Clinical Investigational Plan Synopsis

Reference:
SJM-CIP-XXXX

Title:	PAS1- ODE lead continued follow-up of current RESPECT patients
Acronym:	PAS1
Purpose:	To evaluate the long term safety and effectiveness of PFO closure compared to medical therapy alone in patients that have a patent foramen ovale (PFO) had a previous cryptogenic stroke through long term follow-up in the RESPECT study.
Objectives:	The primary objective is to show that PFO closure continues to be safe and effective.
Endpoints:	• Rate of recurrent ischemic stroke at 5 years • Rate of serious adverse events at 5 years
Design:	The PAS1 is designed to report on the continued follow-up of subjects from the RESPECT IDE trial. There is no change to the follow-up schedule, assessments or risks previously identified in the RESPECT IDE trial. Therefore subjects will not be re-consented for this continued follow-up. All subjects will be followed for 5 years. The last subject was enrolled in the RESPECT IDE trial in Dec 2011. No additional subjects will be enrolled in this post approval study. Subject follow-up in the post approval study is expected to be completed no later than March 31, 2017. The 5-year rate of the primary endpoint in the device and medical management groups of the RESPECT trial will be summarized via Kaplan-Meier estimates. The hazard rate for the primary endpoint will be estimated from a Cox proportional hazards model and presented along with 95% confidence intervals. Freedom from serious adverse events in the device and medical management groups at 5 years will be summarized by Kaplan-Meier estimates. Each adverse event type will be summarized within each group by the number of events and the rate of occurrence per patient-year of follow-up.
Devices used:	AMPLATZER PFO Occluder
Study Population	Patients who are intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) who have had a cryptogenic ischemic stroke due to a presumed paradoxical embolism.

Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> Any subject that was enrolled in the RESPECT IDE and is currently in follow-up. <u>Exclusion Criteria</u> None
Data Collection	Data collection and processing procedures for the PAS1-ODE lead continued follow-up of current RESPECT patient is consistent with the RESPECT IDE study. No change will be made to the CRFs (eCRFs) utilized for the RESPECT IDE trial. Therefore subjects will not be re-consented for this continued follow-up.

Clinical Investigational Plan Synopsis

Reference:
SJM-CIP-XXXX

Title:	PAS2-OSB lead new enrollment study
Acronym:	PAS2
Purpose:	To evaluate the long-term safety and effectiveness of the AMPLATZER PFO Occluder.
Objectives:	• To demonstrate long-term safety of the Amplatzer PFO Occluder by assessing the rate of device- or procedure-related serious adverse events • To demonstrate that the AMPLATZER PFO Occluder is effective by assessing the rate of recurrent ischemic stroke
Endpoints:	Safety: The composite, 5-year rate of device- or procedure-related serious adverse events, including: • New Onset Atrial Fibrillation • Pulmonary Embolism • Device Thrombus • Device Erosion/Embolization • Major Bleeding requiring transfusion • Vascular Access Site Complications requiring surgical intervention • Device- or procedure-related serious adverse event leading to death Effectiveness: The 5-year rate of the composite of: • recurrent non-fatal ischemic stroke • fatal ischemic stroke Ischemic stroke is 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 findings of a new, neuroanatomically relevant, cerebral infarct.
	Descriptive Endpoints: • Components of primary effectiveness endpoint • All-cause mortality • *Transient Ischemic Attack (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 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. • *Effective closure* –Grade 0 or 1 shunt through the PFO at rest and/or Valsalva as assessed by TTE at 1 year • *Technical success* - Successful delivery and release of the

	AMPLATZER PFO Occluder for subjects in whom delivery system entered the body • *Procedural success* - Successful implantation of the AMPLATZER PFO Occluder with no reported in-hospital SAEs for subjects in whom delivery system entered the body
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. Approximately 806 subjects will be enrolled in this study and the study will be conducted in approximately 80 centers in the U.S. Subjects will be followed for 5 years post implant according to the following schedule: pre-hospital discharge, 1-month, 6-months, 12-months and annually thereafter. The total duration of the study is expected to be 8 years. .
Statistical Considerations:	*Primary Effectiveness:* Hypothesis: The rate of primary effectiveness endpoint at 5-years is less than the pre-specified performance goal of 4.4%. The hypothesis is based on the proportion of subjects 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 subjects successfully implanted with the AMPLATZER PFO Occluder, and will be carried out when all subjects reach 5-year follow-up. The analysis will be carried out by estimating the 5-year using the Kaplan-Meier method. The null hypothesis will be rejected if the 95% upper confidence bound (UCB) for π is less than 4.4%. The 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 group of the RESPECT IDE trial using the extended follow-up dataset (data cutoff: 14 Aug 2015). *Primary Safety:* Hypothesis: The rate of primary safety endpoint at 5-years is less than the pre-specified performance goal of 4.0%. The primary safety hypothesis is based on the proportion of subjects experiencing at least one of the following device- or procedure-related serious adverse events 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

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

H_0: $p \geq 4.0\%$

H_1: $p < 4.0\%$

Analysis of the endpoint will include subjects who are attempted to be implanted with the AMPLATZER PFO Occluder, and will be carried out when all subjects 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 in the extended follow-up dataset (data cutoff: 14 Aug 2015) of the RESPECT IDE trial. The following table provides the number of events for the components of the safety endpoint from the RESPECT trial, and shows 10 subjects who experienced at least one safety endpoint, corresponding to a proportion of 10/499 (2.0%):

Device- or Procedure-Related Event	**Number of Subjects with Event**
Atrial Fibrillation	2
Pulmonary Embolism	2
Device Thrombus	0
Device Erosion/Embolization	0
Major Bleeding requiring transfusion	3
Vascular Access Site Complications requiring surgical intervention	4
Device- or procedure related serious adverse event leading to death	0
Total Events	**11**
Total Number of Subjects With Events	**10**

Sample Size

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

	attrition rate of 25%, 806 subjects are required to be enrolled.
Devices used:	AMPLATZER PFO Occluder
Study Population	Patients who are intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) who have had a cryptogenic ischemic stroke due to a presumed paradoxical embolism.

Inclusion/Exclusion Criteria	*Note: Final Inc/Exc criteria will be based on the approved labeling for the AMPLATZER PFO Occluder. Below are proposed criteria based on the RESPECT IDE trial.* <u>Inclusion Criteria</u> • Subjects with PFO who have had a 'cryptogenic stroke' within the last 270 days, with stroke defined as follows: 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. <u>Exclusion Criteria</u> • Atherosclerosis or other arteriopathy of the intracranial and extracranial vessels of >50% of lumen diameter supplying the involved lesion • Intracardiac thrombus or tumor • Acute or recent (within 6 months) myocardial infarction or unstable angina • Left ventricular aneurysm or akinesis • Mitral valve stenosis or severe mitral regurgitation irrespective of etiology • Aortic valve stenosis (gradient >40 mmHg) or severe aortic valve regurgitation • Mitral or aortic valve vegetation or prosthesis • Aortic arch plaques protruding >4mm into the lumen • Left ventricular dilated cardiomyopathy with LVEF <35% • Subjects with other source of right to left shunts identified at baseline, including an atrial septal defect and/or fenestrated septum • Atrial fibrillation/atrial flutter (chronic or intermittent) • Pregnant or desire to become pregnant within the next year • Age <18 years and age >60 years • Active endocarditis, or other untreated infections • 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. • 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 200mg with presence of glucose in the urine. • 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) • Arterial dissection as qualifying event • Signs of progressive neurological dysfunction • Subjects who test positive with one of the following hypercoagulable states; Anticardiolipin Ab of the IgG or IgM, Lupus anticoagulant, B2-glycoprotein-1 antibodies or persistently elevated fasting plasma homocysteine despite medical therapy • Subjects with contraindication to aspirin or clopidogrel therapy • Anatomy in which the AMPLATZER PFO Occluder would interfere with intracardiac or intravascular structures such as valves or pulmonary veins • Malignancy or other illness where life expectancy is less than 2 years • Subjects who will not be available for follow-up for the duration of the trial • Inability to obtain Informed Consent from patient or legally authorized representative • Stroke with poor outcome at time of enrollment (Modified Rankin score >3) • Subjects who are not able to discontinue the use of anticoagulation if randomized to closure
Data Collection	Subjects will has visits/assessments pre-procedure, at the procedure, at 1-, 6-, and 12-month post-procedure, and annually thereafter through 5 years post procedure.

Study Flow Chart

♥ = Required testing	Baseline	Procedure	Discharge	1 month (± 1 week)	6 months (± 1 month)	12 months (± 3 months)	2 years (± 3 months)	3 years (±3 months)	4 years (±3 months)	5 years (±3 months)
Office Follow-up: (if required)										
History and Physical Exam	♥		♥	♥	♥	♥				
Modified Rankin	♥									
Stroke Questionnaire + additional assessments, as necessary	♥			♥	♥	♥	♥	♥	♥	♥
Telephone Follow-up							♥	♥	♥	♥
Transesophageal Echo with bubble study	♥	♥				♥				