AMPLATZER™ PFO Occluder
for the Prevention of Recurrent Ischemic Stroke

SPONSOR'S EXECUTIVE SUMMARY

CIRCULATORY SYSTEM DEVICES PANEL

MEETING DATE: May 24, 2016

Sponsored by St. Jude Medical, Inc.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
AF	Atrial fibrillation
ASCOD	Atherosclerosis-Small vessel disease-Cardiac pathology-Other-Dissection
ASA	Atrial septal aneurysm
AT	As Treated
CEC	Clinical Event Committee
CI	Confidence interval
CT	Computed tomography
DIP	Device In Place
DSMB	Data Safety Monitoring Board
HR	Hazard ratio
ICE	Intra-cardiac echocardiogram
IQR	Interquartile range
ITT	Intention-to-treat
NIHSS	National Institutes of Health Stroke Scale
MM	Medical management
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
ODE	Office of Device Evaluation
OSB	Office of Surveillance and Biometrics
PAS	Post Approval Study
PFO	Patent foramen ovale
PMA	Premarket Approval
SAE	Serious adverse event
SJM	St. Jude Medical
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TTE	Transthoracic echocardiogram
TEE	Transesophageal echocardiogram
UCB	Upper confidence bound
VTE	Venous thromboembolism

Definition of Terms

Ischemic stroke	Acute focal neurological 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 imaging findings of a new, neuroanatomically relevant, cerebral infarct
Cryptogenic stroke	Stroke of unknown cause; to qualify for the RESPECT trial, cryptogenic strokes were defined by ruling out strokes of known mechanism
ASCOD	A system to phenotype patients with ischemic stroke; ASCOD (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection) phenotyping assigns a degree of likelihood of causal relationship to every potential disease (1 for potentially causal, 2 for causality is uncertain, 3 for unlikely causal but the disease is present, 0 for absence of disease, and 9 for insufficient workup to rule out the disease) commonly encountered in ischemic stroke
mRS	Determines the disability caused by a stroke. The scale ranges from 0 to 6, with 0 being no impairment and 6 is patient death.
NIHSS	Validated instrument using a formalized neurological examination that provides a reliable score of neurological impairment. The range is from 0, which is no measurable deficit, to 42, which is the most severe stroke.
TIA	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 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
TOAST	A classification system for subtypes of ischemic stroke based on etiology including: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology

1 SYNOPSIS

A patent foramen ovale (PFO) is a congenital flap-like opening between the right and left upper chambers of the heart, which usually closes after birth. In most people with a persistent PFO, the anomaly does not affect the person's health. However, some people with a PFO experience a stroke, usually at a young age. By providing an open conduit for a thrombus to pass from a venous source to the body's arterial system, a PFO can create a lifelong risk for stroke due to a paradoxical embolism; the paradox being that a venous thrombus passes through the PFO, thereby bypassing the lungs, and entering the body's arterial system. These strokes, the causes of which are not readily apparent, are among those referred to as "cryptogenic."

Upon diagnosis of a cryptogenic ischemic stroke, the American College of Chest Physicians (ACCP) treatment guidelines recommend prescribing a lifetime regimen of antithrombotic (i.e., antiplatelet or anticoagulant) therapy (Whitlock et al, 2012). Unfortunately, even in the setting of strict adherence, antithrombotic therapy does not eliminate the risk for embolic stroke. Young to middle-aged, otherwise healthy people who have experienced an embolic stroke deemed to be associated with PFO have stroke recurrence rates averaging 1-2% per year on aspirin (Mas et al, 2001; Arauz et al, 2012). For this younger patient population, the risk for a potentially devastating stroke during what are usually their most productive years, accumulates over decades. There is an unmet need for further reduction in risk among these patients beyond what can be achieved with medical management alone.

The AMPLATZER™ PFO Occluder is an implantable cardiac device developed by St. Jude Medical (SJM) to close a PFO using a minimally invasive transcatheter procedure in order to reduce the risk of recurrent cryptogenic stroke. Over the last 12 years, SJM has conducted clinical research to evaluate the safety and effectiveness of the AMPLATZER PFO Occluder in patients with a PFO who have had a cryptogenic ischemic stroke due to a presumed paradoxical embolism. In November 2012, SJM submitted a PMA application for the AMPLATZER PFO Occluder based on the primary results of the RESPECT trial. Follow-up has been ongoing since the initial PMA submission. Recently, SJM submitted the extended follow-up results of the RESPECT trial to FDA, with an average patient follow-up of more than 5 years.

SJM is requesting Premarket Approval (PMA) of the AMPLATZER PFO Occluder for patients with a PFO who have had a cryptogenic stroke due to a presumed paradoxical embolism. SJM is proposing the following indication for use of the AMPLATZER PFO Occluder:

> *"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 a presumed paradoxical embolism."*

The AMPLATZER PFO Occluder is a self-expandable, double disc device made from a Nitinol wire mesh. The device is delivered percutaneously via the femoral vein using a delivery wire 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 delivery system consists of a delivery sheath with Touhy-Borst hemostatic adapter, dilator, loader, plastic vise, and delivery cable.

The safety and effectiveness of the AMPLATZER PFO Occluder were evaluated in the pivotal RESPECT randomized clinical trial, which is the largest trial of a transcatheter PFO closure device. The trial randomized 980 patients in a 1:1 ratio to either be implanted with the AMPLATZER PFO Occluder (Device) or to follow one of the medical regimens recommended by national treatment guidelines (Medical Management [MM]). Based on peer-reviewed literature from observational studies, this event-based trial was powered to detect a 75% relative risk reduction for recurrent ischemic stroke with the device compared to guideline-directed medical therapy.

The RESPECT trial enrolled patients over eight years, six years longer than anticipated. Throughout the enrollment period, there was a lack of clinical equipoise among physicians in favor of PFO closure, combined with the availability of approved septal occluders that were being used off-label to close the PFO. These devices are designed to close an atrial septal defect (a large hole between the atria) rather than a PFO (a narrower tunnel or flap between the atria), for which the AMPLATZER PFO Occluder is designed. Additionally, over the first 3.5 years of the trial, the AMPLATZER PFO Occluder was also available under Humanitarian Device Exemption (HDE), which significantly slowed enrollment in RESPECT. Once the device was no longer available under HDE, the enrollment rate doubled to 144 patients per year.

The trial also had a differential rate of patient drop-out, with a higher rate of drop-out in the medical management (MM) arm. Most patients randomized to the MM arm withdrew consent stating they were unhappy with the randomization assignment or in order to seek PFO closure outside the trial.

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

- **Fatal ischemic stroke**
- **Recurrent nonfatal stroke:** defined as acute focal neurological 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 imaging findings of a new, neuroanatomically relevant, cerebral infarct.
- **Post-randomization death:** defined in the MM arm as all-cause mortality within 45 days after randomization, and in the device arm as all-cause mortality 30 days after implant or 45 days after randomization, whichever occurred last.

The primary endpoint was not met in both the intention-to-treat (ITT) raw count and log-rank analyses. The raw count analysis showed an odds ratio of 0.534 favoring the device (Fisher's Exact p = 0.157). Of the 25 primary endpoint events in the ITT analysis, 9 occurred in the Device arm and 16 occurred in the MM arm. There was a 50% relative risk reduction with the device (hazard ratio [HR]: 0.50, 95% CI: 0.22, 1.13; p = 0.089) compared to guideline-directed MM, using a log-rank test and a Cox proportional hazards model.

In the pre-specified Per Protocol analysis, there was a statistically significant and clinically meaningful 63% relative risk reduction in the Device arm (HR: 0.37; 95% CI: 0.14, 0.97; p = 0.03).

Given that the observational data upon which the RESPECT trial design were based overestimated the treatment effect and led to an underpowered trial, the totality of the randomized, controlled AMPLATZER PFO Occluder data were evaluated in a patient-level meta-analysis (Kent et al, 2016). The meta-analysis evaluated two randomized controlled trials of the AMPLATZER PFO Occluder (RESPECT and PC trials). The results showed that, when compared to medical management, PFO closure with the AMPLATZER PFO Occluder resulted in a statistically significant 59% relative risk reduction for recurrent ischemic stroke (HR: 0.41; 95% CI: 0.20, 0.88; p = 0.021).

The RESPECT trial has demonstrated that the AMPLATZER PFO Occluder is a device with a safe implant procedure with a favorable long-term safety profile. The rate of procedure- or device-related serious adverse events was 5%. Nearly all of the procedure- or device-related serious adverse events resolved without long-term sequelae. There were no procedure- or device-related deaths. Finally, there were no intra-procedural strokes, device embolizations or reports of thrombus on the device or device erosions in RESPECT.

In the United States, medical management with antiplatelet or anticoagulant therapy, or surgical closure of a PFO, are the only currently available therapies to treat patients with a PFO who have experienced a cryptogenic stroke. The AMPLATZER PFO Occluder addresses an unmet medical need among patients who suffer a cryptogenic stroke due to a PFO, many of whom will remain at risk for recurrent strokes for decades. Considering the life-long benefit of protection from stroke due to a paradoxical embolism and the low incidence of procedure- or device-related complications, the benefits of the device outweigh any residual risks associated with the device.

This document summarizes the totality of data on the AMPLATZER PFO Occluder in patients with a PFO who have experienced a cardioembolic event. This includes results from the:

- SJM-sponsored RESPECT trial (Section 5),
- Patient level meta-analysis of AMPLATZER PFO Occluder randomized controlled trials against MM (Section 9), and
- SJM-sponsored PFO ACCESS Registry (Section 11).

Also presented are SJM's plan for a post-approval physician training program and a post-market clinical program (Sections 12 and 13).

2 UNMET NEED

Cryptogenic ischemic strokes are ischemic strokes without a known cause despite a thorough diagnostic evaluation. These strokes frequently occur without any of the common risk factors for stroke, such as hypertension, diabetes, atherosclerosis, or history of smoking. Cryptogenic strokes are associated with morbidity and mortality; at 2 years following a cryptogenic stroke, 85% of patients have persistent neurological deficits, 55% are disabled (e.g., cannot work or drive), and 15% require assistance from others for daily living or are dead (Redfors et al, 2012).

Upon diagnosis of a cryptogenic ischemic stroke, the American College of Chest Physicians (ACCP) treatment guidelines recommend prescribing a lifetime regimen of antithrombotic (antiplatelet or anticoagulant) therapy (Whitlock et al, 2012). A lifetime regimen of antithrombotic therapy can come with concerns. Anticoagulant therapy increases the risk for hemorrhage, particularly in individuals with certain hematologic abnormalities, pregnant women, individuals at risk for a fall, and those who participate in certain athletic activities or vocations. Lack of compliance to medical therapy is a well-documented problem. Glader et al (2010) note that the rate of medication compliance among patients in the Swedish Stroke Register declined progressively over the first 2 years, down to 63.7% for antiplatelet drugs and 45% for warfarin. Bushnell et al (2011) reported that only 87% of patients hospitalized for stroke in the AVAIL registry remained on antiplatelet therapy and 68.2% remained on warfarin therapy at 1 year.

Unfortunately, in a real-world setting of being prescribed lifelong medication, antithrombotic therapy does not eliminate the risk for embolic stroke. Young to middle-aged, otherwise healthy people who have experienced an embolic stroke deemed to be associated with PFO have stroke recurrence rates averaging 1-2% per year on aspirin (Mas et al, 2001; Arauz et al, 2012). Given that patients who suffer these strokes are typically in their 30s or 40s, the cumulative risk for recurrent cryptogenic strokes over the course of decades of their remaining life is considerable (Li et al, 2015; Cerrato et al, 2006).

PFOs are present in approximately 25% of U.S. adults (Hagen et al, 1984). In young to middle-aged patients who have experienced a cryptogenic stroke, the presence of a PFO is about 3 times as high as that in patients with a stroke of known mechanism (Handke et al, 2007).

Cryptogenic ischemic strokes typically occur in people younger than 60 years of age (Amarenco et al, 2005) and comprise approximately 25% of all ischemic strokes (Hart et al, 2014). Each year approximately 690,000 ischemic strokes occur in the United States (Mozaffarian et al, 2015). Of these, approximately 160,000 occur in patients younger than 60 years of age (Fonarow et al, 2010), and approximately 40,000 (or 25%) of these are considered cryptogenic (Hart et al, 2014). Finally, of the approximately 40,000 cryptogenic ischemic strokes that occur annually, approximately 16,000 (or 40%) occur in patients who have a PFO (Handke et al, 2007).

Transcatheter PFO closure with the AMPLATZER PFO Occluder is a minimally invasive treatment to further reduce the risk for recurrent stroke among patients with a PFO and presumed paradoxical embolism (i.e., a cryptogenic stroke) beyond that achieved with medical management. This additional risk reduction is achieved by blocking the pathway for a venous embolism from reaching the body's arterial system and the brain.

Although approved atrial septal occluders have been used to perform off-label closure of the PFO, there are shortcomings to using such devices to close the PFO. These devices are not designed to close the PFO. Furthermore, there may be unrecognized risks of implanting unapproved devices in this location since these devices have not been studied for this purpose (Korabathina et al, 2012). Today there lacks labeling and guidance for physicians and patients for PFO closure as there are no approved devices.

For young to middle-aged patients who face a lifelong risk for recurrent stroke, often spanning decades, PFO closure with a safe, minimally invasive technique is an important treatment option.

3 AMPLATZER PFO OCCLUDER

3.1 Investigational Device Description

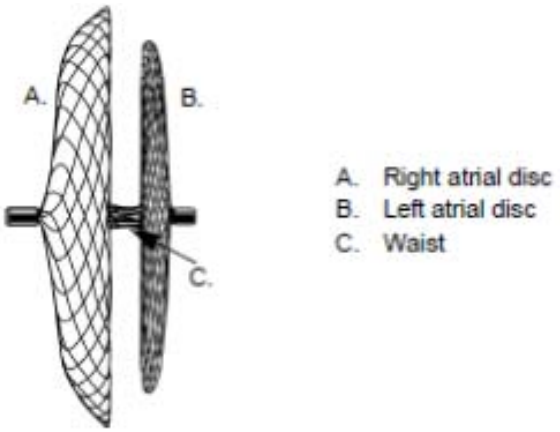
The AMPLATZER PFO Occluder is implanted percutaneously and permanently to close a PFO. The implant procedure is performed using a transcatheter approach under general anesthesia or conscious sedation and can be performed in a catheterization laboratory setting under fluoroscopic and echocardiographic guidance.

3.2 Device Description

The AMPLATZER PFO Occluder is a self-expanding, double disc device made from a Nitinol wire mesh (Figure 1). 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 the device's ability to close the PFO, the discs contain thin polyester fabric. The polyester fabric is 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 and for recapture if required.

The AMPLATZER PFO Occluder is available in 3 sizes (18mm, 25mm and 35 mm). Sizing is determined by transesophageal echocardiogram (TEE) or intra-cardiac echocardiography (ICE) measurements during the procedure.

Figure 1: AMPLATZER PFO Occluder



3.3 Delivery System

The AMPLATZER TorqVue system, which is 510(k) cleared, is used to deliver the device. The delivery system consists of a delivery sheath with Touhy-Borst hemostatic adapter, dilator, loader, plastic vise, and delivery cable. An 8 Fr sheath is recommended for the 18 mm and 25 mm device, and a 9 Fr sheath is recommended for the 35 mm device.

4 CLINICAL PROGRAM AND REGULATORY HISTORY

4.1 CE Mark

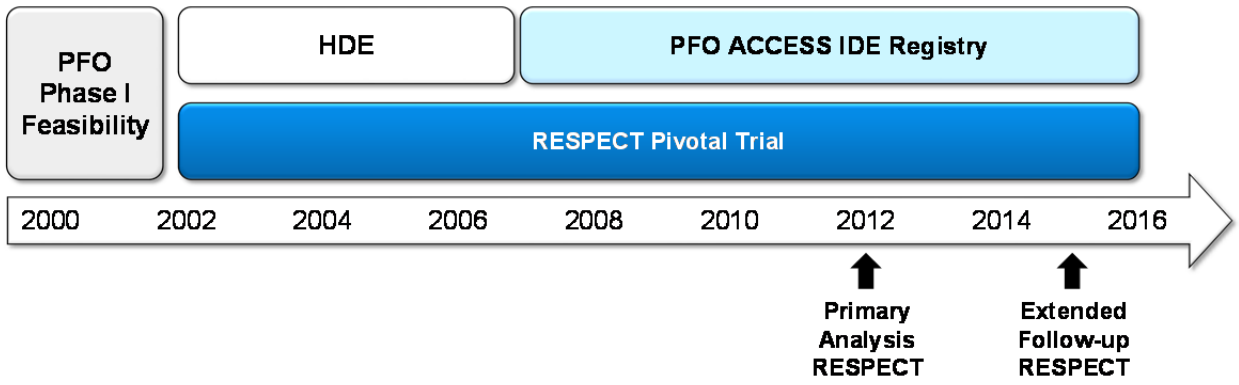
The AMPLATZER PFO Occluder received CE mark in 1998 for patients with a history of stroke or transient ischemic attacks (TIAs) and PFO diagnosed by echocardiography with right-to-left shunting during the Valsalva maneuver. In addition to the European Union, the device is commercially available in 60 countries with 85,408 devices shipped as of March 2016. This includes devices sold when the device was available under the Humanitarian Device Exemption (HDE) (See Section 4.4). The device is investigational in the United States.

4.2 United States Regulatory History

The U.S. PFO stroke clinical program for the AMPLATZER PFO Occluder includes the following investigational device exemption (IDE) studies: a Phase I feasibility study, the PFO ACCESS Registry, and the pivotal RESPECT trial (Figure 2).

- A Phase I feasibility study was conducted in 2000.
- Humanitarian Device Exemption (HDE) was approved in 2002. In 2006, all PFO device manufacturers withdrew their devices as the projected patient population exceeded the HDE regulatory limit.
- The PFO ACCESS Registry was initiated in 2006.
- The pivotal RESPECT clinical trial was initiated in 2002. Follow-up in this trial is ongoing.

Figure 2: PFO Stroke Clinical Program Timeline



4.3 Feasibility Study

In April 2000, FDA approved a Phase I feasibility clinical study to assess the safety of percutaneous PFO closure with the AMPLATZER PFO Occluder in patients with a PFO who experienced a cryptogenic stroke, a transient ischemic attack (TIA), or a peripheral embolism due to presumed paradoxical embolism (primary group), or who experienced a cryptogenic ischemic stroke while on warfarin therapy with therapeutic INR (registry group).

The Phase I study enrolled 79 patients (51 in primary group and 28 in registry group) at 6 investigative sites in the United States. Patients were followed for 1 year post-implant.

There were no unanticipated adverse device effects (UADE) or device-related serious adverse events (SAEs) in the study. No deaths occurred in the primary group and 4 deaths occurred in the registry group, none of which were related to the device. There was 1 procedure-related SAE (groin hematoma) in the primary group that resolved with surgical repair of an arteriovenous fistula, and 1 procedure-related SAE (pseudoaneurysm of the right iliofemoral artery) requiring no treatment in the registry group.

In 2002, the PFO Phase I feasibility study was completed in the U.S. and results were submitted to FDA in support of a pivotal trial, the RESPECT trial.

4.4 Humanitarian Device Exemption

In parallel to the FDA's review of the RESPECT protocol, FDA granted approval of the AMPLATZER PFO Occluder in 2002 under HDE for non-surgical closure of a PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO, who had failed conventional drug therapy. Through 2006, approximately 9,700 AMPLATZER PFO Occluders were shipped under the HDE. In 2006, FDA assessed that the eligible patient population in the U.S. exceeded the HDE regulatory limit of 4,000 patients per year, and all HDE-approved PFO occluders were withdrawn.

4.5 PFO ACCESS Registry

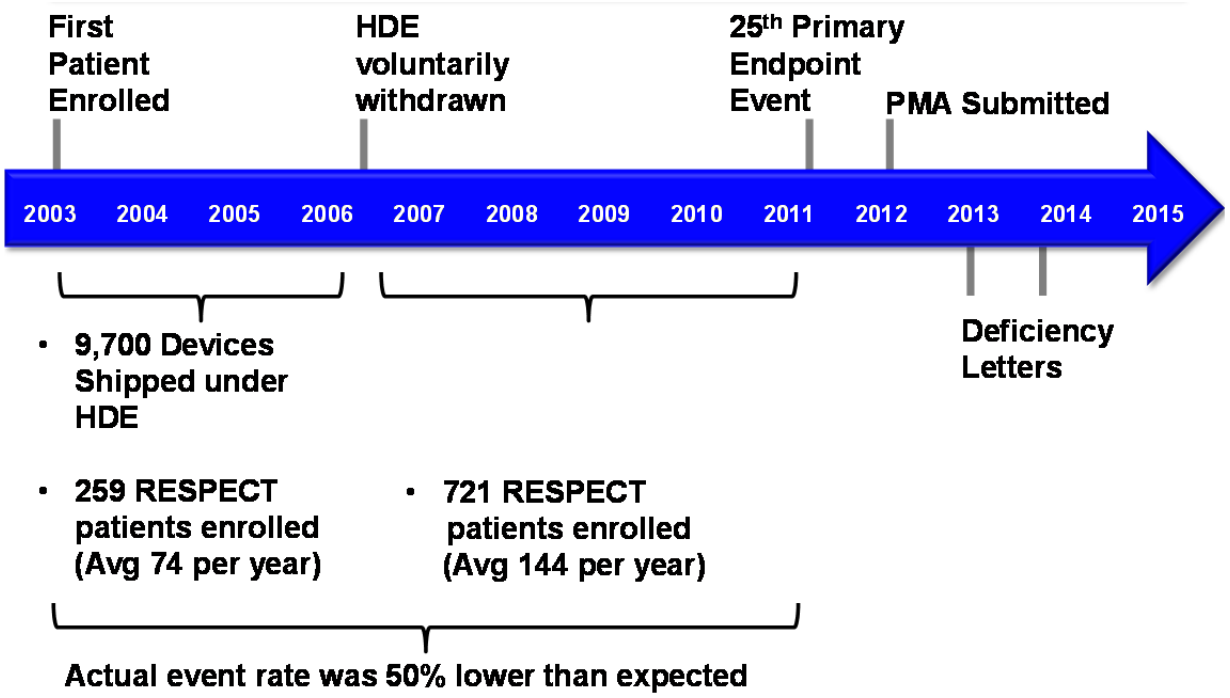
Upon withdrawal of HDE-approved PFO occluders, SJM initiated the PFO ACCESS IDE Registry in order to provide access to the device for patients with recurrent cryptogenic stroke while on anticoagulation or antiplatelet therapy (i.e., two or more strokes, one of which must have occurred while on anticoagulation or antiplatelet therapy). The registry is ongoing with over 600 patients enrolled.

4.6 RESPECT Trial

The RESPECT trial is a randomized (1:1), controlled, open label trial in patients with a prior cryptogenic stroke and a PFO. The trial was designed to demonstrate superiority of the AMPLATZER PFO Occluder over medical therapy in reducing the risk of a recurrent ischemic stroke. The event rates assumed in this event-driven trial were based on observational studies in published literature.

The first patient was enrolled in August 2003. As noted above, over the first 3 years of the trial, the device was also available under HDE, which significantly slowed enrollment in RESPECT. The trial enrolled 259 patients during the 4 years (74 patients per year) in which the device was available under HDE. Once the device was no longer available under HDE, the enrollment rate doubled to 144 patients per year. Enrollment continued until 2011 when the 25th pre-specified primary endpoint event was observed. The observed event rate in RESPECT was 50% lower than expected. The reduced event rate, coupled with the slower than expected enrollment, extended the duration of the trial to 8 years (Figure 3).

Figure 3: RESPECT Trial Timeline



SJM has worked interactively with FDA during the pre-market approval (PMA) application review process. Key discussions and meetings include:

- In November 2012, SJM submitted the PMA application (May 2012 data lock).
- In February 2013, FDA issued a deficiency letter, which included, but was not limited to, requests for information on the following topics:
  - Clinical evaluations conducted at the time of the recurrent stroke events
  - Potentially relevant findings, including the status of the PFO, that could have been associated with the recurrent stroke
  - Statistical analyses including patient accountability and reasons for exclusion of patients for each analysis population
  - Reasons for medication non-compliance (e.g., costs, side effects) and efforts carried out to reduce the rate of non-compliance
  - Sensitivity analyses on Per-Protocol and As Treated populations related to the definition of medication compliance
  - Basis for selection of violations of inclusion/exclusion criteria that excluded patients from the Per-Protocol population
  - Testing used to assess exclusion of other potential causes of index stroke
  - Rationale for patients to withdraw from the trial, efforts undertaken to minimize patient withdrawals and the proportion of control patients who withdrew from the trial to pursue PFO closure outside of the trial
  - Reason for lack of divergence of Kaplan-Meier curves for time to primary endpoint in the intention to treat population until after 1 year

  - Request for updated data on new clinical events, particularly primary endpoint events
  - Current status of the PC Trial, another randomized controlled trial of the AMPLATZER PFO Occluder, conducted outside the U.S.
  - Clinical study report on the PFO ACCESS Registry
- In February 2014, SJM submitted a response to FDA's February 2013 letter.
- In April 2014, SJM filed a PMA amendment regarding a potential narrower indication for patients with atrial septal aneurysm (ASA, defined as excursion of the septum primum ≥10mm) or substantial (grade III) right-to-left shunt at rest or during Valsalva.
- In September 2014, FDA issued a deficiency letter, which included, but was not limited to, requests for information about the following topics:
  - Comprehensive review of the clinical literature to address the selection of the specified subgroup and proposed indications for use
  - Listing and narratives for suspected stroke or transient ischemic attack (TIA) events who underwent Clinical Events Committee (CEC) adjudication and were found not to fulfil criteria for primary endpoint events
  - Whether a core lab confirmed the metrics used for the definitions of shunt and ASA and test-to-test variability
  - Safety and effectiveness outcomes in the subgroup of patients excluded from the narrowed indication
  - Request for update on trial endpoint data
  - Potential narrower indication and subgroup identification was not pre-specified (FDA and SJM agreed not to pursue this)
- In February 2015, SJM met with FDA to define the pathway forward for the PMA.
- In September 2015, SJM submitted responses to the September 2014 questions, as well as a clinical study report which included extended follow-up results on the overall trial population (August 2015 data lock).
- In December 2015, SJM provided FDA with an individual patient-level meta-analysis publication on randomized controlled PFO occluder trials.

4.7 Proposed Indication for Use

St. Jude Medical is seeking Premarket Approval for the AMPLATZER PFO Occluder with the following proposed indication:

> *"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 a presumed paradoxical embolism."*

5 RESPECT TRIAL DESIGN

Summary

- RESPECT is a prospective, multicenter, randomized, event-driven, open-label trial with blinded endpoint adjudication.
- Patients were randomized 1:1 to the Device or Medical Management (MM) arm.
- The primary endpoint was a composite of fatal ischemic stroke, recurrent nonfatal stroke, and post-randomization death.
- Secondary endpoints were absence of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death; absence of TIA; and PFO closure assessment at 6 months. The secondary endpoints did not adjust for multiple testing and, thus, SJM considers the results to be exploratory.
- RESPECT was powered to detect a 75% relative risk reduction for the primary endpoint, which was an assumption based on observational data available at the time of the trial design. It was estimated that 25 primary endpoint events would provide 80% power for the assessment of the primary endpoint at the 2-sided 5% significance level.
- The primary analysis was a comparison of raw counts based on Fisher's exact test in the intention-to-treat (ITT) analysis population. A two-sided log-rank test was also pre-specified to address differential follow-up between arms. A supportive analysis was pre-specified in the Per-Protocol analysis population.
- All potential endpoint events were adjudicated by a blinded Clinical Events Committee.

5.1 Trial Design

RESPECT is a prospective, multicenter, randomized, event-driven, open-label trial with blinded adjudication of endpoints. RESPECT was designed to evaluate the safety and effectiveness of the AMPLATZER PFO Occluder.

RESPECT randomized patients in a 1:1 ratio to implant of the AMPLATZER PFO Occluder to close the PFO (Device arm) or to MM (i.e., one of the medical regimens allowed per protocol). Randomization was stratified by investigational site, presence of atrial septal aneurysm (defined as a total excursion of the septum primum ≥10mm), and the medical regimen assigned at randomization. Follow-up in the trial is at 1, 6, 12, 18, and 24 months, and annually thereafter.

At each investigational site, there was both a neurology and cardiology investigator. Prior to randomization, the neurology investigator assigned each patient to a protocol-approved medical regimen in the case that the patient was randomized to the MM arm. The protocol-approved choices for medical regimen were based on the ACCP treatment guidelines published in 2001, which outlined that optimal therapy for secondary stroke prevention in patients with PFO and prior cryptogenic stroke included antithrombotic (i.e., antiplatelet or anticoagulant) therapy (Alberts et al, 2001). The medical regimens allowed initially per protocol were: (a) aspirin alone; (b) warfarin alone; (c) clopidogrel alone; (d) aspirin combined with dipyridamole or clopidogrel.

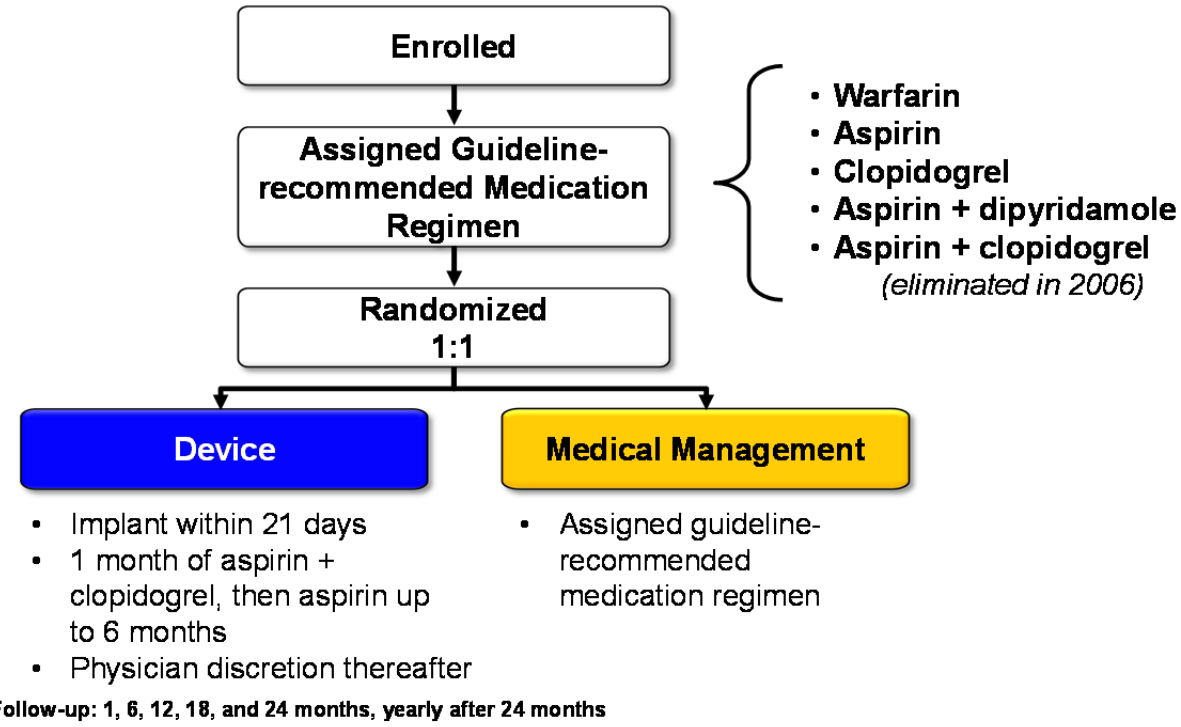
In 2006, the medical regimen of aspirin combined with clopidogrel was eliminated from the protocol based on the updated American Heart Association/American Stroke Association guidelines (Sacco et al, 2006).

For MM patients, physicians were allowed to change the medical regimen after randomization as long as it remained within the confines of the medical regimens specified in the protocol. Patients in the Device arm were to be implanted within 21 days of randomization, after which they were required to receive clopidogrel daily for 1 month and aspirin daily for 6 months. After 6 months, the medical regimen was at the investigator's discretion.

The primary results are based on a data lock date of May 2012, which included approximately 1,400 device patient-years of follow-up and a median of 2 years of follow-up per patient. Although enrollment has concluded, follow-up in the trial has been ongoing since the initial PMA submission, with an average of 5 years of follow-up per patient and over 5000 total patient-years of follow-up (2769 in the Device arm and 2376 in the MM arm). Follow-up will continue until a regulatory decision on the AMPLATZER PFO Occluder is reached. The primary results and results from extended follow-up form the basis for seeking approval of the AMPLATZER PFO Occluder for commercial use in the United States.

The primary results of the trial were published in the *New England Journal of Medicine* in March of 2013 (Carroll et al, 2013). A copy of the article is included in Appendix G.

Figure 4: RESPECT Trial Design



5.2 Trial Objective

The objective of the trial is to investigate whether percutaneous PFO closure is superior to standard of care medical treatment in the prevention of recurrent ischemic stroke.

5.3 Trial Oversight

Several committees were utilized for trial governance and to review and adjudicate endpoint and safety data:

- A Steering Committee was the governance board throughout the duration of the trial. Its role was to provide input into trial design and oversee execution, ensure overall trial integrity, answer questions regarding medical practice standards of care, address patient-related or clinical issues, interact with trial investigators, regulatory agencies, and other stakeholders, provide guidance on data analysis and interpretation, and oversee the dissemination of results through publications and presentations.
- An independent Data Safety Monitoring Board (DSMB) adjudicated all reported adverse events for seriousness and relatedness, and reviewed study progress with regard to safety and interim analyses.
- An independent Clinical Events Committee (CEC), which was blinded to randomization assignment and treatment, adjudicated potential neurologic events and deaths to determine whether the event met primary and secondary endpoint definitions. The committee consisted of a neurologist, a cardiologist and a neuroradiologist.
- An independent Echocardiography Core Laboratory adjudicated PFO closure status at 6 months for Device patients who received a device.
- Upon completion of the primary endpoint analysis, an ASCOD adjudication committee was formed in order to determine the mechanisms of recurrent strokes. This committee consisted of the two neurologists from the Steering Committee and the neuroradiologist from the CEC.

Appendix A outlines the membership of the above committees.

5.4 Trial Endpoints and Statistical Methodology

5.4.1 Primary Endpoint

The primary endpoint of the trial was a composite of:

- **Fatal ischemic stroke**
- **Recurrent nonfatal stroke:** defined as acute focal neurological 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 imaging findings of a new, neuroanatomically relevant, cerebral infarct
- **Post-randomization death:** defined in the MM arm as all-cause mortality within 45 days after randomization, and in the Device arm as all-cause mortality 30 days after implant or 45 days after randomization, whichever occurs last

The primary trial hypothesis was to demonstrate a significant relative risk reduction for the primary endpoint in Device patients compared to MM patients.

5.4.2 Secondary Endpoints

Secondary endpoints included the following:

- Absence of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death
- Absence of transient ischemic attack (TIA)
- PFO closure assessment: Complete closure of the defect demonstrated by TEE and bubble study at the 6-month follow-up and adjudicated by the Echocardiography Core Laboratory for the Device arm. Complete closure is defined as an absence of microbubbles in the left atrium at rest and during Valsalva within 3 cardiac cycles after right atrial opacification.

The secondary endpoints did not adjust for multiple testing and, thus, SJM considers the results to be exploratory.

5.4.3 Sample Size Determination

RESPECT was designed as an event-driven trial. At the time of the trial design, it was assumed that the AMPLATZER PFO Occluder would demonstrate a 75% relative risk reduction compared to MM in the rate of primary endpoint events. This assumption was derived from the event rates in the published literature on observational studies:

- In patients treated with medical therapy, the 2-year rate of stroke or death was estimated as 4.3% (Bogousslavsky et al, 1996; DeCastro et al, 2000; Mas et al, 1995).
- In patients receiving the AMPLATZER PFO Occluder or other PFO closure devices, the 2-year rate of stroke or death was estimated as 1.05% by averaging across results in the published literature (Beitzke et al, 2002; Brandt et al, 2002; Butera et al, 2001; Martin et al, 2002; Onorato et al, 2003; Sievert et al, 2001).

It was determined that 25 primary endpoint events would provide at least 80% power at the two-sided 5% significance level to detect a 75% relative risk reduction.

5.4.4 Statistical Analyses

Initially, the statistical analysis plan specified a comparison of the raw count of primary endpoint events in each of the arms using Fisher's exact test. This was based on an assumption that the distributions of follow-up time would be approximately equal in the two arms. Over the course of the trial, differential follow-up was observed between the two arms, with MM patients having a higher rate of withdrawal. In order to address differential follow-up, the analysis plan was revised prior to unblinding to reflect that the log-rank test would be used to evaluate the primary endpoint.

Cox proportional hazards models were used to estimate the hazard ratio for primary endpoint events between the Device and MM arms. Accounting for patient follow-up does not eliminate

bias due to patient drop-out; therefore, sensitivity analyses were conducted to understand the impact of drop-out on the primary endpoint analysis results.

Enrollment in RESPECT continued until 25 primary endpoint events were observed. The database was locked for analysis in May 2012 for the PMA submission.

5.4.5 Analysis Populations

Two analysis populations were specified in the protocol: the intention-to-treat (ITT) population and the supportive Per-Protocol population, described below:

- **ITT Population:** This population includes all randomized patients. Patients are analyzed according to their randomized treatment, regardless of whether or not they received the assigned treatment. The analysis compares patients based on the randomized assignment.
- **Per-Protocol Population:** This population includes only patients who adhered to all significant clinical trial protocol requirements. This population therefore excludes patients from analysis who violated key eligibility criteria, did not ultimately receive the therapy to which they were randomized, or did not comply with one of the protocol required medical regimens. This analysis compares patients based on the randomized assignment but who adhered to all significant protocol requirements. The RESPECT Steering Committee defined non-compliance to medical regimen as a compliance level less than 67%, which was based on optimal time in therapeutic range for oral anticoagulant therapy. Compliance was measured by calculating the proportion of total follow-up duration in which the patient was compliant to any one of the protocol-defined medical regimens.

Exploratory analyses have also been conducted on two additional patient populations, As Treated (AT) and Device in Place (DIP).

- **AT Population:** This population includes patients who received a protocol-specified treatment regardless of how they were randomized. Therefore, patients randomized to the Device arm, who refused a device but were >67% compliant with a protocol-specified medical regimen are included in the analysis. The analysis compares patients based on actual protocol treatment received.
- **DIP Population:** This population includes all randomized patients. The analysis compares patients based on device implanted and in place at the time of the primary endpoint event, regardless of adherence to the protocol.

See Table 33 and Table 34 in Appendix D for details on the analysis for each population and Table 35 for patient accountability and Table 36 for reconciliation of events in each of the analysis populations.

5.5 Inclusion/Exclusion Criteria

Patients 18 to 60 years of age with a PFO who had experienced a cryptogenic ischemic stroke (i.e., stroke from an undetermined mechanism) within the last 270 days were eligible for the trial.

- Ischemic stroke was defined by the protocol 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 imaging findings of a new, neuroanatomically relevant, cerebral infarct.
- PFO was defined as visualization of microbubbles per transesophageal echocardiogram (TEE) in the left atrium within 3 cardiac cycles from the right atrial opacification at rest and/or during Valsalva release. Patients that had a transient ischemic attack (TIA) without evidence of a stroke were not included in the trial.

Confirmation of cryptogenic stroke at the time of patient enrollment was based on a rigorous set of exclusion criteria to rule out known mechanisms of stroke, which is further detailed in Section 5.6. Other key exclusion criteria included other sources of right-to-left shunt, signs of progressive neurological dysfunction, positive test for arterial hypercoagulability, contraindication to aspirin or clopidogrel, and inability to discontinue anticoagulants.

The complete list of inclusion and exclusion criteria is included in Appendix B.

5.6 Confirmation of Qualifying Cryptogenic Stroke

RESPECT's exclusion criteria were designed to be rigorous in order to rule out patients with known mechanisms of stroke that could not be related to a PFO. Prior to enrollment, patients had a standardized evaluation for stroke etiology, and must not have had an identified mechanism of stroke. The diagnosis of a cryptogenic stroke was typically established by the trial neurologist prior to screening potential patients for the trial. However, if the protocol-required full evaluation had not been completed at the time of the qualifying stroke, the remaining tests could be performed after obtaining informed consent. The required testing was embedded in the trial entry criteria, which is consistent with current national guidelines (Latchaw et al, 2009). The evaluations assessed co-morbidities and medications that could be a likely mechanism for ischemic stroke. The trial neurologist evaluated the results of the baseline tests and assessments, including those conducted at the time of the index stroke, to confirm that the qualifying event was a cryptogenic stroke.

Table 1 outlines the tests and assessments required to rule out known mechanisms for the index stroke.

Table 1: Assessments Required to Exclude a Stroke of Known Mechanism

Protocol-required Baseline Test/Assessment	Ruling out Potential Cause of Stroke	Exclusion Criteria
MRI or CT	Small vessel disease	Lacunar infarct probably due to intrinsic small vessel as qualifying event
Transesophageal echocardography	• Atherosclerosis (aortic arch atheroma) • Cardiac pathology	• Intracardiac thrombus or tumor • Mitral or aortic valve stenosis • Left ventricular aneurysm or akinesis • Left ventricular dilated cardiomyopathy with LVEF <35%

Protocol-required Baseline Test/Assessment	Ruling out Potential Cause of Stroke	Exclusion Criteria
		• Mitral or aortic valve vegetation or prosthesis • Active endocarditis • Aortic arch plaques protruding >4mm into the lumen • Other source of right to left shunt identified at baseline
ECG or Holter study	Cardiac pathology	• Atrial fibrillation or atrial flutter • Myocardial infarction within 6 months
Intra and extracranial artery imaging: MRA, CT angiography, Contrast angiography, or TCD	Atherosclerosis	• Atherosclerosis or other arteriopathy >50% of lumen diameter supplying the involved vessel • Arterial dissection
Coagulation parameters (arterial)	Other causes of stroke, e.g., Systemic Lupus Antiphospholipid antibody syndrome	Positive test for 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
Physical Exam and Medical History Review	Atherosclerosis, Cardiac pathology, Other causes of stroke	• Malignancy or life expectancy <2 years • Pregnant or desire to become pregnant within 1 year • Uncontrolled hypertension or uncontrolled diabetes • Organ failure (kidney, liver, and lung) • Signs of progressive neurological dysfunction

5.7 Ascertainment and Adjudication of the Etiology of Neurologic Events

5.7.1 Event Ascertainment

To minimize ascertainment bias, a wide net was cast to capture all potential neurologic events post-randomization. Neurologic events were captured via the following triggers:

- At unscheduled clinic visits, patients were educated about the symptoms of stroke and instructed to call trial personnel if any of these symptoms occurred. In the event that such symptoms occurred, patients were brought in for an evaluation either in the outpatient clinic or the emergency department.
- Patients were asked at every scheduled follow-up visit if they had been hospitalized for any reason.
- Site personnel administered the structured Neurologic Symptoms General Interview form at every scheduled follow-up visit. This form was developed based on the Asymptomatic Carotid Atherosclerosis Study (ACAS) TIA/stroke methodology (Lefkowitz et al, 1992). This instrument has been validated in randomized trials and

epidemiologic studies as a sensitive measure for stroke detection. The interview asks patients about the occurrence of symptoms in any of 6 major domains, including weakness, dizziness, or problems with speaking, vision, or sensation. If new stroke or TIA symptoms were identified, the Neurologic Symptoms Detailed Interview, and the Neurologic Endpoint Assessment & Diagnosis form were also completed by the investigator. Copies of these forms can be found in Appendix C.

5.7.2 Recurrent Stroke Etiology Adjudication

For events adjudicated by the CEC as meeting the definition of a primary endpoint stroke event, the etiology was further classified according to the TOAST classification system (Adams et al, 1993). This system classifies strokes as one of the following:

- large-artery atherosclerosis
- cardioembolism
- small-vessel occlusion
- stroke of other determined etiology, and
- stroke of undetermined etiology

The TOAST classification system was used to assess the secondary endpoint of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death. Determination of whether a stroke was cryptogenic was based on the TOAST system.

6 RESPECT TRIAL RESULTS

Summary

- The RESPECT trial population consisted of young to middle-aged, otherwise healthy cryptogenic stroke survivors, with a mean age of approximately 46 years.
- The trial took four times as long as anticipated to enroll, and withdrawal rates were correspondingly greater than anticipated.
- At the time of the primary assessment, there was a higher rate of patient discontinuation in the MM arm than in the Device arm (17.5% vs. 10.0%). Patients who discontinued from the trial tended to have baseline characteristics that were higher risk for stroke, such as smoking and history of recurrent stroke.
- The implant success rate for the AMPLATZER PFO Occluder was 99.6% and the median procedure duration was well under an hour.
- More than 80% of Device patients were on a single antiplatelet therapy at 2 years. Less than 2% of Device patients and ~18% of MM patients were on warfarin at 2 years.
- All 25 primary endpoint events were recurrent ischemic strokes. The primary endpoint was not met in both the ITT raw count and log-rank analyses. The raw count analysis showed an odds ratio of 0.534 favoring the device (Fisher's Exact p = 0.157) and the ITT log-rank analysis showed a 50% relative risk reduction for recurrent ischemic stroke with the device (HR: 0.50; 95% CI: 0.22, 1.13; log-rank two-sided p = 0.089).
- In the pre-specified supportive Per-Protocol analysis, there was a statistically significant 63% relative risk reduction for recurrent ischemic stroke in the Device arm (HR: 0.37; 95% CI: 0.14, 0.97; p = 0.03). Exploratory analyses demonstrated that the results are robust to missing follow-up, even under very conservative assumptions.
- Exploratory AT and DIP analyses were supportive of the effectiveness of the device (70-72% relative risk reduction for recurrent ischemic stroke).
- One of the key assumptions of the primary endpoint was that the preponderance of recurrent ischemic strokes would be due to an undetermined mechanism that could be prevented by PFO closure. This assumption proved true during the primary assessment as 19 of the 25 primary endpoint events (76%) were of undetermined mechanism.
- With extended follow-up, aging of the patient population led to greater exposure for strokes of a known mechanism that cannot be prevented by PFO closure; only 3 of 9 recurrent strokes (33%) in the Device arm during extended follow-up were of an undetermined mechanism compared to 7 of 8 recurrent strokes (88%) in the MM arm. The breakdown of this key trial assumption during extended follow-up diminished the treatment effect for recurrent ischemic stroke overall. Therefore, blinded adjudication of stroke mechanism was required to evaluate device effectiveness in extended follow-up.
- Post-hoc analysis of extended follow-up data with blinded adjudication of stroke mechanism showed a significant relative risk reduction of 54% (HR: 0.46; 95% CI: 0.21, 0.99; nominal p = 0.042) in recurrent ischemic strokes of undetermined mechanism in the ITT population.

6.1 Demographics and Baseline Characteristics

The RESPECT trial population consisted of young to middle-aged cryptogenic stroke survivors (mean age ~46 years). Most of the patients were otherwise healthy and had minimal co-morbidities (Table 2 through Table 4). The prevalence of traditional vascular risk factors for stroke was similar to the general U.S. population (Fonarow et al, 2010). The most frequently observed risk factors for atherosclerotic vascular disease in the RESPECT population were hypercholesterolemia (39.9%), family history of ischemic heart disease (32.4%), and hypertension (31.9%). The proportion of patients with hypercholesterolemia and hypertension in the RESPECT population is consistent with that reported in the general U.S. population.[1] The rate of serious cardiac, respiratory, and vascular conditions was very low. A history of deep vein thrombosis (DVT) was present in 3-4% of patients. Approximately 10% of patients experienced a stroke prior to the qualifying cryptogenic stroke and more than one-third of the patients had self-reported medical history of migraine.

Table 2: Demographics and Baseline Characteristics

Variable	Mean ± SD or n (%)	
	Device (N=499)	Medical Management (N=481)
Age, years	45.7 ± 9.7	46.2 ± 10.0
Time from qualifying stroke to randomization, days	130 ± 70	130 ± 69
Sex, male	268 (53.7%)	268 (55.7%)

Table 3: Medical History

Medical History	n (%)	
	Device (N=499)	Medical Management (N=481)
Chronic obstructive pulmonary disorder	4 (0.8%)	7 (1.5%)
Congestive heart failure	3 (0.6%)	0 (0.0%)
Coronary artery disease	19 (3.8%)	9 (1.9%)
Deep vein thrombosis	20 (4.0%)	15 (3.1%)
Migraine	195 (39.1%)	186 (38.7%)
Peripheral vascular disease	5 (1.0%)	1 (0.2%)
Previous myocardial infarction	5 (1.0%)	2 (0.4%)
Previous transient ischemic attack	58 (11.6%)	61 (12.7%)
Stroke prior to qualifying cryptogenic stroke	53 (10.6%)	51 (10.6%)

[1] http://www.cdc.gov/cholesterol/facts.htm; http://www.cdc.gov/nchs/products/databriefs/db133.htm (accessed 20April 2016)

Table 4: Risk Factors for Stroke

Risk Factor	n (%)	
	Device (N=499)	Medical Management (N=481)
Birth control/hormone replacement therapy	41 (8.2%)	51 (10.6%)
Current smoker	75 (15.0%)	55 (11.4%)
Diabetes mellitus	33 (6.6%)	41 (8.5%)
Family history of ischemic heart disease	161 (32.6%)	157 (32.7%)
Family history of stroke	136 (27.5%)	109 (22.7%)
Former smoker	134 (26.9%)	143 (29.7%)
Hypercholesterolemia	196 (39.3%)	195 (40.5%)
Hypertension	160 (32.1%)	153 (31.8%)
Other risk factor[1]	37 (8.1%)	40 (9.0%)

[1]The most frequent "other" risk factors include dyslipidemia/hyperlipidemia, sleep apnea, and obesity.

Table 5 summarizes the baseline antithrombotic medication patients were taking prior to randomization in the trial. Approximately 28% of patients were taking an anticoagulant at baseline.

Table 5: Baseline Antithrombotic Medications Category

Medication Category	n (%)	
	Device (N=499)	Medical Management (N=481)
Single antiplatelet therapy	282 (56.5%)	270 (56.4%)
Dual antiplatelet therapy	72 (14.4%)	71 (14.8%)
Anticoagulant (with or without antiplatelet therapy)	144 (28.9%)	135 (28.1%)
Other [1]	1 (0.2%)	3 (0.6%)
None	0 (0.0%)	2 (0.4%)

[1]Includes, but is not limited to, novel anticoagulant medications.

Table 6 summarizes the maximal shunt grade assessed at rest or at Valsalva. Nearly half of the patients had a maximal shunt of grade III. Atrial septal aneurysm (ASA), defined as movement of the septum primum of at least 10 mm relative to the plane of the interatrial septum, was present in a little more than one-third of patients in both the Device and MM arms, which is higher than the prevalence of 12% in the general PFO population (Di Tuillo et al, 2013).

Table 6: Maximal Shunt and Atrial Septal Aneurysm Assessment per Site Investigator TEE Assessment

Variable	n (%)	
	Device (N=499)	Medical Management (N=481)
Maximal shunt grade[1]		
Grade I	108 (21.6%)	114 (23.7%)
Grade II	138 (27.7%)	121 (25.2%)
Grade III	247 (49.5%)	231 (48.0%)
Not assessed	5 (1.0%)	6 (1.2%)
Atrial septal aneurysm[2]	180 (36.1%)	170 (35.3%)

[1] Determined as the most severe grade between assessments at rest and at Valsalva.
[2] Defined as a total excursion of the septum primum ≥10mm relative to the plane of the interatrial septum.

Table 7 shows the proportion of patients in whom the qualifying stroke was confirmed by imaging versus based on symptoms alone. Although all patients underwent CT or MR imaging at the time of the stroke, approximately 90% of patients had the qualifying stroke confirmed by imaging. The remaining 10% of patients had stroke confirmed by symptoms alone (≥ 24 hours).

Table 7: Qualifying Stroke Confirmation by Site Investigator

Visualized baseline infarct (on MR/CT) related to qualifying stroke	n (%)	
	Device (N=499)	Medication Management (N=481)
Yes	447 (89.6%)	451 (93.8%)
No (stroke confirmed by symptoms alone)	52 (10.4%)	30 (6.2%)

6.2 Patient Disposition

Between August 2003 and December 2011, 980 patients were randomized, 499 to the Device arm and 481 to the MM arm at 69 investigational sites: 925 patients were enrolled at 62 sites in the US and 55 patients were enrolled at 7 Canadian sites. Enrollment in RESPECT took 8 years, which was four times as long as anticipated, therefore, the rates of withdrawal were correspondingly higher than anticipated, as well. Table 8 shows a higher rate of discontinuation of patients who did not experience a primary endpoint event in the MM arm than in the Device arm (17.5% vs. 10.0%). The difference in discontinuation rates between the two arms is driven primarily by patient withdrawal of consent (10.4% vs. 4.6%). Most patients in the MM arm withdrew consent because they were unhappy with their randomization assignment or stated that they intended to seek PFO closure outside the trial.

Table 8: Patient Disposition

	Device (N=499)	Medical Management (N=481)
Discontinued	50 (10.0%)	84 (17.5%)
Withdrawal of consent	23 (4.6%)	50 (10.4%)
Lost to Follow-up	21 (4.2%)	27 (5.6%)
Other	6 (1.2%)	7 (1.5%)

[1] Disposition is shown only for patients who did not experience a primary endpoint event

6.3 Patient Follow-up

6.3.1 Duration of Follow-up

At the primary assessment in May of 2012, the median patient follow-up duration was 2.9 years in the Device arm and 2.1 years in the MM arm. The total accumulated follow-up in the Device and MM arms were 1,476 patient-years and 1,284 patient-years, respectively (Table 9). The Device arm had fewer patient-years of follow-up missing than the MM arm: 90 patient-years (5.7%) versus 321 (20%) patient-years. As previously noted, the difference in missing patient follow-up is driven primarily by MM patients withdrawing consent because they were unhappy with their randomization assignment or stating that they intended to seek PFO closure outside the trial. Section 6.5.3 presents sensitivity analyses to evaluate the impact of missing data on outcomes.

Table 9: Patient Follow-up

Follow-up	Device (N=499)	Medical Management (N=481)
Mean (years)	3.0	2.7
Median (years)	2.9	2.1
Total (patient-years)	1,476	1,284
Missing (patient-years)[1]	165 (10%)	313 (20%)

[1] Assumes all discontinued patients would be followed through data lock at primary assessment

6.3.2 Patient Discontinuation

During the early trial enrollment period, SJM implemented a number of measures to reduce patient withdrawal:

- Revised the protocol to allow for telephone follow-up visits starting at 3 years post-randomization
- Provided patient reimbursement for travel expenses related to trial visits
- Allowed transfer of patients between investigational sites for patients who moved, and
- Provided devices at no charge

Demographic and baseline characteristics of patients who discontinued from the trial had few statistically significant differences (at the 10% significance level) compared to those who remained in the trial (Table 37 in Appendix D), with the exception that patients who discontinued tended to have baseline characteristics that were higher risk for stroke than continuing patients, such as current smoker (at baseline) (18% vs. 12%, p = 0.067), history of recurrent stroke (16% vs. 10%, p = 0.023), and former smoker (34% vs. 27%, p = 0.097).

6.4 Medical Regimen and Procedural Data

6.4.1 Assigned Medical Regimens at Randomization

As noted earlier, prior to randomization, investigators indicated which guideline-recommended medication regimen each patient would receive if he or she were randomized to the medical management arm. Table 10 summarizes the assigned medical regimens at randomization for the Device and MM arms. Aspirin alone was the most commonly assigned regimen followed by warfarin alone. Aspirin with clopidogrel was the least commonly assigned regimen as it was removed from the protocol in 2006 following a change to national guidelines.

Table 10: Assigned Medical Regimen at Randomization

Assigned Medical Regimen at Randomization	Device (N=499)	Medical Management (N=481)
Aspirin alone	248 (49.7%)	224 (46.6%)
Warfarin alone	132 (26.5%)	121 (25.2%)
Clopidogrel alone	58 (11.6%)	67 (13.9%)
Aspirin and dipyridamole	27 (5.4%)	39 (8.1%)
Aspirin and clopidogrel[1]	34 (6.8%)	30 (6.2%)

[1] In 2006, aspirin and clopidogrel combination was removed from the protocol as a medical regimen option.

6.4.2 Procedural Success and Procedure Characteristics

Of the 499 patients randomized to the Device arm, 467 patients underwent an implant attempt with the AMPLATZER PFO Occluder and 463 (99.1%) patients were successfully implanted in a first procedure (Table 11). Among the four patients who did not have a successful implant in the first procedure, two had a successful implant in a second procedure Seventeen (17) patients declined to undergo the implant. In another 15 patients, an intra-procedural exclusion was noted (such as fenestrated septum, arteriovenous malformation, or no PFO).

Table 11: Procedural Success

Randomized to Device Arm (ITT)	**N = 499**
No attempt to implant (patient decision)	17
Intra-procedural exclusion (device not introduced)	15
Device implant attempted[1]	**N = 467**
Failure to implant	2
Successful implant	465 (99.6%)
In first procedure	463 (99.1%)
In second procedure[2]	2 (0.4%)

[1] An implant attempt occurs when the AMPLATZER PFO Occluder is introduced into the body.

[2] Two patients underwent successful implant in a second procedure:

- In one patient, a right atrial thrombus was noted during the procedure. The procedure was abandoned and the patient was treated with anticoagulant. The patient had a successful implant in a second procedure one month later.
- In one patient, a cardiac perforation occurred during the procedure that did not require intervention. The procedure was abandoned. The patient had a successful implant in a second procedure three months later.

Table 12 summarizes the procedural characteristics in the 467 Device patients who underwent an attempted implant of the AMPLATZER PFO Occluder. The median time from randomization to procedure was 14 days. The median procedure duration, defined as time from the first catheter in to the last catheter out, was under an hour (44 minutes). More than three-quarters of patients (78.9%) received a 25 mm device.

Table 12: Procedural Characteristics

Procedural Characteristics	**Device Patients Who Underwent Attempted Procedure (N=467)**
Time from randomization to procedure (days), median [IQR]	14 [9, 19]
Procedure Time (min), median [IQR]	44 [33, 65]
Fluoroscopy Time (min), median [IQR]	9.6 [6.8, 14.4]
Device size (among successfully implanted patients), n/N (%)	
18 mm	39/465 (8.4%)
25 mm	367/465 (78.9%)
35 mm	59/465 (12.7%)

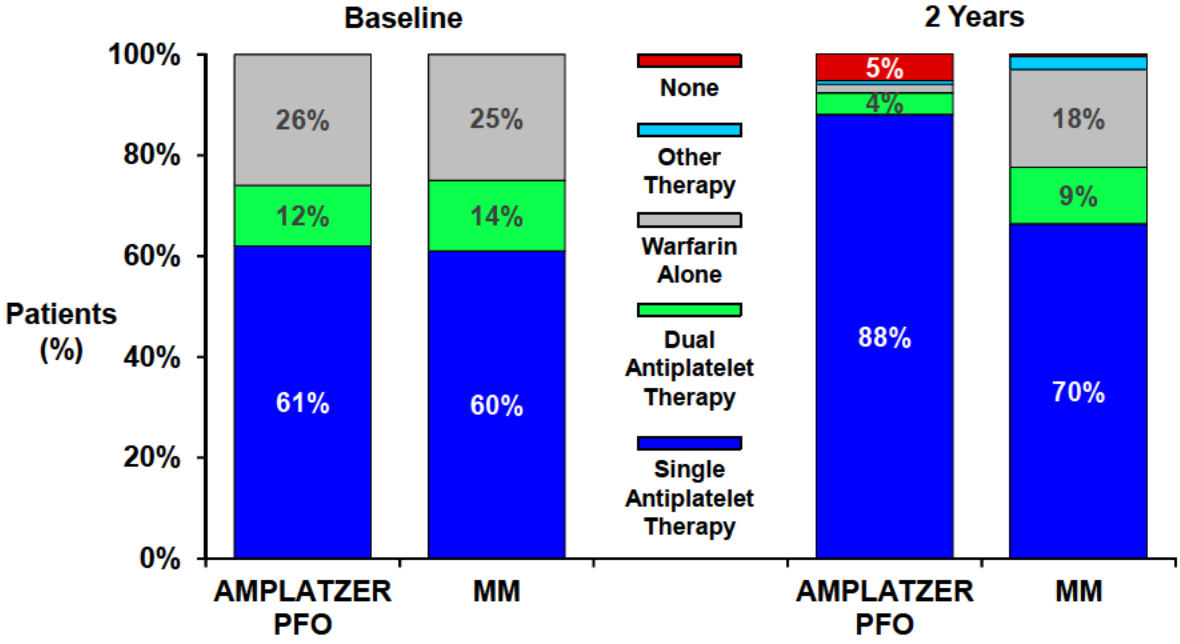
6.4.3 Medications Assigned at Baseline and Medications Taken at 2-Year Follow-up

Figure 5 shows the proportion of patients taking one of the protocol-specified medication regimens in the Device and MM arms at baseline and 2 years in the following categories:

- single antiplatelet therapy (aspirin alone or clopidogrel alone)
- dual antiplatelet therapy (aspirin + clopidogrel or aspirin + dipyridamole)
- warfarin alone
- other medications (in most cases, aspirin + warfarin)
- none

Approximately 25% of patients in both arms were assigned to anticoagulant therapy at baseline. At 2 years, more than 80% of Device patients were on a single antiplatelet therapy at 2 years, shown in blue. Less than 2% of Device patients and approximately 18% of MM patients were on warfarin at 2 years, shown in gray (i.e., more than a 9-fold difference between arms in use of warfarin).

Figure 5: Medications Assigned at Baseline and Medications Taken at 2 Years



6.5 Effectiveness Results

6.5.1 Primary Effectiveness Endpoint Results – ITT Population

The ITT population consists of all 980 patients (499 in Device arm and 481 in MM arm) randomized regardless of treatment received.

Trial enrollment was stopped in Dec 2011 when 25 unique patients were adjudicated by the CEC as having experienced a primary endpoint event. All 25 primary endpoint events were recurrent nonfatal ischemic strokes.

Stroke or TIA symptoms were reported either on a Neurologic Symptoms General Interview form developed from the ACAS TIA/stroke methodology or an Adverse Event case report form. Each event was submitted to the CEC for adjudication as a primary or secondary neurologic endpoint event. This method of ascertainment cast a wide net to capture all potential neurologic events post-randomization, and resulted in a total of 231 events in 139 Device patients, and 245 events in 143 MM patients submitted to the blinded CEC for adjudication, as shown in Table 13. The overall rate of events submitted to the CEC for adjudication were 15.7 and 19.1 per 100 patient-years in the Device and MM arms, respectively. Of the events submitted to the CEC for adjudication, 9 Device patients (10 events) and 16 MM patients (17 events) were adjudicated as meeting the primary endpoint definition of recurrent ischemic stroke. Approximately 3.5% of events were adjudicated as TIA in each arm. Leading other causes of events were dizziness, migraine and numbness in both arms.

Table 13: Neurologic Events Submitted to CEC and Adjudicated as Primary Endpoint Event

	# events (# patients) (rate per 100 pt-yrs[1])	
	Device (N=499, 1476 pt-yrs)	**Medical Management (N=481, 1284 pt-yrs)**
Neurologic events submitted to CEC	231 (139) (15.7 per 100 pt-yrs)[1]	245 (143) (19.1 per 100 pt-yrs)[1]
Adjudicated as primary endpoint event (recurrent ischemic stroke)	10 (9) (0.68 per 100 pt-yrs)[1]	17 (16) (1.32 per 100 pt-yrs)[1]
	n (%)	
Leading other causes of events	TIA: 8 (3.5%) Dizziness: 32 (13.9%) Migraine: 32 (13.9%) Numbness: 29 (12.6%)	TIA: 9 (3.7%) Dizziness: 28 (11.4%) Migraine: 29 (11.8%) Numbness: 34 (13.9%)

[1] Event rates include multiple events within a patient

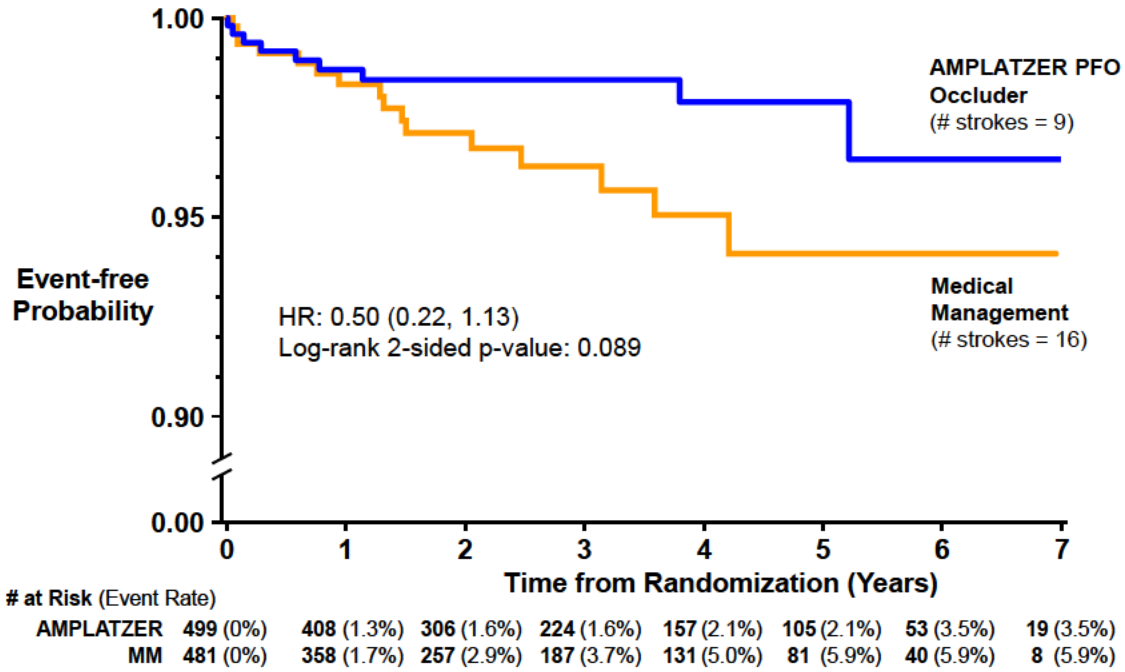
The primary endpoint was not met in either the ITT raw count or log-rank analyses (Table 14). The odds ratio for the raw count analysis was 0.534 (Fisher's Exact p = 0.157).

Table 14: Primary Endpoint - ITT Raw Count Analysis

Patients Total N (N_{Device}/N_{MM})	Events Total n (n_{Device}/n_{MM})	Odds Ratio (Device vs MM) (95% CI)	p-value (Fisher's Exact test)
980 (499/481)	25 (9/16)	0.534 (0.234, 1.220)	0.157

The ITT analysis did not reach the threshold for statistical significance (log-rank two-sided p = 0.089). The Cox proportional hazards model showed a 50% relative risk reduction (HR: 0.50; 95% CI: 0.22, 1.13). Separation between the curves begins around 1.5 years (Figure 6). Although the curves do not separate early, the event rate estimates in the Device and MM arms at year 2 are 1.6% and 2.9%, respectively. At year 5, the estimates are 2.1% and 5.9%, respectively. Importantly, three of the nine strokes in the Device arm occurred without a device implanted at the time of the stroke. Detailed narratives of the primary endpoint stroke events are provided in Appendix E.

Figure 6: Kaplan-Meier Freedom from Primary Endpoint Event, ITT Population – Primary Assessment



Recurrent nonfatal ischemic stroke characteristics

All primary endpoint events had CT or MR imaging performed as part of the recurrent stroke evaluation. Table 15 summarizes the clinical and imaging characteristics of the recurrent nonfatal ischemic strokes that occurred during follow-up in the Device and MM arms.

Stroke was confirmed by imaging in 23 patients (8 Device and 15 MM). Importantly, in the Device arm, 3 patients experienced a stroke without a device implanted at the time of the recurrent stroke. The number of strokes with medium or large lesion size was 7 (1.4%) in the Device arm and 15 (3.1%) in the MM arm. Of the 7 medium or large strokes occurring in the Device arm, 3 were in patients who did not have a device implanted at the time of the stroke. Superficial strokes occurred in 4 Device patients and 11 MM patients; 3 of the 4 Device patients who experienced superficial strokes did not have a device implanted at the time of the stroke.

The average age of patients at the time of recurrent stroke was 43.6 years in the Device arm compared to 50.1 years in the MM arm. Five of the 9 strokes in the Device arm and 10 of the 16 strokes in the MM arm occurred in males.

A variety of stroke symptoms were reported in both arms, ranging from speech impairment, blurring/loss of vision, double vision, numbness/tingling, paralysis or weakness, and dizziness/loss of balance. Symptoms lasted for at least 24 hours in 5 of the 9 strokes in the Device arm and 13 of the 16 strokes in the MM arm.

Residual disability was measured at follow-up by the modified Rankin Score at the nearest follow-up visit after the stroke. Across the two arms, in about a third of the patients who experienced a recurrent stroke, the stroke was severe enough to require assistance from others in activities of daily living. Neurological deficit was measured by the National Institute of Health Stroke Scale (NIHSS). The median NIHSS score was 2 (range 0 to 8) in the Device arm and 2 (range 0 to 23) in the MM arm.

Table 15: Clinical and Imaging Characteristics of Recurrent Nonfatal Ischemic Strokes

	Device (n=9)	Implanted Device Patients (n=6)	Medical Management (n=16)
Confirmation by imaging	8	5	15
Device implanted at the time of stroke	6/9	6/6	0/16
Longest lesion size (assessed by ASCOD Adjudication Committee)			
Small (0 to 1.5 cm)	2	2	1
Medium (1.6 to 5 cm)	4	2	7
Large (> 5 cm)	3	2	8
Location of infarct			
Deep	3	3	2
Superficial	4	1	11
Unknown/Missing	2	2	3
Age at the time of stroke (Average ± SD), years	43.6 ± 13.1	43.7 ± 9.4	50.1 ± 10.6
Sex			
Male	5	3	10
Female	4	3	6
Symptoms	(n=7)	(n=4)	(n=13)
Speech impairment	4	3	9
Blurring/loss of vision	1	1	6
Double vision	1	1	3
Numbness, tingling	4	3	8
Paralysis or weakness	5	3	9
Dizziness/loss of balance	3	2	6

	Device (n=9)	Implanted Device Patients (n=6)	Medical Management (n=16)
Length of symptoms			
< 24 hours	3	1	3
≥ 24 hours	5	4	13
Unknown	1	1	0
Disability measured by modified Rankin Score (mRS) at nearest follow-up visit after stroke			
Independent (mRS ≤ 2)	5	2	10
Not independent/died (mRS ≥ 3)	4	4	4
Not available (discontinued post-stroke)	0	0	2
NIH Stroke Scale			
Median (range) NIHSS score	2 (0 to 8)	2 (2 to 8)	2 (0 to 23)
Not available (discontinued post-stroke)	0	0	1
Death	0	0	1

Medication non-compliance at the time of the recurrent ischemic stroke

Of the 25 patients who experienced a recurrent stroke, two patients in the Device arm and six in the MM arm were non-compliant with protocol-recommended medication. Table 16 contains details on each of these 8 patients. The two patients in the Device arm who were non-compliant with a protocol-recommended medication regimen did not have a device implanted at the time of the stroke. These findings reflect real-world medication usage in the population for which this device is intended.

Table 16: Medication Non-Compliance at the Time of Recurrent Stroke

Patient Identifier	Arm	Details
b(6)	Device	Not implanted with device; not taking aspirin and clopidogrel at the time of recurrent stroke
b(6)	Device	Not implanted with device; not taking aspirin at the time of recurrent stroke
b(6)	MM	Was taking both aspirin and warfarin, a medication regimen not approved under the protocol, at the time of the recurrent stroke
b(6)	MM	Missed aspirin doses during week prior to recurrent stroke
b(6)	MM	Discontinued warfarin 11 days before the recurrent stroke due to a pelvic hematoma
b(6)	MM	Was not taking aspirin as prescribed for approximately 1 week prior to recurrent event

Patient Identifier	Arm	Details
b(6)	MM	Temporarily discontinued Aggrenox 1 day prior to the recurrent stroke for a dental procedure
b(6)	MM	Was not taking warfarin as prescribed for approximately 2 months prior to recurrent event

6.5.2 Primary Effectiveness Endpoint Results – Per-Protocol Population

As described in Section 5.4.5, the Per-Protocol population compares patients based on the randomized assignment but who adhered to all significant protocol requirements. The Per-Protocol population excluded patients who did not meet key inclusion/exclusion criteria, did not comply with their medical regimen, or did not receive the device if they were randomized to the Device arm. Thus, two of the three patients who experienced a stroke without a device in place are excluded from the Per-Protocol population. The Per-Protocol population was defined by the RESPECT Steering Committee before the data lock date, and without knowledge of the trial outcomes or treatment assignment of individual patients.

Of 499 patients randomized to the Device arm:

- 34 patients are excluded due to not having received a device – 2 of these patients experienced a primary endpoint stroke event.
- 1 patient was excluded due to an inclusion/exclusion violation (allergy to aspirin)
- 1 patient was excluded due to non-compliance to medication (patient remained on Clopidogrel rather than aspirin after 30 days - this patient experienced a primary endpoint stroke event)

The remaining 463 (= 499-34-1-1) patients are included in the Per-Protocol Device arm. Note that one patient who experienced a stroke and was subsequently implanted with a device is included in the Per-Protocol Device arm.

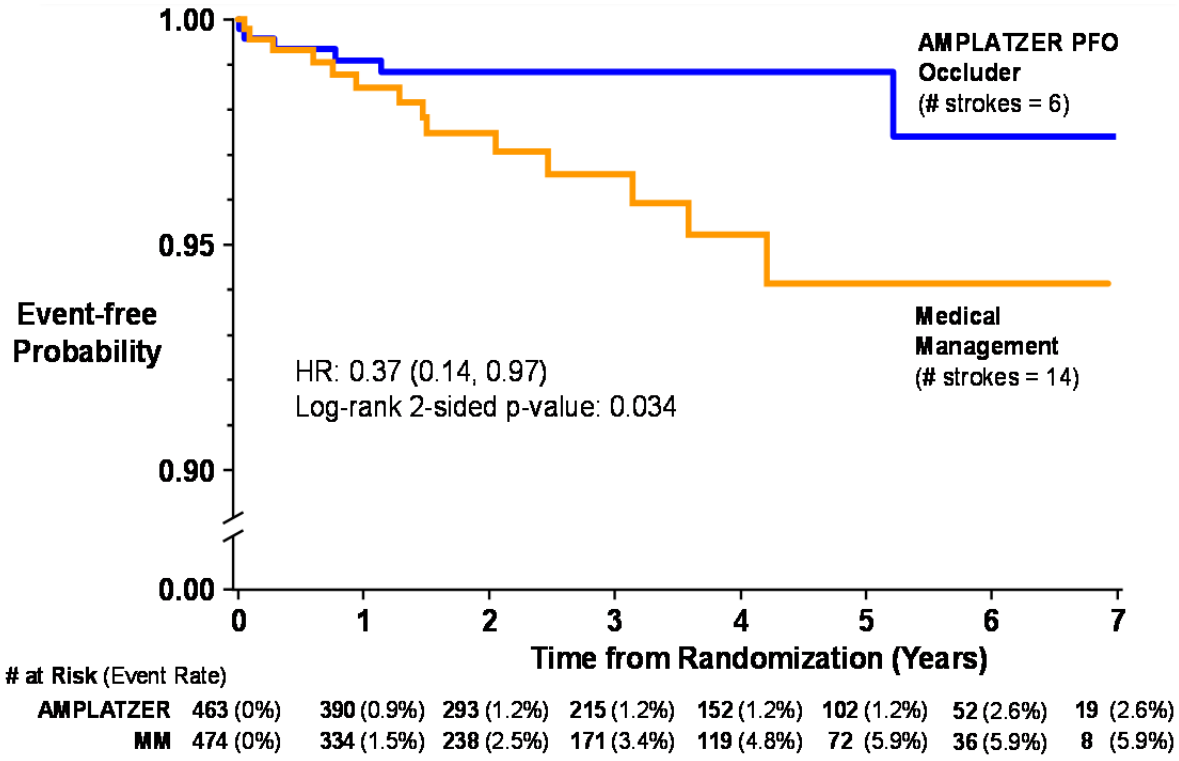
Of 481 patients randomized to the MM arm:

- 4 patients were excluded due to an inclusion/exclusion violation:
  - 3 patients were found not to have a PFO after randomization, and
  - 1 patient's infarct, which was thought to be due to a previous stroke, was determined to be a glioblastoma after the patient was randomized
- 3 patients were excluded due to non-compliance to medication (all 3 patients were on aspirin and clopidogrel, which was not permitted per protocol)

Two of the 7 patients excluded from the MM arm experienced a primary endpoint stroke event. The remaining 474 (= 481-4-3) patients are included in the MM arm of the Per-Protocol population.

The Kaplan-Meier freedom from first recurrent ischemic stroke curves for the Per-Protocol population are shown in Figure 7. The figure shows that the hazard ratio is 0.37 (95% CI 0.14, 0.97), representing a statistically significant relative risk reduction for stroke in the Device arm of 63% (p=0.034).

Figure 7: Kaplan-Meier Freedom from Recurrent Ischemic Stroke, Per-Protocol Population – Primary Assessment



Sensitivity Analyses to Address Missing Data for Per-Protocol Population (Post-Hoc)

As of the primary assessment, 34 Device patients and 83 MM patients in the Per-Protocol population discontinued from the trial without experiencing a primary endpoint event. A sensitivity analysis was conducted to assess the impact of discontinued patients on the Per-Protocol analysis results.

As noted earlier, 6 Device patients and 14 MM patients experienced a primary endpoint recurrent ischemic stroke event in the Per-Protocol population. Thus, the observed event rates in Device and MM arms were 0.42 and 1.19 per 100 patient-years, respectively. Missing follow-up in each of the Per-Protocol Device and MM arms that would have occurred through the cut-off date if patients had not discontinued from the trial were 90 and 321 patient-years, respectively.

A commonly accepted method to assess the impact of missing data is a tipping point analysis. This analysis determines how many events need to have occurred in the treatment (i.e., Device)

arm in order to "tip" the analysis from being statistically significant to statistically insignificant (i.e., $p > 0.05$). Therefore, we performed simulations that imputed for all missing follow-up as follows (Note: this analysis has not been reviewed by FDA):

- The event rate among those patients missing data in the MM arm is assumed to accrue at the same rate as that observed in the trial (1.19 events per 100 patient-years). This represents a favorable assumption given that patients who withdrew had a higher prevalence of stroke risk factors. With 321 additional patient-years of follow-up, we would expect 4 additional events (i.e., 1.19 events/patient-year × 321 patient years of missing data ÷ 100 = 3.82 events).
- Additional events were added to the Device arm until the p-value for the Per-Protocol analysis was no longer significant. Ultimately, 4 events needed to be added to the Device arm among patients with missing data, for a rate of 4.4 events per patient-year, to derive a p-value greater than 0.05. Specifically, 4.4 events/patient-year × 90 patient years of missing data ÷ 100 = 4 events.

With this in mind, the question is whether the additional events needed to "tip" the analysis is clinically plausible. Assuming a constant event rate in the MM arm, the required event rate among missing data in the Device arm to tip the Per-Protocol analysis to statistical insignificance (i.e., 4.4 events per 100 patient-years) equates to a rate that is more than **10 times as high** as that observed among Device patients with complete data in the trial. This assumption appears to be clinically unlikely, providing reasonable assurance of the findings in the Per-Protocol analysis.

6.5.3 Exploratory Analyses in Additional Patient Populations (As Treated and Device In Place)

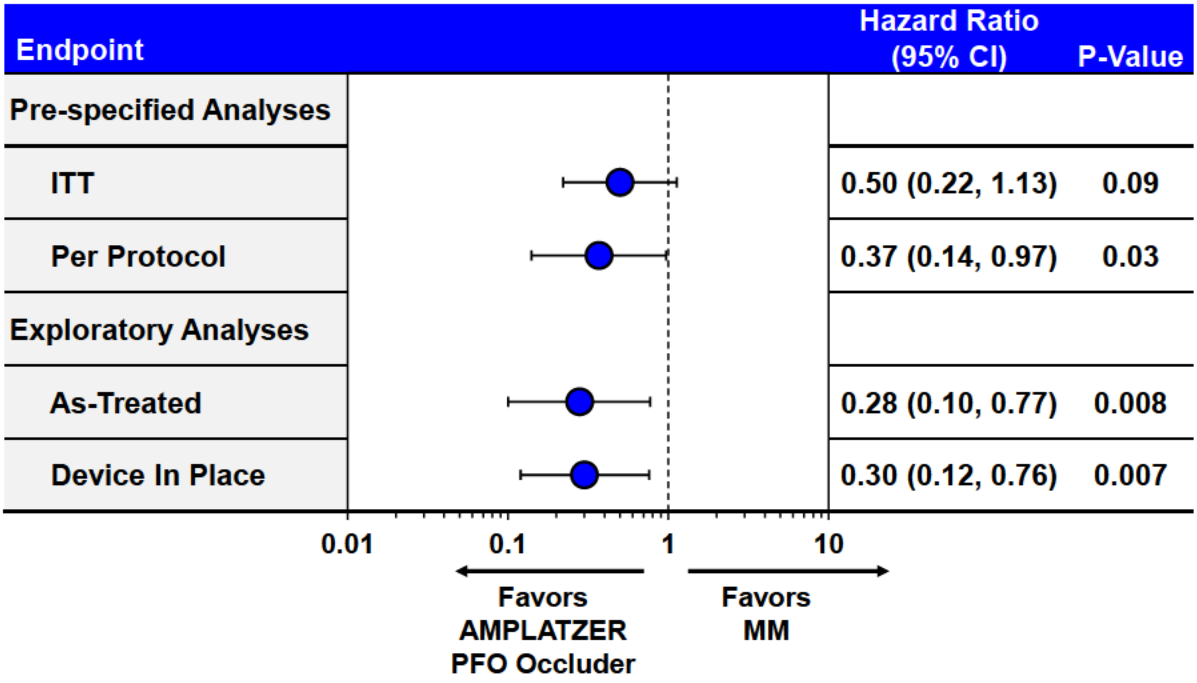
The AT and DIP populations have been previously described (Section 5.4.5). In summary, the AT population is intended to characterize device effectiveness based on actual protocol treatment received, and the DIP population is intended to characterize device effectiveness based on whether or not a device was in place, regardless of adherence to the protocol.

In the AT analysis, the device was shown to be effective in reducing the risk of recurrent ischemic stroke compared to protocol-recommended MM. The hazard ratio for a primary endpoint stroke for device vs MM is 0.28, representing a relative risk reduction for stroke of 72% with the device.

In the DIP analysis, the device was shown to be effective in reducing the risk of recurrent ischemic stroke compared to no device. The hazard ratio for a primary endpoint stroke for device vs MM is 0.30, representing a relative risk reduction for stroke of 70% with the device.

Figure 8 summarizes the results on each of analysis populations. In all analyses populations, there is a relative risk reduction for recurrent ischemic stroke with the device.

Figure 8: Forest Plot for Each Analysis Population



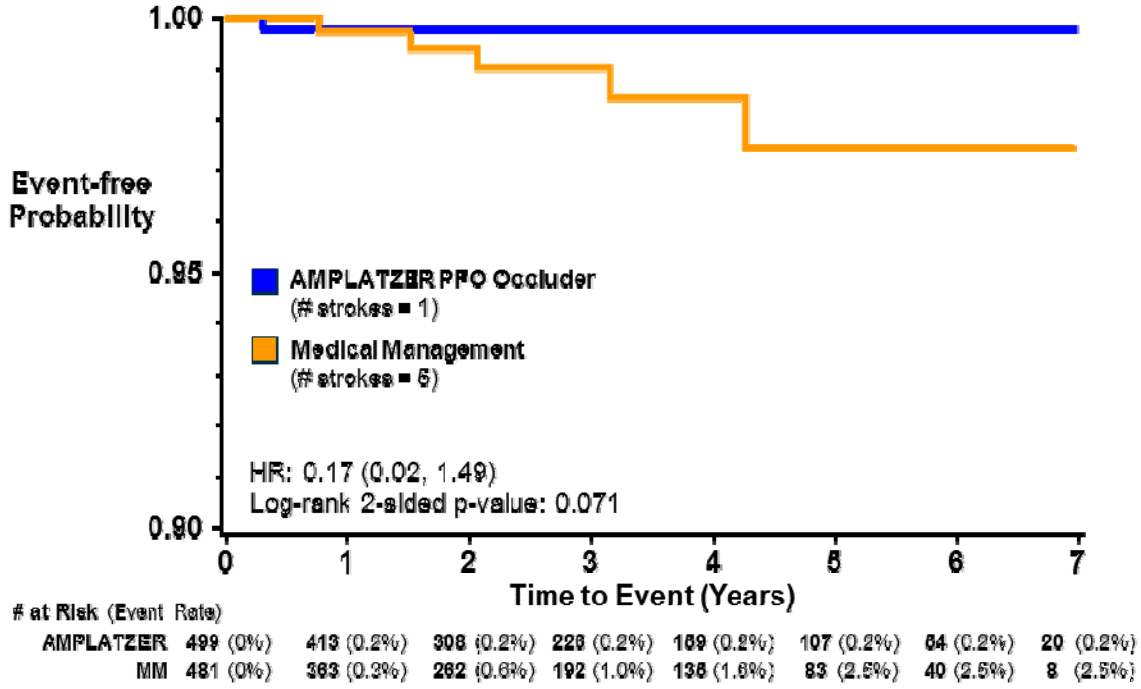
6.5.4 Secondary Endpoint Analysis Results

Secondary endpoints for the RESPECT trial are descriptively summarized as there were no pre-specified hypotheses for these endpoints, and the p-values shown have not been adjusted for multiple testing.

6.5.4.1 Recurrent Cryptogenic Nonfatal Stroke or Cardiovascular Death

The secondary composite endpoint of recurrent symptomatic, cryptogenic, nonfatal stroke or cardiovascular death showed a hazard ratio of 0.17 [95% CI: 0.02, 1.49] in favor of the device, and corresponding to a relative risk reduction of 83% (Figure 9). The log-rank p-value is shown for descriptive purposes only (p = 0.071).

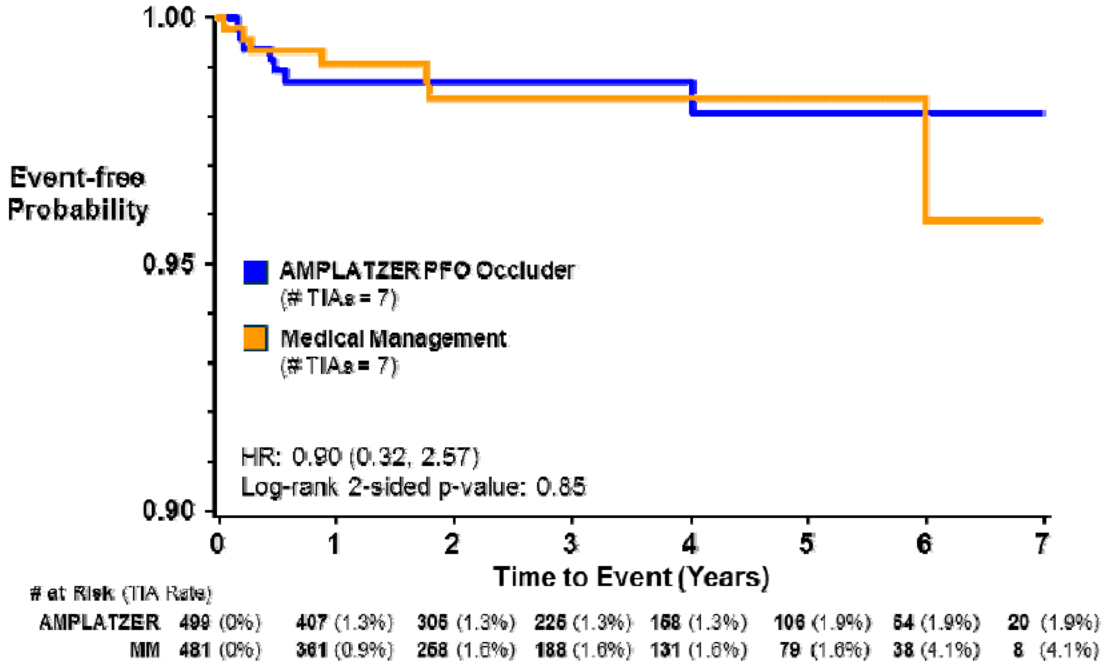
Figure 9: Kaplan-Meier Freedom from Composite Endpoint of Recurrent Symptomatic Cryptogenic Nonfatal Stroke or Cardiovascular Death, ITT Population – Primary Assessment



6.5.4.2 Transient Ischemic Attack (TIA)

The secondary composite endpoint of TIA showed a hazard ratio of 0.90 [95% CI: 0.32, 2.57, p = 0.846] (Figure 10). Inclusion of TIAs likely introduces noise in the analysis and potentially dilutes treatment effect.

Figure 10: Kaplan-Meier Freedom from TIA, ITT Population – Primary Assessment



6.5.4.3 PFO Closure Assessment

For patients in the Device arm who received the device, PFO closure was assessed by TEE and bubble study at the 6-month follow-up, and adjudicated by the Echocardiography Core Laboratory. Complete closure is defined as absence of microbubbles (i.e., grade 0) in the left atrium at rest and at Valsalva within 3 cardiac cycles after right atrial opacification.

A total of 249 of 349 patients had grade 0 shunt both at rest and Valsalva at 6 months, for a complete closure rate of 71.3% (Table 17). The CLOSURE I trial, another randomized controlled trial of a PFO closure device (Furlan et al, 2012), defined "effective closure" as shunt grade of 0 or I at rest and Valsalva. Under this definition, the proportion of patients with "effective" closure was 94.2% at 6 months.

Table 17: Six-Month Closure Rate among Device Patients who Received a Device

Closure	Shunt grade	n/N (%)[1]
Complete	Grade 0 at Rest AND Grade 0 Valsalva	249/349 (71.3%)
Effective[2]	Grade 0/I at Rest AND Grade 0/I Valsalva	323/343 (94.2%)

[1] 6 patients were able to be assessed for complete closure but not effective closure.
[2] Effective closure is based on the definition used in the CLOSURE I trial.

6.5.5 Subgroup Analysis

The primary endpoint was analyzed from the perspective of low-risk versus high-risk anatomy, i.e., patients with Substantial Shunt or atrial septal aneurysm. These subgroups were postulated

based on the premise that incidental PFOs are more likely to be small with a miniscule degree of right to left shunting and not have excessive mobility of the septum primum. Additional post-hoc subgroups, such as age, sex, index infarct topography and planned medical regimen, were investigated to assess potential heterogeneity of device effect. The following is a list of all variables investigated for these subgroup analyses:

- Age (18-45 and 46-60 years)
- Sex (male and female)
- Shunt size (none/race/moderate and substantial)
- Atrial septal aneurysm (present and absent)
- Index infarct topography (superficial, small deep and other)
- Planned medical regimen (anticoagulant and antiplatelet)

The Cox proportion hazards model was used to test for interaction between treatment arm (Device or MM) and baseline variable. The model included treatment arm, the baseline variable, and an interaction term for treatment and the baseline variable. A forest plot for each of the above subgroups is shown in Figure 11 for the ITT population. At the 10% significance level, the analysis suggests that the device may provide an even greater benefit in patients with substantial shunt size or patients with ASA. However, given that the ITT results did not meet the endpoint and the modest number of events, these results must be interpreted with caution.

Figure 11: Forest Plot for Subgroup Analysis, ITT Population – Primary Assessment

	PFO Closure n (%)	Medical Management n (%)	Interaction P-Value
Age			
18-45	4 (1.7%)	5 (2.4%)	**0.53**
46-60	5 (1.9%)	11 (4.1%)	
Sex			
Male	5 (1.9%)	10 (3.7%)	**0.74**
Female	4 (1.7%)	6 (2.8%)	
Shunt Size			
None, trace or Moderate	7 (2.8%)	6 (2.5%)	**0.07**
Substantial (Grade 3)	2 (0.8%)	10 (4.3%)	
Atrial Septal Aneurysm			
Present	2 (1.1%)	9 (5.3%)	**0.10**
Absent	7 (2.2%)	7 (2.2%)	
Index Infarct Topography			
Superficial	5 (1.8%)	12 (4.5%)	**0.39**
Small Deep	2 (3.5%)	1 (1.4%)	
Other	2 (1.3%)	3 (2.2%)	
Planned Medical Regimen			
Anticoagulant	4 (3.0%)	3 (2.5%)	**0.19**
Antiplatelet	5 (1.4%)	13 (3.6%)	

6.5.6 Post-Hoc ASCOD Characterization of Recurrent Strokes

Rationale

One of the principal assumptions underlying the primary endpoint of the RESPECT trial was that the preponderance of recurrent ischemic strokes in the trial would be due to recurrent PFO-related events, and would, therefore, be amenable to PFO closure. PFO closure can only reduce the risk for recurrent stroke mediated by paradoxical embolism, as it cannot prevent strokes stemming from other common mechanisms.

As patients age, they are exposed to a rising tide of traditional stroke risk factors. At the time of the extended follow-up analysis, the RESPECT trial had been ongoing for approximately 12 years – far beyond what was anticipated at the time of the trial design. As such, the RESPECT trial was not designed *a priori* to account for an appreciable number of recurrent strokes from non-PFO related mechanisms.

Methodology

At the recommendation of the RESPECT Steering Committee, a blinded committee was formed **after** the primary endpoint analysis was completed to further characterize the mechanisms of recurrent stroke events. This committee used ASCOD phenotyping, which evaluates the presence or absence of underlying disease states commonly encountered in ischemic stroke and assigns a degree of likelihood that the ischemic stroke can be attributed to that disease (Amarenco et al, 2013). The committee reviewed all of the primary endpoint recurrent ischemic stroke events adjudicated by the CEC. Throughout the adjudication process, the ASCOD committee was blinded to randomization assignment. The five predefined phenotypes are:

- A (atherosclerosis)
- S (small vessel disease)
- C (cardiac pathology)
- O (other cause)
- D (dissection)

Each phenotype is assigned a Grade: 1, if present and potentially causal; 2, if present and causal link is uncertain; 3, if present and causal link is unlikely; 0, if the disease is absent; and 9, if workup is insufficient for grading. If a recurrent stroke in RESPECT could not be attributed to one of the 5 phenotypes, it was considered a stroke of undetermined mechanism, and possibly due to paradoxical embolism.

Phenotyping of strokes during primary assessment period, extended follow-up, and overall

Application of ASCOD phenotyping on the 25 recurrent ischemic strokes in primary assessment showed that 19 (76%) were of undetermined mechanism, 7 in Device arm and 12 in MM arm (Table 18). Of the 7 strokes of undetermined mechanism that occurred in the Device arm, 3 were in patients who did not have a device implanted at the time of the stroke.

Follow-up and event adjudication by the blinded CEC has been ongoing since the PMA was submitted to FDA. Since the time of the primary assessment, overall patient follow-up has nearly doubled in extended follow-up, with over 2,700 patient-years of follow-up in Device patients. In the extended follow-up period, there were an additional 9 recurrent ischemic strokes in the Device arm and 8 in the MM arm. In the Device arm, only 3 of the 9 additional recurrent ischemic strokes (33%) were of an undetermined mechanism that could have potentially been modified by PFO closure, compared to 7 of the 8 additional strokes (88%) in the MM arm (Table 18).

Through all follow-up, a total of 42 patients (18 in Device arm and 24 in MM arm) experienced a recurrent nonfatal ischemic stroke through extended follow-up. Among strokes of undetermined mechanism, approximately half occurred in the Device arm compared to the MM arm (10 vs 19). Of the 10 strokes of undetermined mechanism that occurred in the Device arm, 3 occurred in patients who did not have a device implanted at the time of the stroke.

Table 18: ASCOD Code for Primary Endpoint Stroke Events Assessed by Blinded ASCOD Adjudication Committee – Primary Assessment and Extended Follow-up

ASCOD Code	Device	Medical Management
Primary Assessment only	**(n=9)**	**(n=16)**
Known mechanism	2	4
Undetermined mechanism	7[1]	12
Extended Follow-up only	**(n=9)**	**(n=8)**
Known mechanism	6	1
Undetermined mechanism	3	7
Overall Follow-up	**(n=18)**	**(n=24)**
Known mechanism	8	5
Undetermined mechanism	10[1]	19

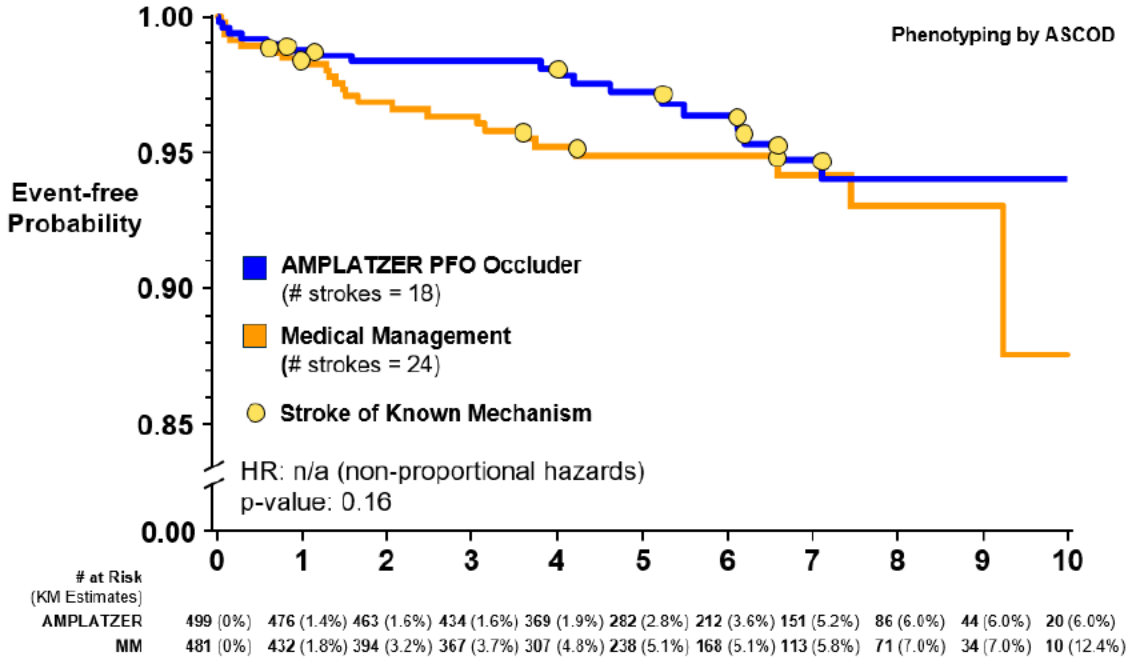
[1] 3 of the strokes in the Device arm occurred in patients who did not have a device implanted at the time of stroke.

6.5.7 Extended Follow-up Effectiveness Results

SJM conducted further analyses of safety and effectiveness through extended follow-up in response to FDA's deficiency letter dated Sep 2014. Analyses presented for data collected through extended follow-up are post-hoc.

Figure 12 shows Kaplan-Meier freedom from first recurrent nonfatal ischemic stroke curves for the ITT population for all-cause stroke, with strokes of known mechanism shown in yellow circles. The curves show potential lack of proportionality of hazards likely due to the competing risks from traditional stroke mechanisms through extended follow-up. These competing risks were more likely to be observed in the Device arm than the MM arm as Device patients remained in the trial longer than MM patients. Additionally, it is likely that more events in the MM arm were missed in comparison with the Device arm.

Figure 12: Kaplan-Meier Freedom from Recurrent Ischemic Stroke, ITT Population – Extended Follow-up, Post-Hoc Analysis



The ASCOD adjudicated phenotype of the recurrent strokes of known mechanism through extended follow-up are shown in Table 19. There were 5 cardioembolic phenotypes (2 in the Device arm and 3 in the MM arm), of which 1 event in the Device arm and 3 events in the MM arm were related to atrial fibrillation. Therefore, there is no evidence of an increased risk of stroke due to atrial fibrillation due to the device, as was observed in the CLOSURE I trial of another PFO closure device (Furlan et al, 2012).

Table 19: Phenotype of Recurrent Strokes of Known Mechanism

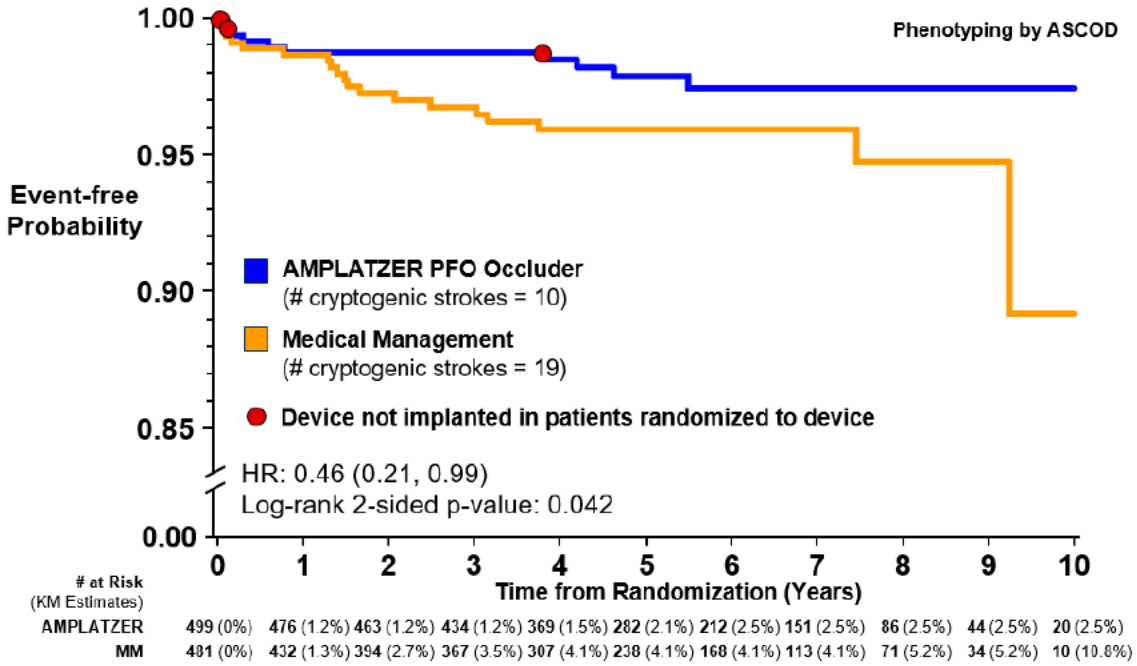
Phenotype	Device (N=8)	Medical Management (N=5)
Atherosclerosis	1	0
Small Vessel Disease	4	2
Cardioembolic	2 (1 AF, 1 Endocarditis[1])	3 (3 AF)
Other	1 (Radiation Arteriopathy)	0
Dissection	0	0

[1] Endocarditis of the mitral valve

Figure 13 shows Kaplan-Meier curves for freedom from stroke of undetermined mechanism based on ASCOD phenotyping. The figure shows a 54% relative reduction in risk of stroke in the Device arm (HR: 0.46; 95% CI: 0.21, 0.99; nominal p = 0.042). The figure also shows that 3 of

the 10 strokes of unknown mechanism that occurred in the Device arm were in patients who did not have a device implanted at the time of the stroke.

Figure 13: Kaplan-Meier Freedom from Stroke of Undetermined Mechanism per ASCOD Phenotyping, ITT Population – Extended Follow-up, Post-Hoc Analysis



A possible concern regarding the analysis of ASCOD adjudicated strokes of undetermined mechanism is that investigations for recurrent stroke etiology may have occurred at a differential rate between the Device and MM arms, leading to the larger number of Device patients than MM patients having a known mechanism for stroke.

Table 20 summarizes investigations carried out for stroke evaluation at the time of the recurrent stroke event. Among patients who experienced a stroke, there was no evidence of a difference in the distribution of tests performed between device and MM patients.

Table 20: Investigations for Recurrent Stroke Etiology

Test	Device (n=18)	Medical Management (n=24)
Any parenchymal imaging	**18/18 (100%)**	**24/24 (100%)**
CT	15/18 (83.3%)	22/24 (91.7%)
MR	16/18 (88.9%)	22/24 (91.7%)
Any echo	**10/18 (55.6%)**	**15/24 (62.5%)**
TEE	6/10 (60%)	7/12 (58.3%)
TTE	7/10 (70%)	6/12 (50%)
Any vascular imaging – Head	**13/18 (72.2%)**	**15/24 (62.5%)**

Test	Device (n=18)	Medical Management (n=24)
CTA Head	5/13 (38.5%)	8/15 (53.3%)
MRA Head	10/13 (76.9%)	8/14 (57.1%)
Intracranial ultrasound	3/13 (23.1%)	4/15 (26.7%)
Any vascular imaging – Neck	**12/18 (66.7%)**	**14/24 (58.3%)**
CTA Neck	2/12 (16.7%)	8/14 (57.1%)
MRA Neck	7/12 (58.3%)	3/13 (23.1%)
Extracranial ultrasound	4/12 (33.3%)	4/14 (28.6%)
Conventional angiogram	**2/18 (11.1%)**	**1/24 (4.2%)**
Any telemetry	**17/18 (94.4%)**	**22/22 (100%)**
EKG	17/17 (100%)	21/22 (95.5%)
In-house telemetry	12/16 (75%)	17/22 (77.3%)
Outpatient Holter	0 (0%)	1/22 (4.5%)

7 RESPECT TRIAL SAFETY

Summary

- Through extended follow-up, the rates of serious adverse events (SAEs) overall were comparable between the Device (37.9%) and MM (34.9%) arms.
- The rate of procedure- or device-related serious adverse events in the Device arm was less than 5%. Nearly all of the procedure- or device-related serious adverse events resolved without long-term sequelae.
- There were 6 deaths in the Device arm and 10 in the MM arm. None of the deaths were adjudicated by the DSMB as related to the procedure, device or protocol.
- There were no intra-procedural strokes, device embolizations or reports of thrombus on any of the devices or device erosions.

A complete safety assessment of the two treatment strategies is summarized through extended follow-up, where median follow-up duration is 5.2 years in the Device arm and 5.1 years in the MM arm. Total follow-up duration is 2769 patient-years in the Device arm and 2376 patient-years in the MM arm.

7.1 Serious Adverse Events (SAEs)

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 21). 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 38 (Appendix D) shows a breakdown of SAEs that occurred in at least 5 patients.

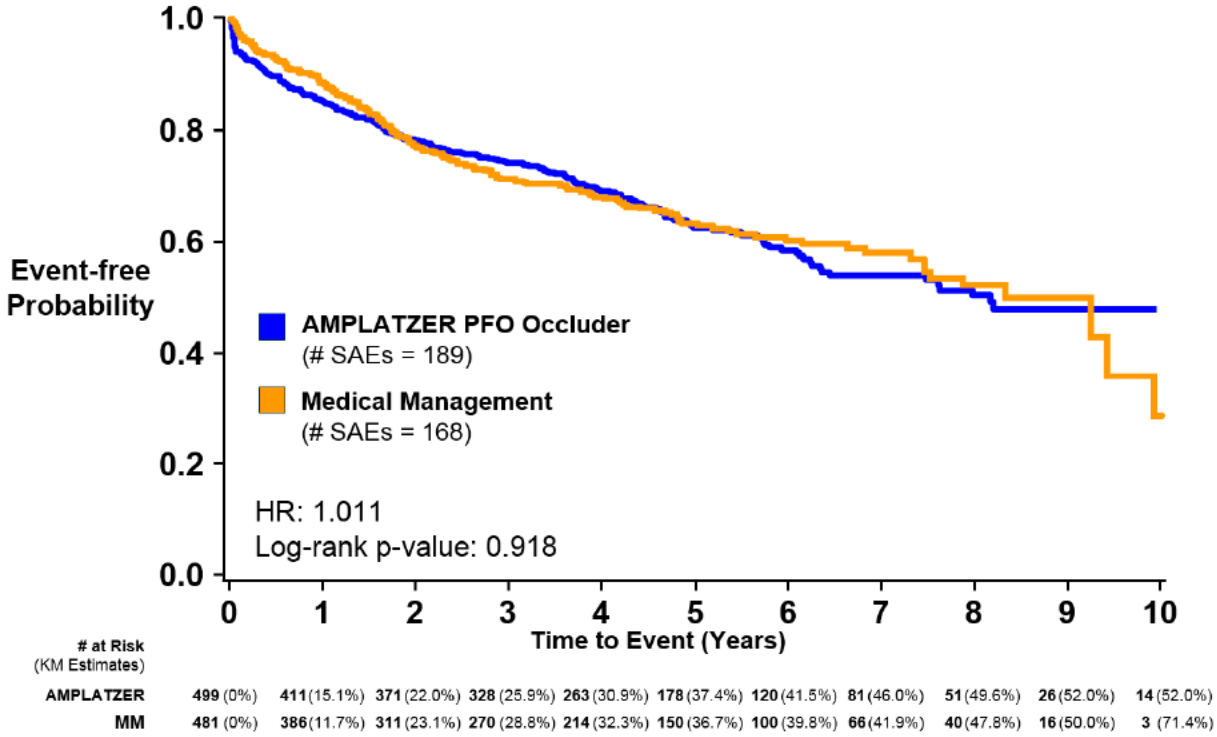
Table 21: Overall Rate of SAEs – Extended Follow-Up

	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[1]	0 (0.0%)	0 (0.0%)	N/A	N/A
Related to procedure[1]	12 (2.4%)	12 (0.4)	N/A	N/A
Related to device[1]	10 (2.0%)	13 (0.5)	N/A	N/A

[1] Relatedness is reported as adjudicated by the DSMB

Figure 14 shows the Kaplan-Meier freedom from SAE curves in the Device and MM arms. Although there is an early procedural risk of SAE in the Device arm, the two arms had comparable overall SAE rates over the length of follow-up.

Figure 14: Kaplan-Meier Freedom from Any SAE – Extended Follow-Up, Post-Hoc Analysis



7.2 Deaths

There were 16 deaths (6 Device, 10 MM), none of which were adjudicated by the DSMB to be related to the procedure, device or protocol. All deaths, except one, occurred more than 6 months after randomization. None of the deaths met the definition of the primary endpoint. The patient who died within 6 months of randomization was in the Device arm and the cause of death was asystole due to coronary artery disease and hyperlipidemia. Detailed narratives of the deaths are provided in Appendix E. Table 22 displays the causes of death in each arm.

Table 22: Causes of Death – Extended Follow-Up

Cause of Death	Device (n=6)	Medical Management (n=10)
Cancer	2	3
Intracerebral hemorrhage	1	1
Asystole	1	0

Cause of Death	Device (n=6)	Medical Management (n=10)
Pulmonary embolism	1	0
Overdose from non-study medication	1	0
Trauma	0	2
Cardiac arrest	0	2
Cardiac dysrhythmia	0	1
Sepsis	0	1

7.3 Procedure-Related SAEs in the Device Arm

Twelve (12) procedure-related SAEs occurred in 12 patients (2.4%).

Cardiac Perforation (n=4): Two patients experienced cardiac perforation with cardiac tamponade which was managed with a pericardiocentesis. Two additional patients experienced cardiac perforation without cardiac tamponade and which did not require procedural intervention: in one patient, the device was implanted uneventfully, but a trivial pericardial effusion was noted one day post-implant without requiring intervention; in the second patient, cardiac perforation was identified during the procedure and the device implant was abandoned. In this second patient the cardiac perforation was caused by the catheter after there was difficulty in crossing the inter-atrial septum and a straight wire was used to gain access into the left atrium. The patient underwent a successful implant procedure in a second attempt.

Access Site Bleeding (n=3): One patient had post-procedure oozing from the access site that required placement of a stitch. The second patient developed a large rectus sheath hematoma post-procedure that resulted in hypotension and required transfusion of 1 unit of blood. The third patient had trauma to the right femoral artery after a failed vascular closure was attempted with a ProGlide device, which resulted in bleeding into the groin with hematoma formation.

Right Atrial Thrombus (n=1): In one patient, a thrombus was discovered in the right atrium during the procedure, but before inserting an AMPLATZER PFO Occluder delivery system. This thrombus was likely pre-existing, and the procedure was abandoned. The patient had a successful implant one month later after treatment with oral anticoagulant.

Deep Vein Thrombus (n=1): One patient had a deep vein thrombosis in the left common femoral vein. The patient had multiple hematomas treated with compression in the left groin and the event resolved 7 months later.

Atrial Fibrillation (n=1): One patient was found to have a fenestrated septum during the procedure, and underwent closure with an atrial septal defect closure device. The patient developed atrial fibrillation during the procedure, and was successfully cardioverted.

Allergic Drug Reaction (n=1): One patient experienced an allergic drug reaction to subcutaneous lidocaine and was treated with intravenous Benadryl with the symptoms resolving within minutes. The patient was discharged home in stable condition.

Vasovagal Response (n=1): One patient experienced a vasovagal response. The patient recovered spontaneously and was treated with intravenous fluid, but remained in hospital overnight and discharged the next day in stable condition.

Acute ischemic stroke due to air or thromboemboli from the device (n=0): There were no acute ischemic strokes due to air or thromboemboli from the device.

Device embolization (n=0): There were no device embolizations.

Table 23: 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%)

7.4 Device-Related SAEs in the Device Arm

Thirteen (13) device-related SAEs occurred in 10 patients (2.0%).

Ischemic Stroke (n=2): Two patients b(6) [redacted]) experienced ischemic strokes, which were adjudicated as primary endpoint events. The first stroke occurred 7 days post-procedure. There was no report of thrombus and no atrial fibrillation. The second stroke occurred 3 months post-procedure. The patient was found to have had a sinus venosus atrial septal defect that was not diagnosed at the time of enrollment, and should not have been enrolled per the trial entry criteria. These events have been previously described (Section 6.5.1).

Pulmonary Embolism (n=2)/Thrombus in Right Atrium (n=1): Two patients experienced pulmonary embolism. The first pulmonary embolism occurred five days post-procedure. This patient presented to the emergency room with shortness of breath, left-sided chest pain, tachycardia, and a cough with 1 episode of hemoptysis. The patient was admitted and treated with Lovenox and started on warfarin therapy. The patient was discharged home in stable condition on aspirin and warfarin antithrombotic therapy. The patient's shortness of breath was reported as improved, but ongoing, 18 months later. The second pulmonary embolism occurred almost six months post-procedure. In this same patient, an echocardiogram revealed a cardiac thrombus in the right atrium that was not attached to the device. Both the cardiac thrombus and the pulmonary embolism event resolved with warfarin 3 months later.

Device Explant (n=2): Two patients had the AMPLATZER PFO Occluder surgically explanted. The first was the patient who was noted to have a sinus venosus atrial septal defect b(6) The second patient had the device explanted due to infective endocarditis upon being hospitalized approximately 18 months post-procedure for sepsis. An echocardiogram identified a 1.5 mm mobile mass on the left atrial side of the PFO Occluder. This was considered infective endocarditis and the device was surgically removed.

Atrial Fibrillation (n=1): There was one event of atrial fibrillation attributed to the device. Three days post-implant, after successful treatment of cardiac tamponade, the patient was found to be in atrial fibrillation with a rapid ventricular rate related to the tamponade. He was given oral and IV metoprolol and spontaneously converted back to sinus rhythm. The patient was discharged home in stable condition the next day.

Residual Shunt (n=1): One patient had a residual shunt at the edge of the AMPLATZER PFO Occluder adjacent to the aortic root. An AMPLATZER ASD (Atrial Septal Defect) Occluder device was placed without complication and no residual shunt.

Other (n=4): Other device-related SAEs included chest tightness, atrial fluter, non-sustained ventricular tachycardia and sepsis.

Thrombus on Device (n=0): There were no reports of thrombus on the device based on TEEs performed through extended follow-up.

Device Erosion (n=0): There were no device erosions through extended follow-up.

Table 24: 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 with septal occluder device)*	1 (0.2%)
Other (*chest tightness, atrial flutter, non-sustained ventricular tachycardia, sepsis*)	4 (0.8%)

7.5 Major Bleeding and Atrial Fibrillation SAEs

Though extended follow-up, SAE rates of major bleeding and atrial fibrillation were comparable between the Device and MM arms. Table 38 (Appendix D) shows a breakdown of SAEs that occurred in at least 5 patients.

Table 25: Major Bleeding and Atrial Fibrillation SAEs

Event	Device (N=499, 2769 patient-years)			Medical Management (N=481, 2376 patient-years)		
	# Patients	# Events	# Events per 100 patient-years	# Patients	# Events	# Events per 100 patient-years
Major bleeding complication[1]	13	17	0.61	14	14	0.59
Atrial fibrillation	5	7	0.25	4	4	0.17

[1]SAEs of either an intracranial hemorrhage or bleeding that led to hemodynamic compromise requiring intervention (eg, pericardiocentesis, blood transfusion) or death

7.6 Venous Thromboembolic Events

During trial conduct, the RESPECT DSMB noted a higher rate of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the Device arm. Per the DSMB's recommendation, SJM issued letters to all sites and FDA regarding the higher incidence of venous thromboembolic (VTE) events (i.e., PEs and DVTs). Table 26 shows the rates of DVT and PE adjudicated by the DSMB as either SAEs or non-SAEs by treatment arm.

Table 26: Rates of Venous Thromboembolic Events through Extended Follow-up

Event	Device (N=499, 2769 patient-years)			Medical Management (N=481, 2376 patient-years)		
	# Patients	# Events	# Events per 100 pt-yrs	# Patients	# Events	# Events per 100 pt-yrs
Deep Vein Thrombosis						
SAEs	4	4	0.14	1	1	0.04
Non-SAEs	7	7	0.25	2	2	0.08
Pulmonary Embolism						
SAE	12	13	0.47	2	2	0.08
Non-SAEs	0	0	0.00	0	0	0.00
All VTEs	18	24	0.87	3	5	0.21

Through extended follow-up, 18 patients (3.6%) in the Device arm [24 events] and 3 patients (0.6%) in the MM arm [5 events] had a VTE. In the Device arm, 4 VTEs were adjudicated by the DSMB to be procedure- or device-related and 20 were adjudicated as not related.

Warfarin Use in the Device Arm Among Patients with VTE

In the Device arm, 22 of the 24 VTE events occurred in patients who were not on anticoagulation therapy at the time of the event. Of the two remaining events, one occurred in a patient who had undergone left total knee arthroplasty 5.5 years after implant, had started warfarin post-surgery, but did not have a therapeutic INR at the time of the event, and one occurred in a patient on warfarin with a therapeutic INR who had experienced a previous VTE during the trial while not on warfarin.

Clinical Summary of VTE Events in Device Arm

- Four (4) VTEs were procedure- or device-related (all within 6 months of procedure).
    - 3 VTEs were serious, and were described in Sections 7.3 and 7.4. In two cases, the patients recovered without effects. In the third case, the patient's shortness of breath had improved 18 months after the event, but had not completely resolved.
    - 1 VTE was assessed as procedure-related but was not serious. The event was noted nine days post-implant while the patient was hospitalized for a cerebrovascular event b(6) Intravenous heparin and warfarin treatment were initiated and the patient was discharged home 3 days later on warfarin. The patient recovered with no residual effects.
- Twenty (20) VTEs were not procedure- or device-related. The first VTE occurred at a median of 26 months post-procedure (range 9 to 100 months).
    - 8 VTEs occurred in the setting of current or recent conditions or events that may have provoked a VTE. These included recent surgery (n = 3), active malignancy (n = 2), motor vehicle accident trauma (n = 1), right and left heart catheterization (n = 1), and immobility (n=1).
    - 3 VTEs occurred in the setting of underlying venous disease (phlebitis or chronic vein wall thickening with incomplete compression following recent leg injury).
    - 3 VTEs occurred in the setting of a hypercoagulable state.
    - 6 VTEs occurred in the absence of an identified risk factor.

Resolution of VTE Events in Device Arm

Of the 24 VTEs in the Device arm, 16 resolved with no residual effects or long-term sequelae. Three VTEs that occurred in 3 patients resolved with some residual effects. Five VTEs in 5 patients had not resolved as of the lock of the extended follow-up database:

- One patient had ongoing shortness of breath after a PE event.
- One patient continued to wear compression stockings after a DVT event.
- One patient had ongoing symptoms of edema and pain in left leg after a DVT event.
- One patient who was found dead more than 6 years after the device implant had PE noted as the cause of death on autopsy.

- One patient who had metastatic colon cancer died without PE resolution.

Predictors of VTE in Device Arm

Chi-square tests or t-tests were used to evaluate predictors of the 14 patients with an unrelated VTE in the Device arm (all occurred more than 6 months post-implant). The rationale for modeling unrelated VTEs is to associate VTEs with the patient's baseline factors, rather than the procedure or device. Demographic and baseline characteristics for patients who experienced a late VTE were compared with those in the remaining patients. The following variables emerged as predictors of VTE (at the 10% significance level):

- History of DVT (5/14 vs. 15/485, $p < 0.001$)
- NIHSS score (2.0 ± 3.3 vs. 0.8 ± 1.7, $p = 0.015$)
- Assigned to warfarin at baseline (7/14 vs. 125/485, $p = 0.061$)
- Family history of stroke (7/14 vs. 129/481, $p = 0.069$)

As noted in Section 6.4.3, MM patients were nine times as likely as Device patients to be on warfarin during follow-up. This suggests that warfarin therapy should be seriously considered in patients at high risk for VTE following PFO closure. The AMPLATZER PFO Occluder Instructions for Use includes a warning and post-procedural recommendations for the use of anticoagulants in patients at high risk for VTE. The impact of patients' medical histories on appropriate medical management after PFO closure to reduce the occurrence of VTE will be one component of the physician training program, and will be evaluated in the post-approval studies.

8 PC TRIAL

The PC trial was a physician-initiated, prospective, multicenter, randomized controlled trial of the AMPLATZER PFO Occluder conducted outside the US in patients with a PFO and cryptogenic ischemic stroke or extracranial peripheral thromboembolic event. SJM provided some financial support but was not the sponsor of the trial.

The trial randomized 414 patients, 204 to receive the device and 210 to medical management. The trial was powered to detect a reduction in annual incidence of recurrent thromboembolic events from 3% per year to less than 1% per year in patients with percutaneous PFO closure, assuming an average follow-up of 4.5 years, successful PFO closure in 95% of patients randomized to device, and annual loss to follow-up rate of 0.5%. The trial enrolled patients between 2000 and 2009.

There were 7 primary endpoint events in the Device arm and 11 in the MM arm. The trial did not demonstrate a statistically significant reduction in the primary composite endpoint of death, nonfatal stroke, TIA or peripheral embolism (HR: 0.63; 95% CI: 0.24, 1.62; p = 0.34). Similar to the results observed in RESPECT, there did not appear to be an impact of PFO closure on the rate of TIA (HR: 0.71; 95% CI: 0.23, 2.24; p = 0.56). In an exploratory analysis where stroke outcomes were assessed using the stroke definition from the RESPECT trial, the PC trial demonstrated a hazard ratio of 0.14 (95% CI: 0.02, 1.17, p = 0.07) (Note: this exploratory analysis is included in the PC trial results publication).

SAEs were reported in 43 device patients (21.1%) and 37 MM patients (17.6%). New onset atrial fibrillation was reported in 6 device patients (2.9%) and 2 MM patients (1.0%). There were no reports of thrombus on the device.

The results of the PC Trial were published in the *New England Journal of Medicine* in March 2013 (Meier et al, 2013). A copy of this article can be found in Appendix G.

9 PATIENT-LEVEL META-ANALYSIS

Summary

- An individual patient-level meta-analysis was conducted by researchers at Tufts University on the three randomized clinical trials evaluating the effectiveness and safety of PFO closure devices compared to medical therapy. Two of these randomized clinical trials used the AMPLATZER PFO Occluder.
- In ITT analysis of the AMPLATZER PFO Occluder trials (N=1394), after adjustment for baseline covariates, PFO closure was associated with a 59% relative risk reduction for ischemic stroke (HR = 0.41, 95% CI: 0.20, 0.88; p = 0.021). An As Treated analysis demonstrated that PFO closure was associated with a 72% relative risk reduction for ischemic stroke (HR = 0.28, 95% CI: 0.12, 0.66; p = 0.004).
- When either (a) TIA and either early death, or (b) TIA and any death were included as part of a composite endpoint, the relative risk reduction was diminished and not statistically significant.

There have been three randomized controlled trials of percutaneous PFO closure devices against medical therapy (RESPECT, PC Trial, and CLOSURE I). The results of the RESPECT, PC and CLOSURE I trials were published in separate reports in the *New England Journal of Medicine* (Carrol et al, 2013; Meier et al, 2013; Furlan et al. 2012). Appendix G contains each of the publications.

A pooled, individual patient-level meta-analysis was independently conducted at Tufts University and supported by grants from the National Institutes of Health (NIH) and the Patient-Centered Outcomes Research Institute (PCORI) (Kent et al, 2016). Meta-analyses were specified for all of the three randomized PFO closure trials as well as for the two trials of the AMPLATZER PFO Occluder (RESPECT, PC Trial). Given the scope of the panel meeting, the analyses presented here includes results on the AMPLATZER PFO Occluder alone. The analysis was conducted independent of the companies that sponsored the trials, and the results were recently published in the *Journal of the American College of Cardiology* (see Appendix G). The methods for the meta-analysis were pre-specified and published in PROSPERO, the international prospective registry of systematic reviews. While several meta-analyses have been conducted on PFO closure trials, and have consistently indicated benefit of device closure versus MM (Kitsious et al, 2013; Rengifo-Moreno et al, 2013; Stortecky et al, 2015), this is the only patient-level meta-analysis assessing the comparative effectiveness of PFO closure.

Table 27 contains an overview of the design of each trial (RESPECT and PC) and Table 28 contains a summary of population characteristics and trial results. Both trials demonstrated a reduction in the risk for stroke in the ITT analysis, although neither trial achieved statistical significance.

Table 27: Trial Design Overview of RESPECT and PC Trial

Feature	RESPECT	PC Trial
Trial design	Prospective, multicenter, superiority trial	Prospective, multicenter, superiority trial
Number of centers	69	29
Trial locations	U.S. and Canada	Europe, Canada, Brazil, Australia
Device	SJM's AMPLATZER PFO Occluder	SJM's AMPLATZER PFO Occluder
Enrollment	Aug 2003 – Dec 2011	Feb 2000 - Feb 2009
Total subjects	980	414
Subject population	Patients 18 to 60 yo with TEE documented PFO and neurologically verified cryptogenic ischemic stroke due to a presumed paradoxical embolism	Patients 18 to 60 yo with TEE documented PFO and clinically and neuroradiologically verified cryptogenic ischemic stroke or extracranial peripheral thromboembolic event
Stopping rules	25 events	None specified
Medical management regimens	Regimens were left to the discretion of the investigator but were limited to the following: (a) aspirin alone (b) warfarin alone (c) clopiodgrel alone (d) aspirin combined with clopidogrel	Regimens were left to the discretion of the investigator and could include antiplatelet and/or oral anticoagulation, as long as the subject was taking at least 1 antithrombotic medication
Primary efficacy endpoint	Composite of early death or recurrent ischemic (fatal or nonfatal) stroke	Composite of death, nonfatal stroke, TIA, or peripheral embolism

Table 28: Population Characteristics and Effectiveness Results of RESPECT and PC Trial

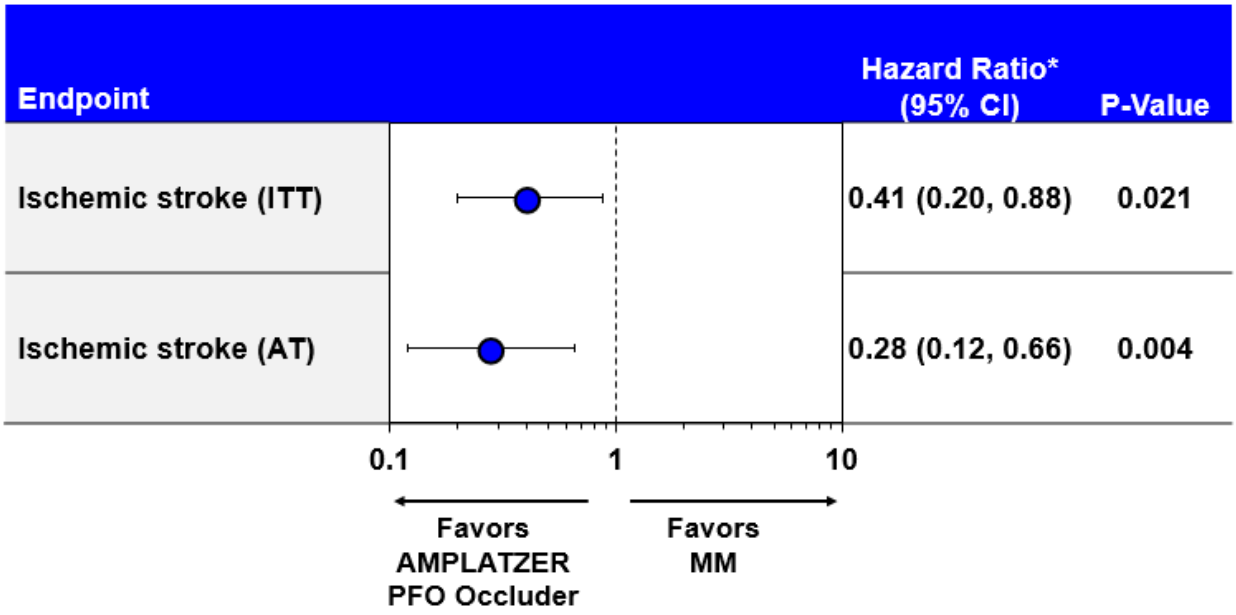
	RESPECT		PC Trial	
	Device (N=499)	MM (N=481)	Device (N=204)	MM (N=210)
Age (years), mean ± SD	45.7 ± 9.7	46.2 ± 10.0	44 ± 10	45 ± 10
Male, %	53.7%	55.7%	45%	54%
History of TIA, %	11.6%	12.7%	16%	20%
Stroke as index event, %	100%	100%	81%	78%
% on anticoagulant at baseline	26.5%	25.2%	21.7%	21.8%
Presence of ASA, %	36.1%	35.3%	23%	24%
PFO size, % Large shunt[1]	49.5%	48.0%	23%	20%
Closure (shunt grade 0 or 1) at 6 months	94.2%	NA	95.9%	NA
Primary efficacy endpoint	1.8%	3.3%	3.4%	5.2%
Hazard ratio (95% CI) for primary endpoint, p-value	0.49 (0.22-1.11) p = 0.089		0.63 (0.24-1.62) p = 0.34	
Hazard ratio (95% CI) for stroke, p-value	0.49 (0.22-1.11) p = 0.089		0.20 (0.02-1.72) p = 0.14	

NA: Not applicable

[1] RESPECT = grade III shunt; PC = "Large shunt", definition not provided

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 15 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 15: Patient-Level Effectiveness Meta-Analysis of AMPLATZER PFO Trials with Adjustment for Baseline Covariates[1]



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

10 PATIENT SATISFACTION QUESTIONNAIRE

With the release of FDA's draft guidance document on patient preference information (FDA, 2015), SJM has attempted to incorporate the perspective of patients continuing to be followed in the trial by implementing a patient satisfaction survey. The survey was initiated in August 2015 and contained the questions outlined in Table 29.

Table 29: Questions in RESPECT Patient Satisfaction Questionnaire

Question	Answer Options	Background
1. As a participant in the RESPECT Trial you were assigned to receive either the AMPLATZER PFO closure device or medication to "thin your blood." Indicate your overall level of satisfaction with your assigned treatment.	Satisfied Neither satisfied nor dissatisfied Unsatisfied, specify reason	This was the primary question of interest for SJM to gain the patient's perspective.
2. Did you remain in the treatment group to which you were originally assigned?	Yes No, specify reason	Although the answer to this question can be known from the data collected in the trial, the reason for the "No" responses was of particular interest.
3. Indicate whether you would recommend the form of treatment (device or medication) you received to someone with a condition similar to yours	Yes Unsure No, specify reason	SJM was particularly interested in learning whether patients would recommend their treatment to others with a similar condition.
4. Indicate why you chose to join the RESPECT Trial?	Free text response	
5. The RESPECT trial enrolled patients who had suffered a stroke of unknown origin and had a patent foramen ovale (PFO). Patients were randomly selected to receive either the AMPLATZER PFO Occluder (device) or "blood thinner" medication. The trial results were published in the New England Journal of Medicine (2013). The trial showed that patients receiving the device experienced approximately half as many recurrent strokes as patients who received medication. The risk of another stroke by the end of 5 years was approximately 2 of every 100 patients who were assigned to the device and approximately 6 of every 100 patients who were assigned to medication. Given the risks of the procedure described to you when you enrolled in the trial, indicate whether you believe the benefit of the PFO closure device outweighs the risks of receiving it.	Yes, specify reason Unsure, specify reason No, specify reason	This was the primary question of interest for SJM to gain the patient's perspective on benefit.

Among 744 patients (408 in the Device arm and 336 in the MM arm) in active follow-up in the trial, a total of 491 surveys were returned (278 in Device arm and 213 in MM arm). Results from these surveys need to be interpreted with caution as it was implemented very late during trial conduct and is limited to a subset of patients who are being followed in the trial.

Results of the survey are provided in Table 30. The results of the survey indicate that Device patients reported being more satisfied with their treatment than medical management patients (97.5% Device versus 74.6% MM), and more device patients than MM patients would recommend their assigned therapy to someone with a similar condition (90.2% Device and 65.6% MM). More Device patients than MM patients responded that the benefits of the PFO closure device outweighed the risks (90.7% Device vs 49.2% MM).

Table 30: RESPECT Patient Satisfaction Survey Responses

Question	Response	Device	Medical Management
1. Overall level of satisfaction with your assigned treatment	Satisfied	268/275 (97.5%)	159/213 (74.6%)
	Neither satisfied nor dissatisfied	5/275 (1.8%)	25/213 (11.7%)
	Unsatisfied	2/275 (0.7%)	29/213 (13.6%)
2. Did you remain in the treatment group to which you were originally assigned?	Yes	270/276 (97.8%)	188/213 (88.3%)
	No	6/276 (2.2%)	25/213 (11.7%)
3. Would you recommend the form of treatment that you received to someone with a condition similar to yours?	Yes	249/276 (90.2%)	139/212 (65.6%)
	Unsure	24/276 (8.7%)	42/212 (19.8%)
	No	3/276 (1.1%)	31/212 (14.6%)
5. Do you believe the benefit of the PFO closure device outweighs the risks of receiving it?	Yes	233/257 (90.7%)	93/189 (49.2%)
	Unsure	18/257 (7.0%)	65/189 (34.4%)
	No	6/257 (2.3%)	31/189 (16.4%)

11 PFO ACCESS REGISTRY

PFO ACCESS is an ongoing prospective, non-randomized, multi-center single-arm study. The objective of the PFO ACCESS Registry is to allow access to the AMPLATZER PFO Occluder in patients with recurrent cryptogenic stroke who have failed conventional drug therapy. Enrollment began in Oct 2006 when the HDE was withdrawn. A total of 640 patients were enrolled in the study as of June 2015 with a follow-up duration of 1 year. Inclusion and exclusion criteria for the registry are as follows:

Inclusion Criteria:

- Documented PFO
- Recurrent cryptogenic stroke while on anticoagulant or antiplatelet therapy (anticoagulant or antiplatelet therapy defined as therapeutic dose of warfarin (INR range 2-3), adequate dosage of aspirin, or adequate dosage of combination aspirin and Plavix or Ticlid)

Exclusion Criteria:

- INR outside 2-3 range (if on warfarin)
- Intracardiac thrombus

Table 31 shows the demographic and baseline characteristics of patients enrolled in the PFO ACCESS Registry. The table shows that patients in this registry are older than patients enrolled in RESPECT, and have a higher proportion of patients with coronary artery disease, deep vein thrombosis, previous myocardial infarction and hypertension.

Table 31: Demographics and Baseline Characteristics of Patients in the PFO ACCESS Registry

Variable	Device (N=640)
Age (years), mean ± SD	59.5 ± 13.4
Sex, male, n (%)	391 (61.1%)
Congestive heart failure, n (%)	18 (2.8%)
Coronary artery disease, n (%)	118 (18.4%)
Deep vein thrombosis, n (%)	48 (7.5%)
Pulmonary embolus, n (%)	19 (3%)
Previous myocardial infarction, n (%)	43 (6.7%)
Hypertension, n (%)	411 (64.2%)

Five hundred ninety-two (592) of the 640 patients (92.5%) consented for the registry ultimately underwent an attempted implant of the AMPLATZER PFO Occluder. Of the 592 patients, 584 patients were implanted with a device (98.6%), 462 patients have completed their 1-year visits and there are 635 cumulative patient-years of follow-up as of June 2015.

Adverse events reported in the study are adjudicated by the same independent DSMB as the RESPECT trial. Table 32 summarizes SAEs of interest in patients with an implanted device as of 25 Jun 2015. Among 584 patients, there were no reports of acute ischemic stroke due to air or thromboemboli, device explantation, device embolization, major vascular complications, surgical intervention possibly related to the device or thrombus on the device. The rate of atrial fibrillation was 0.7%. Incomplete PFO closure at 6 months, as assessed by the investigator, was reported in 7.7% of patients. Among the 16 deaths, none were adjudicated as related to the device and one was adjudicated as acute renal failure related to the procedure (16 days post-procedure). Ischemic stroke occurred in 3.6% of patients, which is lower than the 13.2% rate of recurrent stroke in the first year after an ischemic stroke of uncertain cause (Petty et al, 2000).

Table 32: SAEs of Interest in Patients with a Device in PFO ACCESS Registry

Serious Adverse Event	Patients with Implanted Device (N=584)	
	# Events	n (%)
Major vascular complications	0	0 (0%)
Device explantation/surgical intervention possibly related to device	0	0 (0%)
Pericardial tamponade	0	0 (0%)
Acute ischemic stroke due to air or thromboemboli from the device	0	0 (0%)
Device embolization	0	0 (0%)
Thrombus on device	0	0 (0%)
Device erosion	0	0 (0%)
Major bleeding	11	9 (1.5%)
Pulmonary embolism	5	5 (0.9%)
Atrial fibrillation	4	4 (0.68%)
Ischemic stroke	23	21 (3.6%)
Transient ischemic attack	23	18 (3.1%)
Death from any cause	16	16 (2.7%)
Deep vein thrombosis	2	2 (0.4%)
Incomplete PFO closure at 6 months[1]	40	40/522 (7.7%)

[1] Denominator is implanted patients with a TEE assessment at 6 months (site reported).

The stroke rate is consistent with a higher risk population, yet it is lower than literature reports of recurrent stroke in patients with a previous cryptogenic stroke. These data are supportive of the safety of the AMPLATZER PFO Occluder.

12 PHYSICIAN TRAINING

SJM has developed a standardized methodology for providing physicians with education and training on appropriate patient selection, safe implantation of the AMPLATZER PFO Occluder, and post-procedure care for patients implanted with the AMPLATZER PFO Occluder.

The physician training program covers patient selection, implanting physician qualification, and implant and post-procedure training.

12.1 Patient Selection

SJM believes that proper patient selection is key to ensuring that the benefits of PFO closure with the AMPLATZER PFO Occluder outweigh the risks of the procedure. SJM will train physicians per the American Heart Association (AHA) and the American Stroke Association's (ASA) Healthcare Professional Guide for the diagnosis and treatment of cryptogenic stroke (AHA/ASA, 2015). Specifically, physicians will be trained that the diagnosis of cryptogenic stroke should include, at a minimum, the following (Jauch et al, 2013):

- Noncontrast brain CT or brain MRI
- Blood glucose
- Oxygen saturation
- Serum electrolytes/renal function tests
- Complete blood count, including platelet count
- Markers of cardiac ischemia
- Prothrombin time/INR
- Activated partial thromboplastin time
- Electrocardiogram

In order to ensure appropriate patient selection, the didactic training will also include a review of the AHA/ASA Stroke Prevention in Patients with Stroke or TIA Guidelines and specify the need for a multi-disciplinary team to include a neurologist and an interventionalist. An independent neurologist confirmation of the cryptogenic stroke diagnosis and recommendation for PFO closure for the patient should be obtained.

12.2 Implanting Physician Training Program

SJM will train physicians qualified for left atrial procedures via the right atrium to implant the AMPLATZER PFO Occluder. The training will consist of mandatory physician didactic training and case support.

Physician Didactic Training

The physician didactic training will consist of:

- Device overview and preparation
- Appropriate patient selection
- Clinical data review
- Step by step procedure review
- Post procedural patient care, including antithrombotic therapy

Case Support

Case support will be provided by trained SJM personnel and, as appropriate, a SJM-assigned physician proctor. Implanters with at least 25 AMPLATZER septal closure procedures will have their first cases proctored by certified SJM personnel, who will document that the implanter is ready to independently complete the procedure in the future.

Implanters with fewer than 25 AMPLATZER septal closure procedures will have their first cases proctored by certified SJM personnel and an SJM-certified proctor. The physician proctor will certify the implanter is ready to independently complete the procedure in the future. If further proctoring is needed, a physician proctor is required to attend future cases until proficiency of the implanter is certified by the physician proctor.

Physician proctor training will include the online didactic module. Prior to being certified as a proctor, physicians must demonstrate successful presentation of the didactic module and complete 25 AMPLATZER septal closure procedures as the primary implanter within the last two years.

13 POST-APPROVAL CLINICAL PROGRAM

SJM will work interactively with the Office of Surveillance and Biometrics (OSB) Epidemiology Division and in consultation with the Agency's Clinical Reviewer, Lead Reviewer and other members of the FDA to further define the Post Approval Study (PAS) methodology, assumptions and requisite elements. Careful consideration will be paid to the observations and findings elucidated from the RESPECT trial. As such, the PAS proposal will include specific design elements to assure continued monitoring of safety and effectiveness of the AMPLATZER PFO Occluder in the post-approval setting and outside of the controls of the randomized clinical trial.

The objective of the proposed post approval clinical program is to assess long-term safety and effectiveness of the AMPLATZER PFO Occluder. The proposal is for two non-randomized studies intended to: (i) evaluate the existing RESPECT patient population, (ii) evaluate new patients enrolled under real-world clinical conditions. The first study (PAS1, continued follow-up of current RESPECT patients) is follow-up of active RESPECT patients through a minimum of 5 years (Section 13.1). The second study (PAS2, a new enrollment study) is a prospective post-approval study in the United States (Section 13.2).

13.1 PAS1 – Continued Follow-up of Current RESPECT Patients

Study Design

PAS1 is designed to report on the continued follow-up of patients from the RESPECT IDE trial. Patients active in the RESPECT trial will be followed through the 5-year follow-up visit. No additional patients will be enrolled in this post-approval study. The last patient was enrolled in the RESPECT IDE trial in Dec 2011. All patients are expected to complete 5-year follow-up by March 2017.

Endpoints and Statistical Analyses

The PAS1 endpoints are as follows:

- Rate of recurrent ischemic stroke at 5 years
- Rate of serious adverse events at 5 years

The 5-year rates of the primary endpoint in the Device and MM arms of the RESPECT trial will be summarized via Kaplan-Meier estimates. The hazard ratio for the primary endpoint will be estimated from a Cox proportional hazards model and presented along with 95% confidence intervals. Freedom from SAEs in the Device and MM arms at 5 years will be summarized by Kaplan-Meier estimates. Each adverse event type will be summarized within each arm by the number of events and the rate of occurrence per patient-year of follow-up.

13.2 PAS2 – New Enrollment Study

Study Design

This study is a single arm, multi-center post-approval study that will assess the long-term safety and effectiveness of the AMPLATZER PFO Occluder. This study is comprised of patients not currently implanted with the AMPLATZER PFO Occluder, who, following a screening process to confirm eligibility, will be implanted and followed under this post-approval study. Patients who were previously in the RESPECT MM arm may be eligible for this study.

Study Population

The PAS2 study population consists of patients who are intended for percutaneous, transcatheter closure of a PFO who have had a cryptogenic ischemic stroke due to a presumed paradoxical embolism. In order to ensure appropriate patient selection, patients will be evaluated by a neurologist to determine if the qualifying stroke is a cryptogenic stroke.

Study Procedures

Following a screening process to confirm eligibility for PFO closure with the AMPLATZER PFO Occluder, patients will be implanted and followed under a non-randomized, prospective registry. Patients will have follow-up visits 1, 6, and 12 months post-procedure, and annually thereafter through 5 years post-procedure. All patients will be consented for follow-up of a minimum of 5 years to assure a comprehensive evaluation of the long-term safety and effectiveness profile of the AMPLATZER PFO Occluder. Patients will undergo a transthoracic echocardiogram (TTE) at the 12-month follow-up visit to determine the status of PFO closure.

Endpoints and Statistical Analyses

The study has two co-primary endpoints for safety and effectiveness. Both primary safety and effectiveness endpoints must be met in order for the study to be declared successful. The primary safety and effectiveness endpoints are listed below.

Primary Safety:

The primary safety hypothesis is based on the proportion of patients experiencing at least one of the following device- or procedure-related SAEs through 5-year follow-up:

- 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 rate of primary safety endpoint at 5-years is less than the pre-specified performance goal of 4.0%.

The hypothesis test for the primary safety endpoint is as follows:

H_0: $p \geq 4.0\%$

H_1: $p < 4.0\%$

where p is the probability of a patient experiencing a primary safety endpoint. Analysis of the endpoint will include patients who are attempted to be implanted with the AMPLATZER PFO Occluder. Analysis of the endpoint will be carried out when all patients reach 5-year follow-up. An implant attempt is defined as the AMPLATZER PFO Occluder delivery system entering the

body. The null hypothesis will be rejected if the 95% upper confidence bound (UCB) for *p* is less than 4.0%. The upper confidence bound will be calculated by the Greenwood method.

The primary safety endpoint event rate at 5 years is assumed to be 2.0%. This assumption is based on the adverse event data through extended follow-up in the RESPECT trial.

Primary Effectiveness:

The primary effectiveness endpoint is a composite of the following events at 5 years:

- recurrent non-fatal ischemic stroke
- fatal ischemic stroke

Hypothesis: The rate of primary effectiveness endpoint at 5-years is less than the pre-specified performance goal of 4.4%.

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

H_0: $\pi \geq 4.4\%$

H_1: $\pi < 4.4\%$

Analysis of the endpoint will include patients who are successfully implanted with the AMPLATZER PFO Occluder. Analysis of the endpoint will be carried out when all patients reach 5-year follow-up. The analysis will be carried out by estimating the 5-year rate using the Kaplan-Meier method. The null hypothesis will be rejected if the 95% UCB for π is less than 4.4%. The upper confidence bound will be calculated by the Greenwood method.

The primary effectiveness endpoint event rate at 5 years is assumed to be 2.2%. This assumption is based on the 5-year Kaplan-Meier rate of ischemic stroke for subjects who received a device in the Device arm of the RESPECT trial using the extended follow-up dataset.

Descriptive Endpoints:

The study will also collect and report on the following descriptive endpoints:

- TIA – defined similarly to the event definition used in the RESPECT protocol
- Effective closure – PFO shunt assessments; grade 0 or 1 at rest and Valsalva as assessed by TTE at 12 months
- Complete closure – PFO shunt assessments; grade 0 at rest and Valsalva as assessed by TTE at 12 months
- Technical success (applicable only to patients in whom device closure is attempted), defined as successful delivery and release of the AMPLATZER PFO Occluder for patients in whom delivery system entered the body
- Procedural success (applicable only to patients in whom device closure is attempted), defined as successful implantation of the AMPLATZER PFO Occluder with no reported in-hospital SAEs

Sample Size

The sample size was calculated by simulation of the primary safety and effectiveness endpoints. Events for the primary safety and effectiveness endpoints were simulated from a binomial distribution. The primary endpoints will be analyzed when all subjects reach 5-years of follow-up. With 604 subjects, the trial would have 93% and 90% power at a significance level of 5% to reject the null hypotheses for effectiveness and safety, respectively. Assuming a 5-year attrition rate of 25%, 806 subjects are required to be enrolled.

14 BENEFIT-RISK CONCLUSION

Unlike most stroke patients who are elderly and have a number of age-related diseases such as atherosclerosis, hypertension, diabetes and atrial fibrillation, patients who experience a cryptogenic stroke are typically much younger (i.e., average age of 45 years), and the effects are more disruptive. In patients with a cryptogenic stroke and a PFO, a paradoxical embolism is a likely mechanism for the stroke. Medical management alone does not eliminate the risk for a recurrent stroke. Safely closing the PFO with appropriate concomitant medical management can offer these patients an option to further reduce the risk for recurrent stroke.

The goal of the RESPECT trial was to determine whether PFO closure with the AMPLATZER PFO Occluder reduces the risk of recurrent stroke compared to standard of care medical therapy. RESPECT is the longest stroke-prevention PFO device trial conducted (spanning over a decade) in the largest cohort of patients. The trial was difficult to design, enroll, and execute due to the environment of 1) availability of the device under an HDE from 2003 to 2006, and 2) rampant off-label closure of PFOs using other closure devices.

The trial assumed a recurrent ischemic stroke rate of 4.3% at 2 years in patients managed medically equating to an annualized event rate of 2.2 per 100 patient-years. However, the event rate observed in the trial was about half of that anticipated, 1.2 per 100 patient-years. Whereas the absolute annual risk of stroke for patients managed medically is low, a 50% reduction in risk of stroke can be meaningful for young to middle-aged patients with many decades of life before them. The results of the RESPECT trial support a low number needed to treat (NNT) of 21 patients to prevent one stroke through 5 years (i.e., based on Per-Protocol analysis, 5-year rates were 5.9% in Device arm and 1.2% in MM arm, with an NNT = 1/(0.059-0.012).[2] This number needed to treat must be placed within the context of several well-established pharmacologic secondary stroke prevention treatments, which showed NNTs ranging from 15 to 38 over approximately 2 years (Bandolier).

Despite the limitations stemming from patient discontinuation from RESPECT, sensitivity analyses demonstrated that the results are robust to missing data. Exploratory analyses conducted on various analysis populations are also supportive of a large positive device effect. Meta-analysis combining individual patient-level data from the RESPECT and PC trials demonstrated statistically significant superiority of the device in reducing the risk of recurrent ischemic stroke. Through extended follow-up, the device demonstrated a marked reduction in the risk of subsequent stroke of undetermined mechanism. The substantial device effect is attributed to the PFO closure mechanism which prevents blood clots from travelling from the venous to the arterial system.

RESPECT had rigorous exclusion criteria to exclude strokes of known mechanism. In all cases, the qualifying stroke resulted in clinical symptoms, and in the large majority of patients, the qualifying stroke was imaging confirmed. The diagnosis of cryptogenic stroke was based on results of baseline tests and assessments which are conducted as the standard of care by vascular neurologists on stroke patients. Despite the rigorous criteria to rule out known mechanisms of stroke in the RESPECT population, strokes of known mechanism emerged as they aged during the long trial follow-up.

SJM recognizes the importance of patient selection and the need for implanting physicians to be properly trained. The company will provide a rigorous and comprehensive training and education program to ensure that patients are appropriately selected and treated with the AMPLATZER PFO Occluder.

The totality of the data collected on the AMPLATZER PFO Occluder demonstrates that the device can be safely implanted. The RESPECT trial has demonstrated that the AMPLATZER PFO Occluder is a device with a safe implantation procedure and a favorable long-term safety profile. The trial showed a 5% rate of procedure- or device-related serious adverse events. Nearly all of the procedure- or device-related serious adverse events resolved without long-term sequelae. There were no procedure- or device-related deaths. Finally, there were no intra-procedural strokes, device embolizations or reports of thrombus on the device or device erosions in RESPECT.

In the United States, medical management with antiplatelet or anticoagulant or surgical closure of a PFO are the only currently available therapies to treat patients with a PFO who have experienced a cryptogenic stroke. PFO closure outside of the RESPECT trial pursued by some patients randomized to medical management underscores the unmet need for device-based PFO closure. Approval of the AMPLATZER PFO Occluder will provide patients younger than 60 years of age with decades of life before them, and their physicians, an additional safe and effective treatment option to further reduce the risk of a future stroke. Approval will also provide an on-label percutaneous option that has been vetted and provides labeling and guidance for physicians and patients. Considering the life-long benefit of protection from a paradoxical embolism and the very low incidence of adverse complications associated with the device, the benefits of the device outweigh the risks associated with the device. SJM's patient satisfaction survey results indicated satisfaction with being randomized to the device arm more often than to the medical management arm, suggesting that some patients may prefer this option. Proper patient selection emphasized via a comprehensive training program will further ensure that the benefits of PFO closure with the AMPLATZER PFO Occluder outweigh the risks in the young and middle-aged patients for whom it is intended.

15 REFERENCE LIST

Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41.

Alberts GW, Amarenco P, Easton D, Sacco RL, Teal, P. Antithrombotic and thrombotlytic therapy for ischemic stroke. *Chest* 2001;119(1 suppl):300S-320S.

Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. *Cerebrovasc Dis* 2005; 20 (suppl 2): 68–74.

Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). *Cerebrovasc Dis* 2013;36:1–5.

American Heart Association/American Stroke Association. Understanding diagnosis and treatment of cryptogenic stroke. A Healthcare professional guide. 2015. Retrieved from http://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@hcm/@sta/documents/downloadable/ucm_477051.pdf

Arauz A, Murillo L, Márquez JM, Tamayo A, Cantú C, Roldan F-J, Vargas-Barrón J, Barinagarrementeria F. Long-term risk of recurrent stroke in young cryptogenic stroke patients with and without patent foramen ovale. *Int J Stroke* 2012;7:631-634.

Bandolier. http://www.medicine.ox.ac.uk/bandolier/band38/b38-2.html. Accessed 15 April 2016.

Beitzke A, Schuchlenz H, Beitzke M, Gamillscheg A, Stein HI, et al. [Interventional occlusion of foramen ovale and atrial septal defects after paradoxical embolism incidents]. *Zeitschrift Für Kardiologie* 2002;91(9):693-700.

Bogousslavsky J, Grazi S, Jeanrenaud X, Aebischer N, Van Melle G. Stroke recurrence in subjects with patent foramen ovale: the Lausanne Study. Lausanne Stroke with Paradoxical Embolism Study Group. *Neurology* 1996;46:1301-1305.

Brandt RR, Neumann T, Neuzner J, Rau M, Faude I, et al. Transcatheter closure of atrial septal defect and patent foramen ovale in adult patients using the Amplatzer occlusion device: No evidence for thrombus deposition with antiplatelet agents. *J Am Soc Echocardiogr* 2002;15(Part 1):1094-1098.

Bushnell CD, Olson DM, Zhao X, Pan W, et al. Secondary preventive medication persistence and adherence 1 year after stroke. *Neurology* 2011; 77:1182–1190.

Butera G, Bini MR, Chessa M, Bedogni F, Onofri M, et al. Transcatheter closure of patent foramen ovale in patients with cryptogenic stroke. *Ital Heart J* 2001;2(2):115-118.

Carrol JD, Saver JM, Thaler DE, Smalling RW, Berry S, et al. Closure of patent foramen ovale versus medical therapy for cryptogenic stroke. *NEJM* 2013;368:1092-1100.

Cerrato P, Priano L, Imperiale D, Bosco G, Destefanis E, Villar AM, Ribezzo M, Trevi GP, Bergamasco B, Orzan F. Recurrent cerebrovascular ischaemic events in patients with interatrial septal abnormalities: a follow-up study. *Neurol Sci*. 2006;26(6):411-8.

DeCastro S, Cartoni D, Fiorelli M. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;31:2407-2413.

Di Tullio MR, Zhezhen J, Russo C, Elkind MSV, Rundek T, et al. Patent foramen ovale, subclinical cerebrovascular disease, and ischemic stroke in a population-based cohort. *JACC* 2013;62(1):35-41.

Fonorow GC, Reeves MJ, Zhao X, Olson DM, Smith EE, et al. Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. *Circulation* 2010;121:879-891.

Food and Drug Administration Guidance Document. Patient preference information – submission, review in PMAs, HDE applications, and De Novo requests, and inclusion in device labeling. 2015. Retrieved from http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf

Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *NEJM* 2012;366:991-999.

Glader E-L, Sjölander M, Eriksson M, Lundberg M. Persistent Use of Secondary Preventive Drugs Declines Rapidly During the First 2 Years After Stroke. *Stroke* 2010;41:397-401.

Hagen PT, Scholz DG, Edwards W D. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. In *Mayo Clinic Proceedings* 1984; 59: 17-20.

Handke M, Harloff A, Olschewski M, Hetzel A, & Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *NEJM* 2007; 357(22), 2262-2268.

Hart R, Diener H-C, Coutts S, Easton JD, Granger CB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13(4):429-438.

Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870-947.

Kent DM, Dahabreh IJ, Ruthazer R, Furlan AJ, Reisman M, et al. Device closure of patent foramen ovale after stroke: Pooled analysis of completed randomized trials. *J Am Coll Cardiol* 2016;67(8):907-917.

Kitsious GD, Thaler DT, Kent DM. Potentially large yet uncertain benefits: a meta-analysis of patent foramen ovale closure trials. *Stroke* 2013;44(9):2640-3.

Korabathina R, Thaler DE, Kimmelstiel C. Stroke due to late device thrombosis following successful percutaneous patent foramen ovale closure. *Catheter Cardiovasc Interv* 2012;80(3):498-502.

Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, et al. Recommendations for Imaging of Acute Ischemic Stroke: a scientific statement from the American Heart Association. *Stroke* 2009;40:3646-3678.

Lefkowitz DS, Brust JCM, Goldman L, Johnson JL, Toole JF, et al. A pilot study of the end point verification system in the Asymptomatic Carotid Atherosclerosis Study. *J Stroke Cerebrovasc Dis* 1992;2:92-99

Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Rothwell PM, on behalf of the Oxford Vascular Study. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015; 14: 903–13.

Martin F, Sanches PL, Doherty E, Colon-Hernandez PJ, Delgado G, et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation* 2002;106:1121-1126.

Mas JL, Zuber M. Recurrent cerebrovascular events in subjects with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995;130:1082-1088.

Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, Coste J. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med*; 2001; 345(24): 1740-6.

Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *NEJM* 2013;368:1083-1091.

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. *Circulation* 2015;131(4):e29-322.

Onorato E, Melzi G, Casilli F, Pedon L, Rigatelli G, et al. Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. *J Interv Cardiol* 2003;16(1):43-50.

Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, et al. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke* 2000;31:1062-1068.

Redfors P, Jood, K, Holmegaard L, Rosengren A, Jern C. Stroke subtype predicts outcome in young and middle-aged stroke sufferers. *Acta Neurol Scand,* 2012; 126(5):329-35.

Rengifo-Moreno P, Palacios IF, Junpaparp P, Witzke CF, Morris DL, et al. Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J*, 2013;34(43):3342-52.

Sacco RL, Adams RJ, Albers G, Alberts MJ, Benavente O, et al. American Heart Association/American Stroke Association Council on Stroke. Guidelines for the 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. *Stroke* 2006;37:577-617.

Sievert H, Horvath K, Zadan E, Krumsdorf U, Fach A, et al. Patent foramen ovale closure in patients with transient ischemia attack/stroke. *J Interv Cardiol* 2001;14(2):261-266.

Stortecky S, da Costa BR, Mattle HP, Carroll J, Hornung M, et al. Percutaneous closure of patent foramen ovale in patients with cryptogenic embolism: a network meta-analysis. *Eur Heart J* 2015;36(2):120-8.

Whitlock RP, Sun JC, Fremes SE, Rubens FD, and Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141.2_suppl (2012): e576S-e600S.

16 APPENDIX A: COMMITTEE MEMBERSHIP

Steering Committee

Members	Role	Affiliation
John D Carroll, MD	Cardiologist	University of Colorado
Jeffrey Saver, MD, FAHA, FAAN	Neurologist	UCLA School of Medicine
Richard Smalling, MD, PhD	Cardiologist	University of Texas Houston Health Science Center
David Thaler, MD, PhD	Neurologist	The Comprehensive Stroke Center at Tufts Medical Center

Clinical Event Committee (CEC)

Members	Role	Affiliation
Charles Horowitz, MD	Neurologist	The Minneapolis Clinic of Neurology, Ltd.
Brian T. Larkin, MD	Radiologist	Minneapolis Radiology Associates
Timothy Tanke, MD	Cardiologist	Bellin Health
John G. Davenport, MD (past member)	Neurologist	Park Nicollet Neurosciences
Cathy Helgason, MD (past member)	Neurologist	University of Illinois College of Medicine

Data Safety Monitoring Board (DSMB)

Members	Role	Affiliation
Irfan M. Altafullah, MD	Neurologist	The Minneapolis Clinic of Neurology, Ltd.
Steven Roh, MD	Interventional Cardiologist	North Memorial Heart and Vascular Institute
Scott R. Schultz, MD	Radiologist	Minneapolis Radiology Associates
Marc Schwartz, MS	Biostatistician	Med Analytics, Inc
Shunichi Homma, MD, FACC (past member)	Cardiologist	Columbia-Presbyterian Medical Center

ASCOD Adjudication Committee

Members	Role	Affiliation
Brian T. Larkin, MD	Radiologist	Minneapolis Radiology Associates
David Thaler, MD, PhD	Neurologist	The Comprehensive Stroke Center at Tufts Medical Center
Jeffrey Saver, MD, FAHA, FAAN	Neurologist	UCLA School of Medicine

17 APPENDIX B: INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

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

Exclusion Criteria

a) Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels of >50% of lumen diameter supplying the involved lesion

b) Intracardiac thrombus or tumor

c) Acute or recent (within 6 months) myocardial infarction or unstable angina

d) Left ventricular aneurysm or akinesis

e) Mitral valve stenosis or severe mitral regurgitation irrespective of etiology

f) Aortic valve stenosis (gradient >40 mmHg) or severe aortic valve regurgitation

g) Mitral or aortic valve vegetation or prosthesis

h) Aortic arch plaques protruding >4mm into the lumen

i) Left ventricular dilated cardiomyopathy with LVEF <35%

j) Patients with other source of right to left shunts identified at baseline, including an atrial septal defect and/or fenestrated septum

k) Atrial fibrillation/atrial flutter (chronic or intermittent)

l) Pregnant or desire to become pregnant within the next year

m) Age <18 years and age >60 years

n) Active endocarditis, or other untreated infections

o) Organ failure (kidney, liver or lung)

Kidney failure: Poor urine output of less than 1 cc/kg/hr with elevated BUN levels (above the normal reference range for the laboratory at the investigational site).

Liver failure: Liver enzymes outside the normal reference range for the laboratory at the investigational site: poor liver function as assessed by elevated PT (above the normal reference range for the laboratory at the investigational site) and low total protein and albumin (below the normal reference range for the laboratory at the investigational site)

Lung failure: Respiratory failure is retention of carbon dioxide more than 60 mmHg, poor oxygenation with oxygen tension less than 40 mmHg in room air or the need for assisted ventilation

p) Uncontrolled hypertension or uncontrolled diabetes mellitus

Uncontrolled hypertension: Sustained elevated systemic blood pressure to more than 160/90 with medications

Uncontrolled diabetes: Continued elevated glucose levels in spite of administration of insulin/levels of more than 200 mg with presence of glucose in the urine

q) Lacunar infarct probably due to intrinsic small vessel as qualifying event

Definition: 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)

r) Arterial dissection as qualifying event

s) Signs of progressive neurological dysfunction

t) Patients who test positive with one of the following hypercoagulable states; Anticardiolipin Ab (IgG or IgM), Lupus anticoagulant, B2-glycoprotein-1 antibodies, or persistently elevated fasting plasma homocysteine despite medical therapy

u) Patients with contraindication to aspirin or clopidogrel therapy

v) Anatomy in which the AMPLATZER PFO Occluder would interfere with intracardiac or intravascular structures such as valves or pulmonary veins

w) Malignancy or other illness where life expectancy is less than 2 years

x) Patients who will not be available for follow-up for the duration of the trial

y) Inability to obtain informed consent from patient or legally authorized representative

z) Stroke with poor outcome at time of enrollment (modified Rankin Scale score >3)

aa) Patients who are not able to discontinue the use of anticoagulation if randomized to closure

18 APPENDIX C: STROKE ASCERTAINMENT CASE REPORT FORMS

RESPECT Trial - AGA Medical Corporation | AGA Medical Use only: US Site Code ☐☐☐

RESPECT

#9 NEUROLOGIC SYMPTOMS GENERAL INTERVIEW

AGA Medical Use Only
Date Received _____ 1st Pass _____
Clinical Review _____ 2nd Pass _____
Batch Number _____ 3rd Party Review _____

1.0 General Information

1.1 AGA Subject Code: ☐☐☐☐

1.2 Subject Initials: ☐☐☐

1.3 Person supplying information collected on this form: **(check only one)**
1☐ RESPECT Subject
2☐ Spouse
3☐ Other, specify: _____

1.4 Date of Follow-up: __/__/__ (mm/dd/yy)

1.5 Follow-up Interval:
1☐ 01-Month 7☐ 4-Year
2☐ 06-Month 8☐ 5-Year
3☐ 12-Month 9☐ 6-Year
4☐ 18-Month 10☐ Event
5☐ 2-Year 11☐ 90-days post event
6☐ 3-Year 12☐ Interim

INSTRUCTIONS: This form is completed during the interview portion of each follow-up visit during the study. Its purpose is to document if symptoms of Stroke or TIA have occurred since the questionnaire was last administered.

2.0 New Stroke or TIA

2.1 Since the last time we administered this questionnaire to you, have you been told by a physician that you had a STROKE or TIA? 1☐ Yes 2☐ No 3☐ Don't Know

3.0 New Stroke or TIA Symptoms

Since the last time we administered this questionnaire to you, have you had:

3.1 Any SUDDEN change in your ability to speak clearly and correctly? 1☐ Yes 2☐ No 3☐ Don't Know

3.2 Any SUDDEN blurring or loss of vision? 1☐ Yes 2☐ No 3☐ Don't Know

3.3 A SUDDEN spell of double vision? 1☐ Yes 2☐ No 3☐ Don't Know

3.4 SUDDEN numbness, tingling, or loss of feeling on one side of your body, including your face, arm, or leg? 1☐ Yes 2☐ No 3☐ Don't Know

3.5 Any SUDDEN paralysis or weakness on one side of your body, including your face, arm, or leg? 1☐ Yes 2☐ No 3☐ Don't Know

3.6 Any SUDDEN dizziness, loss of balance, or a sensation of spinning? 1☐ Yes 2☐ No 3☐ Don't Know

If YES to ANY QUESTION in Section 2.0 or 3.0, complete the following for each positive response.
- #9A (Neurologic Symptoms Detailed Information Form)
- #9B (Neurologic Endpoint Diagnosis Form)

4.0 Signatures

4.1 Prepared By: _____ (Signature) 4.2 Date Signed: __/__/__ (mm/dd/yy)

4.3 Reviewed/Approved by: _____ (Principal Investigator Signature) 4.4 Date Signed: __/__/__ (mm/dd/yy)

RESPECT Trial
#9 Neurologic Symptoms General Interview
CONFIDENTIAL

Page 1 of 1

VISP Trial Follow-up Stroke Symptoms Form modified for the RESPECT Trial with permission from J.F. Toole, MD

White copy-AGA Medical; *Yellow copy*-site

AGA-006 Rev J
March 2006

RESPECT Trial - AGA Medical Corporation | AGA Medical Use only: US Site Code ☐☐☐

RESPECT

#9A Neurologic Symptoms Detailed Interview

AGA Medical Use Only

Date Received _____ 1st Pass _____

Clinical Review _____ 2nd Pass _____

Batch Number _____ 3rd Party Review _____

INSTRUCTIONS

This form is completed if the subject has reported a positive response on a #9 Neurological Symptoms General Interview Form. The purpose of this form is to document the detailed symptoms relating to a possible stroke or TIA.

Please complete a separate form for each event, UNLESS, the subject had 3 or more events with like symptoms, each less than 24 hours in duration. Then complete only one form for the first event in the sequence.

Definition of Stroke: Acute focal neurological 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.

Definition of TIA: Acute focal neurological deficit (defined as focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit) presumed due to focal ischemia; symptoms persisting greater than or equal to 5 minutes and less than 24 hours, that is not associated with MR or CT findings of a new, neuroanatomically relevant cerebral infarct.

1.0 General Information

1.1 AGA Subject Code: ☐☐☐☐

1.2 Subject Initials: ☐☐☐

1.3 Person supplying information collected on this form (**check only one**):

1 ☐ RESPECT Subject
2 ☐ Spouse
3 ☐ Other, specify: _____

1.4 Follow-up Interval:

1 ☐ 01-Month 7 ☐ 4-Year
2 ☐ 06-Month 8 ☐ 5-Year
3 ☐ 12-Month 9 ☐ 6-Year
4 ☐ 18-Month 10 ☐ Event
5 ☐ 2-Year 11 ☐ 90-days post event
6 ☐ 3-Year 12 ☐ Interim

2.0 Symptom Details (use 24 hour military time for all questions relating to time)

2.1 Date of Symptom Onset: __ __/__ __/__ __ (mm/dd/yy)

2.2 Date Symptoms Ended: __ __/__ __/__ __ (mm/dd/yy) or ☐ Ongoing

2.3 Time of Symptom Onset: __ __:__ __ (military time)

2.4 Time Symptoms Ended: __ __:__ __ (military time) or ☐ Ongoing

2.5 Did the patient have 3 or more events with like symptoms, each less than 24 hours in duration since the last visit? 1 ☐ Yes* 2 ☐ No 3 ☐ Don't Know

* **If YES,** complete only **ONE** #9A Neurologic Symptoms Detailed Interview - for the first event in the sequence.

RESPECT Trial - AGA Medical Corporation

AGA Subject Code: ☐☐☐☐
Date of Symptom Onset: __ __/__ __/__ __ mm/dd/yy
Time of Symptom Onset: __ __:__ __ (military time)

3.0 New Stroke or TIA Symptoms Detailed Interview

The following questions are about the symptoms with your recent neurologic event.

3.1 **During this event, did you have a SEIZURE or a CONVULSION?** 1☐ Yes 2☐ No 3☐ Don't Know

3.2 **During this event, did you have a HEADACHE?** 1☐ Yes 2☐ No 3☐ Don't Know

3.3 **During this event, did you see FLICKERING or FLASHING LIGHTS?** 1☐ Yes 2☐ No 3☐ Don't Know

3.4 **During this event, did you BLACKOUT or FAINT?** 1☐ Yes 2☐ No 3☐ Don't Know

3.5 **During this event, did you have a SUDDEN change in ability to speak clearly and correctly?** 1☐ Yes 2☐ No 3☐ Don't Know

If NO or DON'T KNOW, skip to 3.6

If YES, Do any of the following describe your change in speech? **(Read all choices)**

3.5 a. Slurred speech like you were drunk. 1☐ Yes 2☐ No 3☐ Don't Know

3.5 b. Could talk but the wrong words came out. 1☐ Yes 2☐ No 3☐ Don't Know

3.5 c. Knew what you wanted to say, but the words would not come out. 1☐ Yes 2☐ No 3☐ Don't Know

3.5 d. Could not think of the right words. 1☐ Yes 2☐ No 3☐ Don't Know

3.5 e. **If MORE than ONE above is YES,** which **ONE** most closely describes your problem? 1☐ a 2☐ b 3☐ c 4☐ d

3.6 **During this event, did you have SUDDEN blurring or loss of vision?** 1☐ Yes 2☐ No 3☐ Don't Know

If NO or DON'T KNOW, skip to 3.7

3.6.1 During the episode, which of the following parts of your vision were affected?
(Read all choices, mark only one)
1☐ Right Eye Only
2☐ Left Eye Only
3☐ Both Eyes (**If YES,** answer 3.6.2)

3.6.2 If BOTH Eyes, did you have?
(Read all choices, mark only one)
1☐ Trouble seeing to the right but not to the left
2☐ Trouble seeing to the left but not to the right
3☐ Trouble seeing both the left and right sides

3.7 **During this event, did you have a SUDDEN spell of double vision?** 1☐ Yes 2☐ No 3☐ Don't Know

If NO or DON'T KNOW, skip to 3.8

3.7.1 If you closed one eye, did the double vision go away? 1☐ Yes 2☐ No 3☐ Don't Know

3.8 **During this event, did you have SUDDEN numbness, tingling, or loss of feeling on one side of your body, including your face, arm, or leg?** 1☐ Yes 2☐ No 3☐ Don't Know

If NO or DON'T KNOW, skip to 3.9

3.8.1 Did the feeling of numbness or tingling occur only when you kept your arms or legs in a certain position? 1☐ Yes 2☐ No 3☐ Don't Know

If YES, skip to 3.9

RESPECT Trial - AGA Medical Corporation

AGA Subject Code: ☐☐☐☐
Date of Symptom Onset: __/__/__ mm/dd/yy
Time of Symptom Onset: __:__ (military time)

3.0 New Stroke or TIA Symptoms Detailed Interview (continued)

3.8.2 During the episode of sudden numbness or tingling, which part or parts of your body were affected?

(Read all choices)	Yes	No	Don't Know		Yes	No	Don't Know
3.8.3 Left arm or hand	1☐	2☐	3☐	3.8.6 Right arm or hand	1☐	2☐	3☐
3.8.4 Left leg or foot	1☐	2☐	3☐	3.8.7 Right leg or foot	1☐	2☐	3☐
3.8.5 Left side of face	1☐	2☐	3☐	3.8.8 Right side of face	1☐	2☐	3☐
				3.8.9 Other,	1☐	2☐	3☐

3.8.9.1 **If YES**, specify: _____

3.8.10 During this episode, did the abnormal sensation start in one part of your body and spread to another, or did it stay in the same place?
1☐ Started in one part and spread to another
2☐ Stayed in one part
3☐ Don't know

3.9 **During this event, did you have SUDDEN paralysis or weakness on one side of your body, including your face, arm, or leg?** 1☐ Yes 2☐ No 3☐ Don't Know
If NO or DON'T KNOW, skip to 3.10

3.9.1 During the episode of sudden paralysis or weakness, which part or parts of your body were affected?

(Read all choices)	Yes	No	Don't Know		Yes	No	Don't Know
3.9.2 Left arm or hand	1☐	2☐	3☐	3.9.5 Right arm or hand	1☐	2☐	3☐
3.9.3 Left leg or foot	1☐	2☐	3☐	3.9.6 Right leg or foot	1☐	2☐	3☐
3.9.4 Left side of face	1☐	2☐	3☐	3.9.7 Right side of face	1☐	2☐	3☐
				3.9.8 Other,	1☐	2☐	3☐

3.9.8.1 **If YES**, specify: _____

3.9.9 During this episode, did the paralysis or weakness start in one part of your body and spread to another, or did it stay in the same place?
1☐ Started in one part and spread to another
2☐ Stayed in one part
3☐ Don't know

3.10 **During this event, did you have SUDDEN dizziness, loss of balance, or a sensation of spinning?** 1☐ Yes 2☐ No 3☐ Don't Know
If NO or DON'T KNOW, skip to 4.0

3.10.1 Did the dizziness, loss of balance or spinning sensation occur only when changing the position of your head or body? 1☐ Yes 2☐ No 3☐ Don't Know

If YES, to ANY QUESTION in sections 2.0 or 3.0, complete a #9B - Neurologic Endpoint Assessment Form.

4.0 Signatures

4.1 Prepared By: _____ (Signature) 4.2 Date Signed: __/__/__ (mm/dd/yy)

4.3 Reviewed/Approved by: _____ (Principal Investigator Signature) 4.4 Date Signed: __/__/__ (mm/dd/yy)

RESPECT Trial - AGA Medical Corporation | AGA Medical Use only: US Site Code ☐☐☐

RESPECT

#9B Neurologic Endpoint Assessment & Diagnosis Form

AGA Medical Use Only

Date Received _____ 1st Pass _____

Clinical Review _____ 2nd Pass _____

Batch Number _____ 3rd Party Review _____

Instructions

This form is **required** to be **completed by a RESPECT Trial Investigator** at the time of possible cerebral infarction or when there is a **Positive** answer on the #9 Neurologic Symptoms General Interview form.

1.0 General Information

1.1 AGA Subject Code: ☐☐☐☐

1.2 Subject Initials: ☐☐☐

1.3 Date of Symptom Onset which led to this review: __ __/__ __/__ __ mm/dd/yy

1.4 Time of Symptom Onset which led to this review: ___ ___ : ___ ___ (military time)

2.0 Reason for Evaluation

What initiated this review? **(There may be more than one positive response)**	Yes	No
2.1 #9 Neurologic Symptoms General Interview	☐	☐
2.2 Hospitalization with a stroke-related diagnosis	☐	☐
2.3 CT/MRI Scan or Report	☐	☐
2.4 Death of subject	☐	☐
2.5 One (or more) point increase in a section of the NIH Stroke Scale with previous 0 score?	☐	☐
2.6 One (or more) point increase in a section of the NIH Stroke Scale with previous positive score, and no increase in a section with a previous 0 score?	☐	☐
2.7 Other: specify: _____	☐	☐

3.0 Diagnostic Information

3.1 Did the MRI or CT indicate a new infarct? 1☐ Yes 2☐ No 3☐ Study Not Done **If YES**, skip to 3.1.2. **If NO**, skip to 3.2

3.1.1 **If Study Not Done**, indicate reason: _____
(**Then,** Skip to 3.2)

3.1.2 Was the new infarct consistent with the symptoms reported in the #9 or #9A form? ☐ Yes ☐ No

3.1.3 Did the CT or MRI indicate a new primary hemorrhagic stroke? ☐ Yes ☐ No

3.2 Duration of subject's symptoms:

1☐ 24 hours or greater 2☐ 5 minutes up to 24 hours 3☐ less than 5 minutes 4☐ Undetermined

RESPECT Trial - AGA Medical Corporation

AGA Subject Code: ☐☐☐☐

Date of Symptom onset __ __/ __ __/ __ __ mm/dd/yy

Time of Symptom onset __ __ : __ __ (military time)

4.0 Diagnosis of ISCHEMIC Stroke – Primary Endpoint

DEFINITION OF ISCHEMIC STROKE: Acute focal neurological deficit presumed to be due to focal ischemia, and either
1) persisting greater than 24 hours; or,
2) persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct.

4.1 Would you diagnose the event leading to this review as a recurrent ISCHEMIC stroke meeting RESPECT primary endpoint criteria? ☐ Yes **If YES,** skip to 4.2 ☐ No **If NO,** complete 4.1.1 & 4.1.2

4.1.1 **If NO**: Reason for not diagnosing symptoms as meeting RESPECT primary endpoint criteria:

_____

_____

4.1.2 Indicate the leading alternative diagnosis for the event: **If completed**, skip to 5.0

_____

_____

4.2 Was the new ischemic stroke cryptogenic in nature? ☐ Yes ☐ No

5.0 Diagnosis of TIA – Secondary Endpoint

DEFINITION OF TIA: Acute focal neurological deficit (defined as focal motor deficit, aphasia, difficulty walking, hemisensory deficit, amaurosis fugax, blindness, or focal visual deficit) presumed due to focal ischemia; symptoms persisting greater than or equal to 5 minutes and less than 24 hours, that is not associated with MR or CT findings of a new, neuroanatomically relevant cerebral infarct.

5.1 Would you diagnose the event leading to this review as a **TIA** meeting RESPECT secondary endpoint criteria? ☐ Yes **If YES,** skip to 6.0 ☐ No **If NO,** answer 5.1.1 & 5.1.2

5.1.1 **If No**: Reason for not diagnosing symptoms as meeting RESPECT secondary endpoint criteria:
If same as 4.1.1 above, please re-indicate

_____

_____

5.1.2 Indicate the leading alternative diagnosis for the event: **If same as 4.1.2 above**, please re-indicate

_____

_____

6.0 Signatures

6.1 Prepared By: _____ (Signature) 6.2 Date Signed: __ __/__ __/__ __ mm/dd/yy

6.3 Reviewed/Approved by: _____ (Principal Investigator Signature) 6.4 Date Signed: __ __/__ __/__ __ mm/dd/yy

RESPECT Trial - AGA Medical Corporation | AGA Medical Use only: US Site Code ☐☐☐

RESPECT

#9C EVENT IMAGING FORM

AGA Medical Use Only

Date Received _____ 1st Pass _____

Clinical Review _____ 2nd Pass _____

Batch Number _____ 3rd Party Review _____

1.0 General Information

1.1 AGA Subject Code: ☐☐☐☐ 1.2 Subject Initials: ☐☐☐

1.3 Date of Symptom Onset which led to this review: __ __/__ __/__ __ mm/dd/yy

1.4 Time of Symptom Onset which led to this review: __ __ : __ __ (military time)

2.0 Parenchymal Imaging of Qualifying Event

(If more than one method was used, complete a separate #13 form for results not reflected below)

		Yes	No	
2.1	Brain MRI Scan Done	☐	☐	2.1.1 **If YES**, Date: __ __/__ __/__ __ mm/dd/yy
2.2	Brain CT Scan Done	☐	☐	2.2.1 **If YES**, Date: __ __/__ __/__ __ mm/dd/yy

2.3 **If BOTH** MRI and CT were done, please specify which test results are reflected below: 1☐ MRI 2☐ CT

2.4 Was a new infarct visualized? ☐ Yes ☐ No **If NO**, skip to 3.0

	Neuroanatomic Location(s)	Yes	No			Yes	No
2.5	Frontal Cortex	☐	☐	2.11	Basal Ganglia	☐	☐
2.6	Parietal Cortex	☐	☐	2.12	Thalamus	☐	☐
2.7	Temporal Cortex	☐	☐	2.13	Cerebellum	☐	☐
2.8	Occipital Cortex	☐	☐	2.14	Brainstem	☐	☐
2.9	Centrum Semiovale	☐	☐	2.15	Other	☐	☐
2.10	Internal Capsule	☐	☐	2.15.1	**If YES**, specify: _____		

	Vascular territory(s)	Yes	No			Yes	No
2.16	Middle Cerebral Artery	☐	☐	2.20	Vertebral Artery	☐	☐
2.17	Anterior Cerebral Artery	☐	☐	2.21	Anterior Choroidal Artery	☐	☐
2.18	Posterior Cerebral Artery	☐	☐	2.22	Other	☐	☐
2.19	Basilar Artery	☐	☐	2.22.1	**If YES**, specify: _____		

2.23 Size of lesion – longest linear diameter

1☐ Small (<0.5 cm) 4☐ Large (3.1-6.0 cm)

2☐ Intermediate (0.5-1.5 cm) 5☐ Massive (> 6.0 cm)

3☐ Moderate (1.6-3.0 cm) 6☐ Size Not Reported

3.0 Cervical Vessel Imaging of Qualifying Event

(If more than one method was used, complete a separate #15 form for results not reflected below)

3.1 Cervical Vessel Imaging Done? ☐ Yes ☐ No **If NO**, skip to section 4.0.

3.2 Diagnostic Method Used (mark only one)

1☐ Carotid ultrasound

2☐ MR angiogram

3☐ CT angiogram

4☐ Catheter angiogram

5☐ Other, specify: _____

3.3 Date of Study: __ __/____/__ __ mm/dd/yy

3.4 Were any cervical vessels stenotic or occluded? ☐ Yes ☐ No **If NO**, skip to section 4.0.

RESPECT Trial - AGA Medical Corporation

AGA Subject Code: ☐☐☐☐
Date of Symptom Onset: __ __/__ __/__ __ mm/dd/yy
Time of Symptom Onset: __ __:__ __ (military time)

	Artery	Stenotic or Occluded Yes	No	Not Assessed	Percent Stenosis (%)	Flow Gap Yes	No
3.5	Right Common Carotid Artery	1☐	2☐	3☐	3.5.1__ __ __	☐	☐
3.6	Right Internal Carotid Artery	1☐	2☐	3☐	3.6.1__ __ __	☐	☐
3.7	Right External Carotid Artery	1☐	2☐	3☐	3.7.1__ __ __	☐	☐
3.8	Right Extracranial Vertebral Artery	1☐	2☐	3☐	3.8.1__ __ __	☐	☐
3.9	Left Common Carotid Artery	1☐	2☐	3☐	3.9.1__ __ __	☐	☐
3.10	Left Internal Carotid Artery	1☐	2☐	3☐	3.10.1__ __ __	☐	☐
3.11	Left External Carotid Artery	1☐	2☐	3☐	3.11.1__ __ __	☐	☐
3.12	Left Extracranial Vertebral Artery	1☐	2☐	3☐	3.12.1__ __ __	☐	☐

4.0 Intracranial Vessel Imaging of Qualifying Event

(If more than one method was used, complete a separate #14 form for results not reflected below)

4.1 Intracranial Vessel Imaging Done? ☐ Yes ☐ No **If NO**, skip to section 5.0.

4.2 Diagnostic Method Used **(mark only one)**

1☐ TCD
2☐ MR angiogram
3☐ CT angiogram
4☐ Catheter angiogram
5☐ Other, specify: _____

4.3 Date of Study: __ __/__ __/__ __ mm/dd/yy

4.4 Were any intracranial arteries stenotic or occluded? ☐ Yes ☐ No **If NO**, skip to Section 5.0.

	Artery	Stenotic or Occluded Yes	No	Not Assessed	Percent Stenosis (%)	Flow Gap Yes	No
4.5	Left Intracranial Carotid Artery	1☐	2☐	3☐	4.5.1__ __ __	☐	☐
4.6	Left Middle Cerebral Artery Stem	1☐	2☐	3☐	4.6.1__ __ __	☐	☐
4.7	Left Middle Cerebral Artery Division	1☐	2☐	3☐	4.7.1__ __ __	☐	☐
4.8	Left Anterior Cerebral Artery	1☐	2☐	3☐	4.8.1__ __ __	☐	☐
4.9	Right Intracranial Carotid Artery	1☐	2☐	3☐	4.9.1__ __ __	☐	☐
4.10	Right Middle Cerebral Artery Stem	1☐	2☐	3☐	4.10.1__ __ __	☐	☐
4.11	Right Middle Cerebral Artery Division	1☐	2☐	3☐	4.11.1__ __ __	☐	☐
4.12	Right Anterior Cerebral Artery	1☐	2☐	3☐	4.12.1__ __ __	☐	☐
4.13	Left Intracranial Vertebral Artery	1☐	2☐	3☐	4.13.1__ __ __	☐	☐
4.14	Right Intracranial Vertebral Artery	1☐	2☐	3☐	4.14.1__ __ __	☐	☐
4.15	Basilar Artery	1☐	2☐	3☐	4.15.1__ __ __	☐	☐
4.16	Left Posterior Cerebral Artery	1☐	2☐	3☐	4.16.1__ __ __	☐	☐
4.17	Right Posterior Cerebral Artery	1☐	2☐	3☐	4.17.1__ __ __	☐	☐

5.0 Signatures

5.1 Prepared By: _____ (Signature)

5.2 Date Signed: __ __/__ __/__ __ mm/dd/yy

5.3 Reviewed/Approved by: _____ (Principal Investigator Signature)

5.4 Date Signed: __ __/__ __/__ __ mm/dd/yy

RESPECT Trial
#9C Event Imaging Form
CONFIDENTIAL

Page 2 of 2

White copy-AGA Medical; *Yellow copy*-site

AGA-006 Rev K
June 2008

19 APPENDIX D: SUPPLEMENTARY TABLES

Table 33: ITT and PP Analysis Populations and Analysis Methods (Pre-Specified)

	Intention-to-Treat (ITT)	Per-Protocol (PP)
Population	All randomized patients	• Device patients who received a device, met key eligibility criteria and were >67% compliant with prescribed medical regimen • MM patients who met key eligibility criteria and were >67% compliant with prescribed medical regimen
Comparison	Compares patients based on the randomized assignment	Compares patients who adhered to all significant protocol requirements based on the randomized assignment
Follow-up start time	At randomization	
Follow-up end time for subjects who did not experience a primary endpoint event	Follow-up is censored on the latest of the following dates: last follow-up date, withdrawal date, or last date of an adverse event (if patient experienced an adverse event)	Follow-up is censored on the date of treatment non-compliance (as reported on the protocol deviation form), or the latest of the following dates: last follow-up date, withdrawal date, or last date of an adverse event (if patient experienced an adverse event)
Analysis	Patients are analyzed according to their randomized treatment regardless of whether or not they received the assigned treatment	

Table 34: AT and DIP Analysis Populations and Analysis Methods (Exploratory Analyses)

	As Treated	Device in Place (DIP)
Population	• Device patients who received a device and were >67% compliant with prescribed medical regimen • Device patients who refused the device but agreed to be followed in a protocol-specified medical regimen and were >67% compliant with prescribed medical regimen • MM patients who were >67% compliant with prescribed medical regimen	All randomized patients
Comparison	Compares patients based on actual	Compares patients based on device

	protocol treatment received	received and in place at the time of the primary endpoint event, regardless of adherence to the protocol
Follow-up start time	At device implant for Device patients who received a device; at randomization for patients managed medically	
Follow-up end time for subjects who did not experience a primary endpoint event	Follow-up is censored on the date of treatment non-compliance (as reported on the protocol deviation form), or the latest of the following dates: last follow-up date, withdrawal date, or last date of an adverse event (if patient experienced an adverse event)	Follow-up is censored on the last follow-up date, withdrawal date (if subject withdrew) or adverse event date (if subject experienced an adverse event), whichever occurred last
Analysis	Patients are analyzed according to the treatment received	

Table 35: Patient Accountability for ITT, PP, AT and DIP Populations

	Device		Medical Management	
	N	Events	N	Events
Intention to Treat (ITT)	499	9	481	16
Per-Protocol (PP)	463	6	474	14
As Treated (AT)	463	5	487	16
Device in Place (DIP)	464	6	516	19

Table 36: Reconciliation of Events in ITT vs. Other Populations

	Device		Medical Management	
	N	Reason for Exclusion from ITT	N	Reason for Exclusion from ITT
Intention to Treat (ITT)	9		16	
Per-Protocol (PP)	6	- #1: patient with stroke who never received device b(6) - #2: patient with stroke who never received device b(6) - #3: patient did not follow protocol medical regimen (b(6)	14	- #5: patient did not meet eligibility criteria b(6) - #6: patient did not follow protocol medical regimen b(6)
As Treated (AT)	5	- #1	16	+ #2 agreed to follow protocol medical regimen

		- #2 - #3 - #4 patient did not have a device implanted at time of stroke b(6)		b(6) - #6
Device in Place (DIP)	6	- #1 - #2 - #4	19	+ #1 + #2 + #4

Table 37: Demographics and Baseline Characteristics of Discontinued and Ongoing Patients (Excluding Patients who Experienced a Primary Endpoint Event)

Variable	Mean ± SD or %		P-value[1]
	Discontinued Patients (N = 134)	Ongoing Patients (N = 821)	
Age, years	44.7 ± 10.3	46.1 ± 9.7	0.141
Sex, male	57.5%	54.1%	0.513
Diabetes mellitus	8.2%	6.9%	0.587
Hypertension	33.6%	30.7%	0.546
Current smoker	17.9%	11.8%	0.067
Former smoker	34.3%	27.0%	0.097
Hypercholesterolemia	35.8%	40.1%	0.391
Coronary artery disease	3.7%	2.7%	0.570
Previous myocardial infarction	1.5%	0.5%	0.201
Peripheral vascular disease	2.2%	0.4%	0.039
Previous transient ischemic attack	14.9%	11.4%	0.251
Stroke prior to qualifying cryptogenic stroke	16.4%	9.6%	0.023
Family history of stroke	25.4%	24.8%	0.914
Migraine	44.0%	38.2%	0.215
Deep vein thrombosis	3.7%	3.4%	0.799
Congestive heart failure	0.0%	0.4%	1.000
Chronic obstructive pulmonary disorder	3.0%	0.7%	0.039
Birth control/hormone replacement therapy	9.0%	9.7%	0.875

Variable	Mean ± SD or %		P-value[1]
	Discontinued Patients (N = 134)	Ongoing Patients (N = 821)	
Maximal shunt grade[2]			
Grade I	20.0%	23.0%	0.251
Grade II	30.0%	26.7%	
Grade III	48.7%	49.6%	
Atrial septal aneurysm	37.3%	35.1%	0.627

[1] Based on a 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).
[2] Determined as the most severe grade between assessments at rest and at Valsalva.

Table 38: SAEs Occurring in At Least 5 Patients – Extended Follow-Up

Event	Device (N=499, 2769 patient-years)			Medical Management (N=481, 2376 patient-years)		
	# Patients	# Events	# Events per 100 patient-years	# Patients	# Events	# Events per 100 patient-years
Appendicitis	4	4	0.14	2	2	0.08
Arterial Hypertension/Hypertension	4	4	0.14	1	1	0.04
Atrial Fibrillation	5	7	0.25	4	4	0.17
Bowel Obstruction	3	4	0.14	2	2	0.08
Caesarean Section	4	4	0.14	3	4	0.17
Cancer	5	6	0.22	7	7	0.29
Cellulitis	2	3	0.11	6	6	0.25
Chest Pain	16	17	0.61	15	16	0.67
Cholecystitis	1	1	0.04	4	4	0.17
Deep Vein Thrombosis	4	4	0.14	1	1	0.04
Depression	2	3	0.11	4	4	0.17
Elective Surgery	24	29	1.05	17	20	0.84
Fall	3	3	0.11	2	2	0.08
Gastrointestinal Bleeding	5	5	0.18	3	3	0.13
Headache	4	4	0.14	1	1	0.04
Hysterectomy	5	5	0.18	3	3	0.13
Migraine	12	15	0.54	6	7	0.29
Myocardial Infarction	4	4	0.14	1	1	0.04

Numbness	3	3	0.11	4	4	0.17
Osteoarthritis/Degenerative Joint Disease	2	3	0.11	6	7	0.29
Overdose	4	7	0.25	3	4	0.17
Pneumonia	5	9	0.33	5	5	0.21
Pulmonary Embolism	12	13	0.47	2	2	0.08
Sepsis	3	6	0.22	3	5	0.21
Spells	1	1	0.04	4	4	0.17
Suicide Attempt	4	4	0.14	1	1	0.04
Syncope	3	3	0.11	3	3	0.13
Transient Ischemic Attack	7	7	0.25	10	13	0.55
Trauma	4	4	0.14	2	2	0.08
Vaginal Child Birth	10	10	0.36	5	6	0.25
Vertigo	3	3	0.11	2	2	0.08

(b) (4) [redacted]

b(6) [redacted]

b(6) [redacted]

(b) (4) [redacted]

(b) (5)

[redacted]

b(6)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

(b) (4)

[redacted]

b(6)

[redacted]

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4) [redacted]

[redacted]

b(6)

[redacted]

b(6)

[redacted]

(b) (4)

[redacted]

b(6)

[redacted]

(b) (4)

[redacted]

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

b(6)

(b) (4)

[redacted]

b(6)

b(6)

b(6)

(b) (4)

b(6)

(b) (4)

b(6)

(b) (4)

(b) (4) [redacted]

21 APPENDIX G: PUBLICATIONS