneous, transcatheter occlusion device intended for 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. The AMPLATZER PFO Occluder has been developed as a potential alternative to the current standard of care for reduction in risk of recurrent stroke in patients with a PFO who have experienced a cryptogenic stroke. Currently, the standard of care for these patients includes four types of medical therapy regimens: (1) Aspirin, (2) Coumadin, (3) Clopidogrel or (4) Aspirin combined with Dipyridamole or surgical closure of the PFO.

VI. Marketing History

The AMPLATZER PFO Occluder was first marketed in the European Union after it received CE marking February 24, 1998. In addition, the device is marketed in the following countries: Algeria, Argentina, Armenia, Australia, Azerbaijan, Bahrain, Bangladesh, Belarus, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Cuba, Egypt, El Salvador, India, Indonesia, Iraq, Israel, Jordan, Kazakhstan, Kenya, Korea, Kuwait, Kyrgyzstan, Lebanon, Liechtenstein, Malaysia, Mexico, Moldova, Monaco, Mongolia, Morocco, Nepal, New Zealand, Oman, Pakistan, Panama, Paraguay, Peru, Philippines, Qatar, Romania, Russia, Saudi Arabia, Singapore, South Africa, Sri Lanka, Syria, Tunisia, Turkey, Ukraine, United Arab Emirates, Uruguay, Uzbekistan, Venezuela, Yemen. The AMPLATZER PFO Occluder has not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

VII. Potential Adverse Events

Potential adverse events associated with the use of the AMPLATZER PFO Occluder include:

Air embolus	Headache/migraine
Allergic dye reaction	Hypertension/hypotension
Allergic drug reaction	Myocardial infarction
Anesthesia reactions	Pacemaker placement secondary to PFO device closure
Apnea	Palpitations
Arrhythmia	Pericardial effusion
Bacterial endocarditis	Pericardial tamponade
Bleeding	Pericarditis
Brachial plexus injury	Peripheral embolism
Cardiac perforation	Pleural effusion
Cardiac tamponade	Pulmonary embolism
Cardiac thrombus	Reintervention for residual shunt/device removal
Chest Pain	Sepsis

Deep vein thrombosis	
Device embolization	Stroke
Device erosion	Transient ischemic attack
Death	Thrombus
Endocarditis	Valvular regurgitation
Esophagus injury	Vascular access site injury
Fever	Vessel perforation

VIII. Summary of Preclinical Studies

Biocompatibility

Based on the results of the biocompatibility testing performed, the materials used in the AMPLATZER PFO occluder were determined to be biocompatible, non-mutagenic, non-toxic and, therefore, safe for the device's intended use. Testing was conducted in accordance with ISO 10993-1, Biological Evaluation of Medical Devices. A summary of the tests performed, the test objectives and test results are presented in **Table 1** below:

Table 1: Biocompatibility Tests and Results

BIOLOGICAL TEST	OBJECTIVES	TEST METHOD/ EXTRACT/ANIMAL or CELL LINE USED	RESULTS
Cytotoxicity	Determine if leachables extracted from the test article cause cytotoxicity	Minimum Essential Medium Elution (1X MEM) - Mouse fibroblast cells L929	**Passed** Non-cytotoxic - Grade 0
Sensitization	Evaluate the potential of the test article to cause delayed dermal contact sensitization in the guinea pig maximization test	Maximization Test (Kligman) NaCl and Sesame Oil (Polar and non-polar) Guinea Pig Model	**Passed** Non-sensitizer for both extracts
Intracutaneous Reactivity (Irritation)	Determine if leachables from the test article cause local dermal irritation effects following injection into rabbit skin	NaCl and Sesame Oil (Polar / non-polar) Rabbit (New Zealand White)	**Passed** Difference between extracts and control was 1.0 or less
Systemic Toxicity (acute)	Determine if acute systemic toxicity occurs following injection into mice	NaCl and Sesame Oil (Polar / non-polar) Mouse	**Passed** No evidence of systemic toxicity

BIOLOGICAL TEST	OBJECTIVES	TEST METHOD/ EXTRACT/ANIMAL or CELL LINE USED	RESULTS
Pyrogenicity	Determine if an extract of the test article induces a pyrogenic response following intravenous injection in rabbits	Materials mediated Sterile, non-pyrogenic 0.9% sodium chloride solution (SNPS) Rabbit (New Zealand White)	**Passed** Non-pyrogenic
Hemocompatibility – Hemolysis	To determine if the test article would cause hemolysis in vitro by direct contact or extraction	Hemolysis - direct method	**Passed** Non-hemolytic
Hemocompatibility - Complement Activation	Determine the complement activation potential of a medical device by detecting the presence of C3a and SC5b-9	Complement Activation - C3a and SC5b-9	**Passed** C3a - Not considered a potential activator SC5b-9 - Not considered a potential activator
Genotoxicity - Bacterial reverse mutation assay	Evaluate if a test article extract would cause mutagenic changes in Salmonella typhimurium and Escherichia coli strains in the presence or absence of mammalian metabolic activation	Bacterial reverse mutation assay / DMSO and NaCl Tester Strains - TA98, TA100, TA1535, TA1537	**Passed** Non-mutagenic
Genotoxicity - Mouse Lymphoma Assay	Evaluate the mutagenic potential of a test article extract using the mouse lymphoma forward mutation assay procedure	Mouse Lymphoma Assay (4 and 24 hour) / $RPMI_0$ Medium and DMSO	**Passed** DMSO and RPMI - No increase in mean mutant frequency in the presence of or absence of metabolic activation
Genotoxicity - Mouse Micronucleus Assay	Evaluate the potential for a test article extract to cause damage to chromosomes or the mitotic apparatus of murine erythroblasts by measuring the frequency of micronucleated reticulocytes in mice	Mouse Micronucleus Assay NaCl and Sesame Oil (Polar and non-polar)	**Passed** The test article did not induce micronuclei in mice
Implantation	Evaluate the local tissue response to the test article when implanted in muscle tissue	1 and 4 week implant Rabbit (New Zealand White)	**Passed** Non-irritant at 1 week Slight irritant at 4 weeks
Sub chronic toxicity	Evaluate the potential for systemic toxicity of the test article following	13 Week Implant Rat	**Passed** Slight irritant

BIOLOGICAL TEST	OBJECTIVES	TEST METHOD/ EXTRACT/ANIMAL or CELL LINE USED	RESULTS
	subcutaneous implantation in rats for up to 13 weeks		

Bench Testing

Design verification testing and material characterization was performed on the AMPLATZER PFO occluder to ensure the design meets all required inputs per the product specification. All test results demonstrate the PFO occluder meets all design requirements. The testing is summarized in **Table 2** below:

Table 2: Design Verification Testing

Test	Sample Size	Specifications/Criteria	Evaluation Time points	Results
Visual Inspection	All sizes, 29 each	Meet design requirements	t = 0 and t = 5years	**Pass**
Proximal and Distal Disc Diameter, Waist Length (Pre Deployment)	All sizes, 29 each	Waist length 3±0.5mm Proximal and distal disc 18 +0.5/-1.5 25 +0.5/-1.5 35 +0.5/-1.5	t = 0 and t = 5years	**Pass**
End Screw Attachment	All sizes, 29 each	Minimum 4 Full Turns of Thread	t = 0 and t = 5years	**Pass**
Load Force	All sizes, 29 each	Less than 8.0 Lbs.	t = 0 and t = 5years	**Pass**
Handoff Force	All sizes, 29 each	Less than 5.0 Lbs.	t = 0 and t = 5years	**Pass**
Advancement Force	All sizes, 29 each	Less than 5.0 Lbs.	t = 0 and t = 5years	**Pass**
Recapture Force	All sizes	Less than 8.0 Lbs.	t = 0 and t = 5years	**Pass**
Deployment and Retrieval	All sizes, 29 each	Minimum 3 times	t = 0 and t = 5years	**Pass**
Device release	All sizes, 29 each	Minimum four turns of thread and no rotation while in the simulated model	t = 0 and t = 5years	**Pass**
Visual Inspection of Device while in Simulated PFO Model	All sizes, 29 each	Device apposes model septal wall, device maintains intended shape, device fits in simulated model with no sharp edges	t = 0 and t = 5years	**Pass**
Pull Through	All sizes, 29 each	Greater than 1.0 Lbs.	t = 0 and t = 5years	**Pass**

Proximal and Distal Disc Diameter, Waist Length (Post Deployment)	All sizes, 29 each	Waist length 3±0.5mm Proximal and distal disc 18 +0.5/-1.5 25 +0.5/-1.5 35 +0.5/-1.5	t = 0 and t = 5years	**Pass**
Tensile Strength	All sizes, 29 each	Greater than 12 Lbs.	t = 0 and t = 5years	**Pass**
Packaging Testing				
Bubble Leak	Inner and outer pouch 30each	No leaks	t = 0 and t = 5years	**Pass**
Seal Strength	Inner and outer pouch 15 each	Equal to or greater than 0.5lbs	t=5 years	**Pass**
Endurance Testing				
Fatigue Testing	N= 22, 18 mm	N/A	400 million Cycles- Ten Year Fatigue	**Pass**
Particulate Testing				
Particulate Testing	N=10, 35 mm	USP<788>	t=0 and t= 3years	**Pass**
Corrosion Testing				
Galvanic Corrosion	18mm and 35mm, 3 each	ASTM G71	N/A	**Pass** Time to corrode: Nitinol: 7532 years 316LSS: 110 years
Potentiodynamic Corrosion	18mm and 35mm, 5 each	N/A	Pre- and post- 400 M cycle fatigue testing	Minimal localized pitting observed through SEM analysis

Sterilization

The AMPLATZER PFO occluder is provided sterile and for single use only. The PFO device is sterilized via ethylene oxide. The sterilization cycle was validated to meet a minimum Sterility Assurance Level (SAL) of 10^{-6}.

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.

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

- 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.

Animal Studies
A chronic GLP study was performed to evaluate the AMPLATZER PFO occluder for delivery, handling and device implant safety and performance using a natural PFO in a healthy porcine model.

Six female porcine were implanted with the PFO device. Device performance and handling parameters were assessed during the implant procedure. Interim procedures utilizing echocardiography and fluoroscopy were performed and the device was imaged and evaluated on post-implant day 1 or 2, day 13-15, day 29-30, day 90-92, and day 181-183 (termination). Plasma and urine levels of nickel pre- and post-implantation over the course of the study and tissue levels of nickel at sacrifice were evaluated. At sacrifice, the hearts were harvested and processed for histopathological analysis.

Each animal survived to its designated time point. The average age at implant was 93 ±1 days, the average weight at implant was 46.0 ±2.3 kg and the average weight at sacrifice was 90.5 ±11.1 kg. There were no complications or adverse events associated with the implant or follow-up procedures. Complete PFO closure and device stability were demonstrated in all cases as confirmed by follow-up echocardiography and fluoroscopy at designated time points. All neurologic exams performed on all animals prior to implant and the day of follow up procedures

were normal. There were no occurrences of heart block or arrhythmias at implant or during follow up procedures.

IX. Summary of Clinical Studies

RESPECT Trial

a. Study Design

The objective of the RESPECT trial was to investigate whether percutaneous PFO device closure with the AMPLATZER™ PFO Occluder is superior to standard of care medical treatment in the prevention of recurrent ischemic stroke in subjects who had a cryptogenic stroke due to presumed paradoxical embolism.

The RESPECT trial was a prospective, multicenter, randomized (1:1), open-label clinical trial with an event-driven primary endpoint comparing the effectiveness of the AMPLATZER PFO Occluder with standard medical therapy in preventing recurrent ischemic stroke. Subjects were randomized to either receive the AMPLATZER PFO Occluder or standard of care medical management. Device subjects were treated with clopidogrel daily for 1 month and aspirin daily for 6 months following device placement**.** After 6 months, antithrombotic therapy in device subjects was left to the discretion of the treating physician. The four medical therapy regimens allowed per protocol in the medical management (MM) group were: (a) Aspirin alone, (b) Coumadin alone, (c) Clopidogrel alone or (d) Aspirin combined with dipyridamole.

Subjects were eligible to participate in the trial if they had a PFO and had experienced a cryptogenic ischemic stroke within 270 days prior to randomization. Ischemic stroke was defined as an acute focal neurologic deficit, presumed to be due to focal ischemia, and either 1) symptoms persisting 24 hours or greater, or 2) symptoms persisting less than 24 hours, but associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.

Subjects were followed at 1, 6, 12, 18 months, and 24 months, then annually thereafter until the device was approved by FDA or if the subject chose to withdraw from the trial. Study endpoints were:

Primary Endpoint: Composite of the following:

- Recurrence of a nonfatal ischemic stroke
- Post-randomization death defined as all-cause mortality within 45 days of randomization in the MM group and within 30 days after implant or within 45 days after randomization whichever occurs last in the device group
- Fatal ischemic stroke

Secondary Endpoint:

- Complete closure of the defect demonstrated by TEE and bubble study at the 6-month follow-up (to be assessed in device group only)
- Absence of recurrent symptomatic cryptogenic nonfatal stroke or cardiovascular death
- Absence of TIA

There were no hypotheses associated with the secondary endpoints. Enrollment was to continue until 25 primary endpoint events were accumulated, at which time analysis of the primary endpoint was to be conducted.

Safety Endpoints

There were no formal safety endpoints or hypotheses. Adverse events were collected for all subjects from the time of randomization.

b. Description of Patients

A total of 980 subjects were enrolled at 69 investigational sites: 62 sites in the US and 7 sites in Canada. The mean (SD) age was 45.9 (9.8) years and gender was 54.7% male.

At the time of the primary 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 extended follow-up, 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.

Analyses were conducted on the intent to treat (ITT) and Per Protocol (PP) populations. The ITT population consists of all subjects randomized. The PP population excludes subjects who were not compliant to the protocol (i.e., who did not meet key eligibility criteria, did not comply with one of the protocol recommended medical regimens, or did not receive the therapy to which they were randomized). **Table 3** presents demographics and baseline characteristics.

Table 3: Subject Demographics and Baseline Characteristics

Variable	Device (N=499)	Medical Management (N=481)	p-value[1]
Age, years[2]	492 45.7 (9.7) 46.7 [18.1, 61.0]	476 46.2 (10.0) 47.6 [18.4, 60.9]	0.491
Time from stroke to randomization, days	499 130 (70) 117 [10, 277]	481 130 (69) 121 [10, 286]	0.891
Sex, male	268 (53.7%)	268 (55.7%)	0.564
Previous myocardial infarction	5 (1.0%)	2 (0.4%)	0.452
Previous transient ischemic attack	58 (11.6%)	61 (12.7%)	0.626
Stroke prior to qualifying cryptogenic stroke	53 (10.6%)	51 (10.6%)	1.000
Substantial Shunt at Rest or Valsalva	247 (49.5%)	231 (48.0%)	0.655
Atrial septal aneurysm[3]	180 (36.1%)	170 (35.3%)	0.842

Continuous variables are reported as n, mean (SD), median [min, max] and categorical variables as n (%).
[1] 2-sample t-test (age), Wilcoxon-Mann-Whitney test (days from stroke to date randomized) and Fisher's Exact test.
[2] The IRB at one site (12 subjects) did not allow recording of subject birthdates on CRFs.
[3] Defined as a total excursion of the septum primum ≥10mm

c. Procedural Outcomes

Of the 499 subjects who were assigned to the device group, 467 underwent the procedure and the AMPLATZER PFO Occluder was implanted in 465 of them. The rate of successful delivery and release of the device at the time of first procedure in subjects in whom a device was attempted was 99.1% (463/467). Two subjects had a successful implant during a second procedure. The rate of procedural success (implantation with no in-hospital serious adverse events) was 96.1%. The mean procedure time was 52.0±28.8 minutes, and the mean fluoroscopy time was 11.8±8.9 minutes.

d. Results

Primary Endpoint Analysis Results:

Results of analyses of the primary endpoint are summarized in **Table 4**. While the ITT analysis demonstrated a 50% relative risk reduction for the primary endpoint, the analysis did not achieve statistical significance (p = 0.089). The PP analysis showed a

statistically significant relative risk reduction of 63% (p = 0.034). These analyses support the conclusion that there is a true device effect on recurrent ischemic stroke, explained by elimination of a conduit through which venous source emboli can travel to the brain.

Table 4: Summary of Primary Endpoint Analyses Results

Analysis Type	Analysis Population	# Subjects (# Events)		Kaplan-Meier Estimate at 5 years		Hazard Ratio (Relative Risk Reduction)	Two-sided p-value (Device vs MM)
		Device group	MM Group	Device group	MM Group		
Pre-specified in protocol	Intent to treat	499 (9)	481 (16)	0.021	0.059	0.50 (50%)	0.089
Pre-specified in protocol	Per Protocol	463 (6)	474 (14)	0.012	0.059	0.37 (63%)	0.034

Extended Follow-up Analysis Results:

Results of analyses through extended follow-up at 5 and 8 years are shown in **Table 5**. As subjects aged, strokes of traditional mechanism emerged, motivating a separate post-hoc analysis to characterize device effect. Strokes in which a disease was adjudicated to be present and likely to be the potential cause of the stroke by ASCOD phenotyping (*Overlap of Diseases Underlying Ischemic Stroke: The ASCOD Phenotyping* by Sirimarco et al 2013) were excluded. Such strokes are unlikely to be due to the PFO. This analysis showed a relative risk reduction of 54% for stroke (p= 0.042).

Table 5: Kaplan-Meier event rates at 5 years and 8 years, hazard ratio estimates and log-rank p-value (post-hoc analyses)

ITT Analysis	# Subjects (# Subjects with Events)		Kaplan-Meier Estimate At 5 years At 8 years		Hazard Ratio (Relative Risk Reduction)	p-value (Device vs MM)
	Device group	MM Group	Device group	MM Group		
Freedom from stroke of undetermined mechanism	499 (10)	481 (19)	0.021 0.025	0.041 0.052	0.46 (54%)	0.042

Secondary Endpoint Results:

The secondary endpoint of complete closure was defined as shunt grade 0 at rest and Valsalva at 6-months post-procedure in device group subjects. The complete closure rate observed in device group subjects was 71.3% (**Table 6)**. Given that it may take more than 6 months after PFO closure for the device to completely endothelialize, effective closure, defined as a maximum of shunt grade at rest and Valsalva of 0 or I, was also calculated. The effective closure rate was 94.2%.

Table 6: 6-Month closure data, device group subjects

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

For the composite secondary endpoint of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death, there was an 82.6% relative risk reduction in favor of the device group.

The secondary endpoint of TIA yielded a 9.9% reduction for device versus medical management.

Safety Evaluation

There were 386 SAEs in 189 patients in the Device arm and 298 SAEs in 168 patients in the MM arm. The proportions of patients experiencing an SAE in the two arms were similar (37.9% in the Device arm and 34.9% in the MM arm; Table 7). 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 (UADE) were reported in the trial.

Table 7: Overall Rate of SAEs-Extended Follow-Up

	Device (N=499, 2769 patient-years)		Medical Management (N=481, 2376 patient-years)	
	n (%)	Events (rate per 100 patient-years)	n (%)	Events (rate per 100 patient-years)
Any SAE	189 (37.9%)	386 (13.9)	168 (34.9%)	298 (12.5)
Unanticipated adverse device effect	0 (0.0%)	0 (0.0%)	N/A	N/A
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

Twelve (12) procedure-related SAEs occurred in 12 patients (2.4%), and are summarized in **Table 8**.

Table 8. Procedure-related SAEs in the Device Arm (N = 467)

Event	n (%)
Cardiac perforation (*required pericardiocentesis*)	2 (0.4%)
Cardiac perforation (*no treatment required*)	2 (0.4%)
Access site bleeding (*1 required a stitch, 1 required transfusion, 1 required no treatment*)	3 (0.6%)
Right atrial thrombus (*detected during procedure – procedure abandoned*)	1 (0.2%)
Deep vein thrombosis	1 (0.2%)
Atrial fibrillation (*successfully cardioverted*)	1 (0.2%)
Other (*allergic drug reaction, vasovagal response*)	2 (0.4%)

Thirteen (13) device-related SAEs occurred in 10 patients (2.0%), and are summarized in **Table 9**.

Table 9. Device-related SAEs in the Device Arm (N = 467)

Event	n (%)
Ischemic stroke (*primary endpoint*)	2 (0.4%)
Pulmonary embolism	2 (0.4%)
Thrombus in right atrium (*not attached to device*)	1 (0.2%)
Explant/surgical intervention	2 (0.4%)
Atrial fibrillation (*successfully cardioverted*)	1 (0.2%)
Residual shunt requiring closure	1 (0.2%)
Other (*chest tightness, atrial flutter, non-sustained ventricular tachycardia, sepsis*)	4 (0.8%)

Meta-analysis

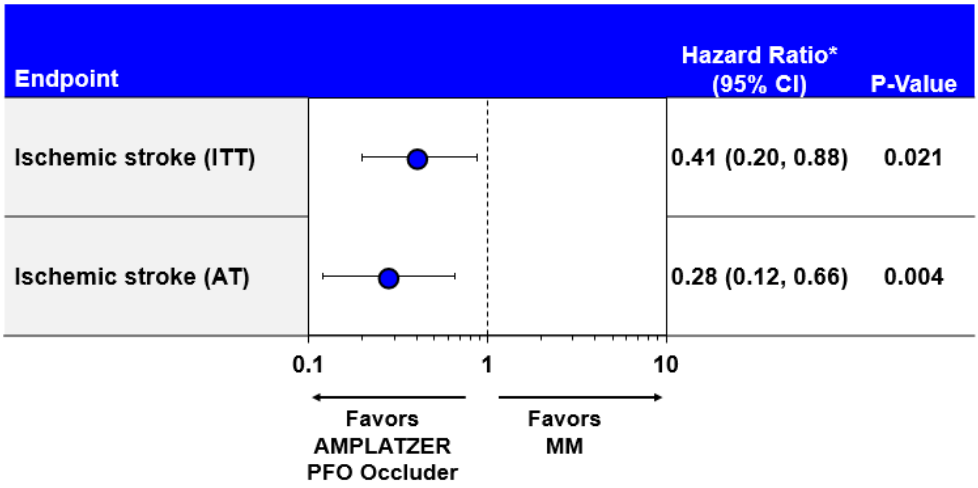
A pooled, individual patient-level meta-analysis was conducted at Tufts University, supported by an NIH-funded grant, independent of the companies that sponsored the trials[i]. While several meta-analyses have been conducted on PFO closure trials, this is the only patient-level meta-analysis assessing the comparative effectiveness of PFO closure to medical management.

The publication presented pooled, patient-level data from three randomized trials (RESPECT Trial, PC Trial, and CLOSURE I). These trials represent the totality of randomized evidence of PFO closure devices against medical therapy. Although the pooled analysis results across the three trials are valuable to evaluate overall effect of PFO closure and support a risk reduction for

recurrent stroke, the focus of the results is limited to the two AMPLATZER PFO device trials (RESPECT Trial and PC Trial).

The ITT population for the AMPLATZER PFO Occluder trials consisted of 1394 patients; 980 patients from RESPECT and 414 patients from the PC Trial. An "as treated" analysis was also carried out effects to comparing outcomes among patients who underwent device closure (attempted or successful, depending on the trial) with control patients. **Figure 1** shows ITT and "as treated" analysis results for recurrent ischemic stroke in both analyses. There was a statistically significant 59% relative risk reduction with PFO closure (HR: 0.41; 95% CI: 0.20, 0.88, p=0.021) for ischemic stroke. Results were nearly identical without covariate adjustment (HR: 0.39; 95% CI: 0.19, 0.82; p = 0.013). The "as treated" analysis showed a larger relative risk reduction of 72% with PFO closure (HR: 0.28; 95% CI: 0.12, 0.66, p=0.004) for ischemic stroke versus medical management.

Figure 1. Endpoint ITT Analysis: Covariate Adjusted Results



* Note: Hazard ratios are adjusted for: age, sex, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, atrial septal aneurysm, shunt size

X. Conclusions Drawn from the Studies

In the RESPECT trial, the AMPLATZER PFO Occluder demonstrated a 99.1% rate of successful delivery and release of the device at the time of first procedure in subjects in whom a device was attempted, and a 94.2% rate of effective PFO closure. 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 (UADE) were reported in the trial.

The RESPECT trial, along with the pooled meta-analysis, showed that closure of the PFO with the AMPLATZER PFO Occluder is effective in reducing the rate of recurrent ischemic stroke in subjects who have a PFO and a cryptogenic stroke due to presumed paradoxical embolism.

XI. Panel Recommendations

To be determined

XII. CDRH Decision

To be determined

XIII. Approval Specifications

Instructions 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: See Approval Order

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[i] Kent, D.M., Dahabreh, I.J., Ruthazer, R., Furlan, A.J., Reisman, M., …Thaler, D.E. (2016). Device Closure of Patent Foramen Ovale after Stroke. *JACC,* 67(8), 907-917