



PRIMA Trial

**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study**

Clinical Investigational Plan

AGA 010E, Revision G

22 March 2011

Sponsored By:

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**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study (PRIMA Trial)**

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Investigational Plan Signature Page

I have read and agree to adhere to the investigational plan and all regulatory requirements applicable in conducting this clinical study. I will provide copies of this investigational plan and all pertinent information to study personnel and will discuss this information with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to applicable regulations, to applicable laws, and to hospital Institutional Review Board (IRB)/Ethics Committee (EC) requirements.

Investigator Name Printed

Investigator Signature

Date

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1. Study Synopsis

Table 1 summarizes the PRIMA Trial.

Table 1. PRIMA Trial Study Synopsis

| | |
|-----------------------------|--|
| Title | Prima - <u>P</u> ercutaneous Closure of Patent Foramen Ovale In <u>M</u> igraine with <u>A</u> ura - A Randomized Prospective Study |
| Sponsor | AGA Medical Corporation |
| Study Background | Observational studies support a causal link between a PFO and migraine with aura. Percutaneous closure of a PFO or a secundum atrial septal defect for secondary prevention of paradoxical embolism has been shown to unexpectedly reduce migraine frequency in subjects with concomitant migraine with aura. In addition, observational studies showed a reduction of migraine frequency with oral anticoagulation and low-dose aspirin, supporting the hypothesis of paradoxical embolism as potential trigger mechanism of migraine attacks. |
| Study Design | This is a prospective, randomized, multi-center, global clinical study designed to evaluate the difference in migraine day reduction between closure of a patent foramen ovale with the AMPLATZER® PFO Occluder and standard medical management practices. |
| Study Scope | Data from at least 144 randomized subjects who have migraine with aura and a PFO will be collected at approximately 20 institutions located in Canada and Europe. |
| Study Objective | To evaluate whether percutaneous PFO closure is effective in reducing the incidence of migraine headaches in subjects diagnosed with migraine with aura who are refractory to medical treatment |
| Primary Endpoint | Reduction in migraine days one year after randomization. |
| Secondary Objectives | <ul style="list-style-type: none"> • Change in Responder Rate - The responder rate is defined as the proportion of subjects who have a 50% or greater reduction in the number of migraine days relative to baseline. • Change in the Number of Migraine Attacks and Attacks with Aura - A change in the number of migraine and aura attacks will be assessed by comparing the mean number of migraine attacks during the 3 month baseline roll-in phase and the mean number of migraine attacks during months 10, 11 and 12 of the treatment phase (device group versus control group). • Change in Use of Acute Migraine Medications - A reduction in the use of acute migraine medications during the treatment phase will be compared to those noted at baseline. Acute migraine medications taken throughout the screening and follow-up period will be recorded on the medication log and in the subject headache diary. • Change in MIDAS Score - A change in level of headache-related disability, as assessed by the MIDAS Evaluation, will be measured at baseline and follow-up visits at 3, 6, 9 and 12 months. |

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PRIMA Trial Study Synopsis (Cont'd)

| | |
|-----------------------------|--|
| Secondary Objectives | <ul style="list-style-type: none"> • Change in Quality of Life - A change in quality of life, as assessed by the Quality of Life Questionnaire SF-12v2™, will be measured at baseline and follow-up visits 1, 3, 6, 9 and 12 months. • Change in Beck Depression Score - A change in the depression score will be assessed using the Beck Depression Inventory® at baseline and follow-up visits 1, 3, 6, 9 and 12 months. • Effects of Anti-Thrombotic Medication - The main analysis of the effects of anti-thrombotic medication (aspirin and clopidogrel) will be assessed by comparing the number of headache days-during months 1, 2, 3 and 4, 5 and 6, when medication is taken, against the number of headache days during screening, and months 10, 11 and 12, when medication is not taken. • Adverse Event Classification - The type, relatedness, and seriousness of adverse events experienced by study subjects will be classified. • PFO Closure - Incidence of complete foramen ovale closure by 12 months in device group subjects will be assessed by TEE. |
| Device Description | <p>The AMPLATZER® PFO Occluder is a self-expandable, double-disc device made from a Nitinol wire mesh. A polyester fabric is securely sewn to each disc by a polyester thread.</p> |
| Inclusion Criteria | <ol style="list-style-type: none"> 1. Willingness to sign informed consent. 2. Migraine with aura diagnosed by a neurologist at the first screening visit, according to the criteria of the International Headache Society (IHS). 3. Age of migraine onset less than 50 years. 4. Experience on average in the 3-month baseline roll-in phase a minimum of either 3 migraine attacks or 5 migraine headache days per month and no greater than 14 total headache days per month. 5. Failed or shown to be refractory or unresponsive or contraindicated to two previous commonly accepted preventative medication trials for migraine headache as documented by either a headache diary or medical record. 6. Daily preventative medications (if currently taking) have remained at a stable dose for the 4 weeks preceding baseline headache diary distribution and remain stable-throughout the screening period. Slight/small changes of the dose which in the perspective of the investigator have no impact on migraine frequency are allowed. 7. PFO documented using transesophageal contrast echocardiography. 8. Willingness to accept randomization. 9. Willingness to participate in the required follow-up visits for a minimum of 12 months. 10. Willingness to comply with maintaining a headache diary during the 3 month baseline roll-in phase with at least 80% compliance and for 12 months thereafter. |

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A Randomized Prospective Study (PRIMA Trial)**

PRIMA Trial Study Synopsis (Cont'd)

| | |
|----------------------------------|---|
| <p>Exclusion Criteria</p> | <ol style="list-style-type: none"> 1. Age < 18 years or > 65 years. 2. Overused acute migraine treatments prior to randomization. 3. Subjects with a clinical history of stroke as defined by the neurologist. 4. Contraindication to aspirin and/or clopidogrel therapy (i.e. thrombocytopenia). 5. Indication for ongoing aspirin therapy (e.g. established coronary artery disease). 6. Subjects taking warfarin. 7. Contraindication to undergo catheterization and PFO device closure (i.e. renal failure, ongoing active infection). 8. Contraindication to undergo transesophageal echocardiography (i.e. anatomy, sedative). 9. Anatomy in which AMPLATZER® PFO Occluder would interfere with intracardiac or intravascular structures (e.g. valves or pulmonary veins). 10. Subjects whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate sheath size. 11. Subjects treated with Botox for any reason, up to 4 months prior to baseline headache diary distribution or during the screening period. 12. Malignancy or other illness where life expectancy is less than 2 years. 13. Pregnancy or the wish to become pregnant within 1 year. 14. Intracardiac thrombus or tumor. 15. History of known coronary disease or known, unrepaired significant structural heart disease (except PFO). 16. Subjects with moderate to severe valvular regurgitation. 17. Subjects with other source of right to left shunts (aside from PFO). 18. Subjects with a fenestrated septum where the PFO Occluder cannot fully cover the defect. 19. Any atrial fibrillation/atrial flutter (chronic or intermittent). 20. Any metabolic, central nervous system or other medical disorder that would interfere with completion or evaluation of trial results. 21. Severe psychiatric illness that, in the opinion of Investigators, will interfere with the completion of the trial. 22. Significant reaction to nickel on a Nickel Patch Test (grade ++ or grade +++). 23. Concurrent participation in other clinical trials which in the opinion of Investigators will interfere with the completion of the trial. |
| <p>Follow-up</p> | <p>All subjects will have regular follow-up with a clinical visit and detailed questionnaires for headache, depression and quality of life at 1, 3, 6, 9 and 12 months after randomization. In subjects that are implanted with a study device, follow-up assessments will also be conducted annually until the last 12 month follow-up visit is completed. After the 12 month follow-up visit, subjects will have the option of an in-person visit, a phone follow-up or completing a survey via mail.</p> |

2. Introduction

2.1. Name and Intended Use

The AMPLATZER® PFO Occluder is a percutaneous, transcatheter occlusion device intended for the non-surgical closure of patent foramen ovale (PFO) in subjects who have suffered from migraine headaches with aura. The AMPLATZER® PFO Occluder has been developed as a potential alternative to the current standard of care. Current standard of care is medical treatment.

2.2. Background

With an estimated prevalence of 8 to 13% in the Western population, more than 55 million Europeans and Americans have migraine.^{1, 2} Migraine can severely affect quality of life and has an important socio-economic impact.³ On average, migraineurs are unable to work or to attend school due to headache during three days over a three months period.⁴ One of three subjects with migraine has at least occasional migraine attacks associated with transient focal neurological symptoms, so called migraine with aura. The neurological symptoms of a migraine aura are likely related to a self-propagating wave of cortical excitation followed by temporary depression of neuronal activity, a phenomenon called “cortical spreading depression”.⁵ This phenomenon is accompanied by changes in regional cerebral blood flow and is believed to activate trigeminal afferents, finally resulting in migraine headache. The exact nature of triggers initiating migraine attacks in vivo is not known.⁶

Recently, transcranial contrast Doppler studies have shown a higher prevalence of right-to-left shunts in subjects with migraine with aura (41 to 48%) compared with controls (16 to 20%).^{7, 8} Results of transesophageal contrast echocardiography demonstrated these shunts were patent foramina ovalia (PFO).⁹

2.2.1. Migraine and Patent Foramen Ovale

Observational studies support a causal link between a PFO and migraine with aura:

- Percutaneous closure of a PFO or a secundum atrial septal defect for secondary prevention of paradoxical embolism has been shown to unexpectedly reduce migraine frequency in subjects with concomitant migraine with aura.¹⁰⁻¹³ Subjects with migraine with aura and a PFO have larger shunts than controls and more frequently present with a right-to-left shunt even at rest, i.e. without provoking Valsalva maneuver.^{9, 14} In addition, observational studies showed a reduction of migraine frequency with oral anticoagulation and low-dose aspirin, supporting the hypothesis of paradoxical embolism as potential trigger mechanism of migraine attacks.¹⁵⁻¹⁷
- In the experimental setting, the aura phenomenon preceding migraine headache can be initiated by hypoxia.⁵ In vivo, cerebral ischemia has been postulated as one of several potential triggers for migraine attacks.¹⁸ Although the likelihood of shunt-related cerebral microembolism is dependent on blood flow distribution, the visual cortex features the lowest glial to neuronal cell ratio, and might therefore be most susceptible for migraine initiation.⁵ This offers an explanation for the predominance of visual symptoms as aura initiating migraine attacks.⁴

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Because a right-to-left shunt is present in only half of subjects with migraine with aura, other factors are as important in migraine pathophysiology as right-to-left shunting. To verify the hypothesis of a patent foramen ovale contributing to migraine attacks, a randomized clinical trial is indicated to prospectively investigate the effects of shunt closure on migraine frequency.

2.3. Study Objectives

The objective of this study is to evaluate whether percutaneous PFO closure is effective in reducing the incidence of migraine headaches in subjects diagnosed with migraine with aura who are refractory to medical treatment. This purpose will be evaluated by investigating whether subjects with percutaneous PFO closure experience a significant reduction in migraine headaches 12 months post-PFO closure in comparison to a control group who will be receiving standard of care therapy.

2.3.1. Primary Endpoint

The primary endpoint is the reduction in migraine days one year after randomization compared between the 3-month baseline roll-in phase and treatment phase. This will be calculated as the mean number of migraine headache days in the final three months of the treatment phase for completed subjects, subtracted from the mean number of migraine headache days in the 3-month baseline roll-in phase.

A migraine day is defined as a calendar day in which the subject experiences a migraine headache according to International Headache Society (IHS) criteria.

2.3.2. Secondary Objectives

- **Change in Responder Rate**
The responder rate is defined as the proportion of subjects who have a 50% or greater reduction in the number of migraine days during the treatment phase relative to the number of migraine days at baseline. The change in responder rate, then, is the difference between the device group and control group in the responder rate.
- **Change in the Number of Migraine Attacks and Attacks with Aura**
A change in the number of migraine and aura attacks will be assessed by comparing the mean number of migraine attacks during the 3 month baseline roll- in phase and the mean number of migraine attacks from months 9 through 12 in the treatment phase (device group versus control group).
- **Change in Use of Acute Migraine Medications**
A change in the use of acute migraine medications during the treatment phase will be compared to those recorded at baseline. Acute migraine medications taken throughout the follow-up period will be recorded in the subject headache diary and medication log.
- **Change in MIDAS (Migraine Disability Assessment Questionnaire) Score**
A change in level of headache-related disability, as assessed by the MIDAS Evaluation, will be measured at baseline and follow-up visits at 3, 6, 9 and 12 months.
- **Change in Quality of Life**
A change in Quality of Life, as assessed by the Quality of Life Questionnaire SF-12v2™, will be measured at baseline and follow-up visits 1, 3, 6, 9 and 12 months.

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- **Change in Beck Depression Score**
A change in the depression score will be assessed using the Beck Depression Inventory[®] at baseline and follow-up visits 1, 3, 6, 9 and 12 months.
- **Effects of Anti-Thrombotic Medication**
The main analysis of the effects of anti-thrombotic medication (aspirin and clopidogrel) will be assessed by comparing the number of headache days during months 1, 2, 3 and 4, 5 and 6, when medication is taken, against the number of headache days during screening and months 10, 11 and 12, when medication is not taken.
- **PFO Closure**
Incidence of complete foramen ovale closure by 12 months in device group subjects will be assessed by TEE.
- **Adverse Event Classification**
The type, relatedness, and seriousness of adverse events experienced by study subjects will be classified.

3. Methodology

All centers will follow the same version of the PRIMA Trial Clinical Investigational Plan. Study data is intended to be used to support CE Mark approval and for regulatory approvals in other geographies as needed, as well as for AGA Medical Corporation internal review purposes.

3.1. Study Design

The PRIMA trial is a prospective, randomized, multi-center, global clinical study. It is designed to evaluate the difference in migraine day reduction between closure of a patent foramen ovale with the AMPLATZER[®] PFO Occluder and standard medical management practices.

To satisfy enrollment for the primary endpoint, data from at least 144 randomized subjects who have migraine with aura and a PFO will be collected. Approximately 72 subjects will undergo percutaneous PFO closure, in addition to established medical therapy for migraine (i.e. device group). Approximately 72 subjects will not undergo percutaneous PFO closure, but will continue on established medical therapy for migraine (i.e. control group). It is estimated that 72 randomized subjects in each arm will be required to achieve 12-month follow-up data collection from a minimum of 60 subjects.

Enrollment will be stopped when 144 subjects have been randomized. The primary study report will be based on data collected on or before the date when at least 60 subjects in the device group and 60 subjects in the control group have completed the 12-month follow-up visit.

See Figure 1 for study overview.

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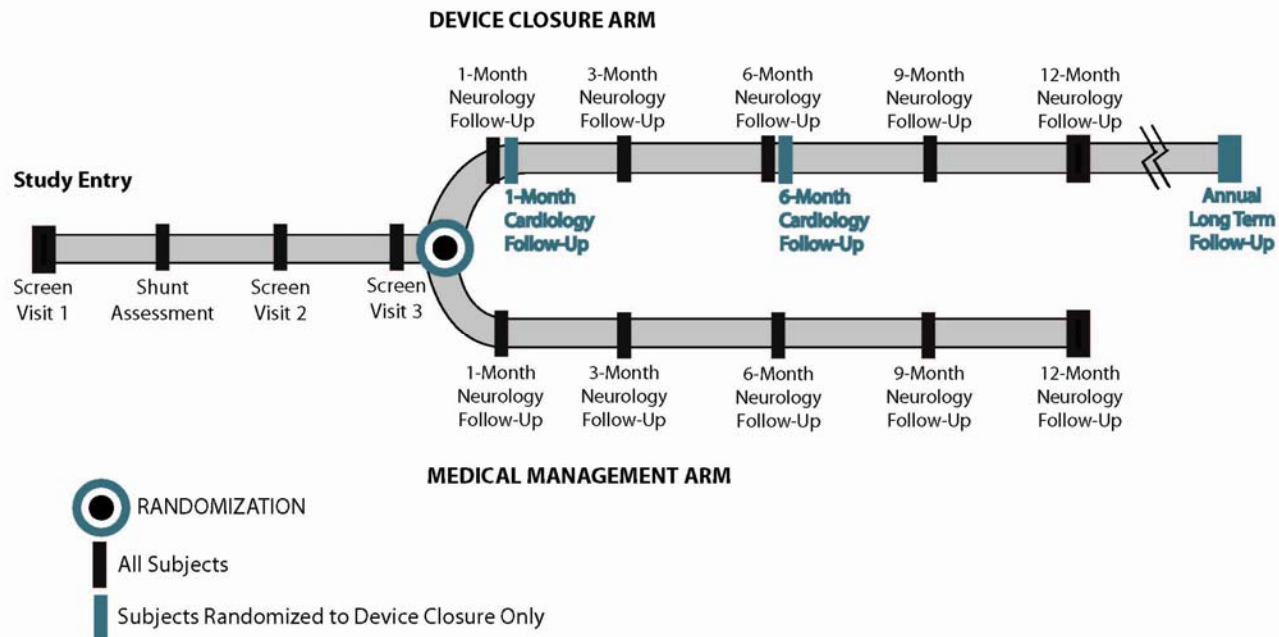


Figure 1 – Study Design

3.2. Clinical Center Scope

The study will be conducted at approximately 20 institutions located in Canada and Europe. The distribution of centers will be approximately 8 centers in Canada and 12 centers in Europe. Attachment A contains a list of current institutions and Principle Clinical Investigators.

3.3. Study Enrollment Rate

To satisfy enrollment for the primary endpoint, the enrollment period is expected to take approximately 48 months. There is no minimum requirement for enrollments per center. In order to prevent a center from enrolling a majority of subjects for the primary endpoint, the maximum number of randomized subjects at a single center will be 40.

3.4. Study Duration

The total study duration will include a 3-month baseline roll-in phase followed by 12-months of follow-up. In subjects that are implanted with a study device, additional follow-up assessments will be conducted annually until the last subject's 12 month follow-up visit is completed. After the 12 month follow-up visit, subjects will have the option of an in-person visit, a phone follow-up or completing a survey via mail.

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3.5. Subject Selection

Those subjects meeting all inclusion criteria and not restricted from participation due to exclusion criteria may participate in this study.

3.5.1. Inclusion Criteria

1. Willingness to sign informed consent.
2. Migraine with aura diagnosed by a neurologist at the first screening visit, according to the criteria of the International Headache Society (IHS).
3. Age of migraine onset less than 50 years.
4. Experience on average in the 3-month baseline roll-in phase a minimum of either 3 migraine attacks or 5 migraine headache days per month and no greater than 14 total headache days per month.
5. Failed or shown to be refractory or unresponsive or contraindicated to two previous commonly accepted preventative medication trials for migraine headache as documented by either a headache diary or medical record.
6. Daily headache preventative medications (if currently taking) have remained at a stable dose for the 4 weeks preceding baseline headache diary distribution and remain stable throughout the screening period. Slight/small changes of the dose which in the perspective of the investigator have no impact on migraine frequency are allowed.
7. PFO documented using transesophageal contrast echocardiography.
8. Willingness to accept randomization.
9. Willingness to participate in the required follow-up visits for a minimum of 12 months.
10. Willingness to comply with maintaining a headache diary during the 3 month baseline roll-in phase with at least 80% compliance and for 12 months thereafter.

3.5.2. Exclusion Criteria

1. Age < 18 years or > 65 years.
2. Overused acute migraine treatments prior to randomization.
3. Subjects with a clinical history of stroke as defined by the neurologist.
4. Contraindication to aspirin and/or clopidogrel therapy (i.e. thrombocytopenia).
5. Indication for ongoing aspirin therapy (e.g. established coronary artery disease).
6. Subjects taking warfarin.
7. Contraindication to undergo catheterization and PFO device closure (i.e. renal failure, ongoing active infection).
8. Contraindication to undergo transesophageal echocardiography (i.e. anatomy, sedative).
9. Anatomy in which AMPLATZER® PFO Occluder would interfere with intracardiac or intravascular structures (e.g. valves or pulmonary veins).
10. Subjects whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate sheath size.
11. Subjects treated with Botox for any reason, up to 4 months prior to baseline headache diary distribution or during the screening period.
12. Malignancy or other illness where life expectancy is less than 2 years.
13. Pregnancy or the wish to become pregnant within 1 year.
14. Intracardiac thrombus or tumor.
15. History of known coronary disease or known, unrepaired significant structural heart disease (except PFO).
16. Subjects with moderate to severe valvular regurgitation.
17. Subjects with other source of right to left shunts (aside from PFO).
18. Subjects with a fenestrated septum where the PFO Occluder cannot fully cover the defect.

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19. Any atrial fibrillation/atrial flutter (chronic or intermittent).
20. Any metabolic, central nervous system or other medical disorder that would interfere with completion or evaluation of trial results.
21. Severe psychiatric illness that, in the opinion of Investigators, will interfere with the completion of the trial.
22. Significant reaction to nickel on a Nickel Patch Test (grade ++ and grade +++).
23. Concurrent participation in other clinical trials which in the opinion of Investigators will interfere with the completion of the trial.

4. Study Procedures

4.1. Center Initiation

Prior to enrolling any subjects in the study, all local and national regulatory requirements must be met. At a minimum, each center must have written documentation of Ethics Committee approval of the current version of the Clinical Investigational Plan and Informed Consent Form, current signed and dated Investigator curriculum vitae, signed Investigator agreements, and documentation of study training.

4.2. Recruitment of Subjects

Subjects who consult the investigative centers or referring neurologists will be verbally pre-screened to assure that they satisfy some of the basic inclusion/exclusion criteria of the study. A Pre-Screening Questionnaire eCRF may be completed for each subject.

Subjects who appear to satisfy some of the basic inclusion/exclusion criteria of the study will be invited to attend study Screening Visit 1.

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4.3. Informed Consent

At Screening Visit 1, prior to initiation of any study-specific procedures, informed consent must be obtained.

The process for obtaining informed consent must comply with the ethical principles defined in the current version of the Declaration of Helsinki. The Informed Consent Form must be provided to the subject in a language that he/she is able to read and understand. Non-Compliance issues found with respect to the Informed Consent will result in a protocol deviation and corrective action for the same will be taken.

Document in the subject medical record and Screening Visit 1 eCRF that informed consent has been obtained by recording the date the subject signed the Informed Consent Form. File the signed Informed Consent Form in the hospital/clinic chart or with the study subject documentation. The signed Informed Consent Form must be available for monitoring.

A template of the Informed Consent Form is attached in Attachment B. Any changes to this Informed Consent Form template must be approved by AGA Medical Corporation and the reviewing Ethics Committee before any subject may be enrolled in the study.

4.4. Point of Enrollment

Enrollment is defined as the time at which the subject provides informed consent by signing the approved site-specific consent form.

4.5. Subject Screening Phase

All subjects will begin Screening Visit 1 with informed consent as previously noted. Table 2 summarizes the recommended sequence of subject screening events required prior to randomization.

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Table 2. Recommended Sequence of Subject Screening Events

| Screening Visit 1 - Neurology Assessment | Neurology | Cardiology |
|--|---|---------------------------------------|
| Subject Informed Consent | √ | |
| Medical History, Risk Factors, Physical/Neurological Assessment | √ | |
| Headache History, IHS Headache Classification, Headache Medications | √ | |
| Inclusion/Exclusion Criteria Review | √ | |
| Headache Diary Distribution Begin 3 Month Baseline Roll-In Phase | √ | |
| Shunt Assessment | Neurology | Cardiology |
| Contrast Transthoracic Echocardiography (TTE) or Transcranial Doppler (TCD) | May be completed at Screening Visit 1 | May be completed at Screening Visit 2 |
| Screening Visit 2 - Cardiology Assessment | Neurology | Cardiology |
| Transesophageal Contrast Echocardiography (TEE), Inclusion/Exclusion Criteria Review | | √ |
| ECG | | √ |
| Routine Blood Work | | √ |
| Nickel Patch Test | Neurology | Cardiology |
| Nickel Patch Test (kit provided by AGA) | Recommend distribution at Screening Visit 2 and review of test results at Screening Visit 3 | |
| Screening Visit 3 - Neurology Assessment | Neurology | Cardiology |
| Headache Diary Review (a minimum of 3 months of data is required) | √ | |
| Medication History, Inclusion/Exclusion Criteria Review | √ | |
| Pregnancy Test (kit provided by AGA) | √ | |
| MIDAS Evaluation | √ | |
| Beck Depression Inventory | √ | |
| SF-12v2™ Quality of Life | √ | |
| Request for Randomization Assignment | √ | |

4.5.1. Definitions

The following definitions are taken from current International Headache Society Guidelines:

- *Headache day* – A calendar day in which the subject experiences a headache.
- *Attack* – Individual migraine attacks are separated by at least 24 hours of headache symptom free time.
- *Medication overuse* – Includes subjects taking acute medications 10 or more days per month or analgesic medications 15 or more days per month.-See IHS guidelines for additional detail.

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4.5.2. Medication Log

All medications and dietary supplements taken by the subject at the time of Screening Visit 1 through the 12-month follow-up visit must be recorded on the Medication Log eCRF.

Medication name, indication, dose, unit, frequency, start and end dates will be collected for concomitant and preventative medications. Only dates taken will be captured on the medication log for acute migraine medications. Medication changes (type, dose, and/or frequency) made between study visits will be captured at the next scheduled or unscheduled visit.

4.5.3. Headache Medications

4.5.3.1. Preventative Headache Medications

All preventative headache medications taken during the study must be recorded on the Medication Log eCRF.

Any change in preventative medication type, dose and/or frequency is discouraged throughout the course of the trial. This includes the prospective 3 month baseline roll-in phase and the 12-month treatment phase.

4.5.3.2. Acute Headache Medications

All acute headache medications taken during the study must be recorded on the Medication Log eCRF.

An acute medication is defined as a medication taken to treat a migraine attack rapidly. Acute therapies may be used in conjunction with preventative medications.

4.5.4. Headache Diary

PRIMA Trial headache diaries will be provided to each subject with instructions. Subject headache diaries will be reviewed at Screening Visit 3 and each follow-up visit. Subjects must complete a minimum of 80% of calendar days to be considered compliant with headache diary completion. Subjects who are not compliant with headache diary completion during the screening period will be excluded.

4.5.5. Pregnancy Test

A pregnancy test must be done for all female subjects of child bearing potential. Subjects that are two or more years post menopause or who have undergone surgical sterilization do not need to have a pregnancy test performed. A positive pregnancy test is exclusionary for the study.

4.5.6. Study Surveys

The following data are collected at screening and follow-up evaluations.

- *Migraine Disability Assessment Survey (MIDAS)* - This questionnaire is collected at Screening Visit 3 and at 3, 6, 9 and 12 months and is used to determine the level of pain and disability caused by headaches. It also serves as a measure of headache frequency. The survey consists of a set of five questions which will be added to give a MIDAS score.

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- *Beck Depression Inventory (BDI)* - The BDI is a self-administered 21 item self-report scale measuring supposed manifestations of depression. This questionnaire is collected at Screening Visit 3 and at 1, 3, 6, 9 and 12 months.
- *SF-12v2™ Quality of Life* – This survey includes one multi-item scale that assesses eight health concepts. This questionnaire is collected at Screening Visit 3 and at 1, 3, 6, 9 and 12 months.

4.5.7. Diagnosis of a PFO

Subjects complying with the inclusion/exclusion criteria assessed in Screening Visit 1 will undergo a minimally invasive diagnostic procedure, contrast Transcranial Doppler (TCD) or contrast Transthoracic Echocardiography (TTE), to detect an intracardiac shunt. Subjects without evidence of a right-to-left shunt will be discontinued from the study. If the TCD or TTE is inconclusive, the investigator may choose to conduct a TEE.

Subjects with evidence of right-to-left shunt seen in a bubble study by either TCD or TTE will undergo a transesophageal contrast echocardiography (TEE) to confirm the presence of Patent Foramen Ovale (PFO) and rule out any other intracardiac abnormality that may exclude the subject from the study.

- Note: Crossing of microbubbles at rest or Valsalva through the defect must be demonstrated for confirmation of PFO.

If a subject underwent a TCD or TTE prior to Screening Visit 1 and the investigative center has the required source documentation to assess the presence of an intracardiac shunt, a repeat TCD/TTE is not required as part of the study screening process.

If a subject underwent a TEE prior to Screening Visit 1 and the investigative center has the required source documentation to confirm the presence of a PFO, a repeat TEE is not required as part of the study screening process.

4.5.8. Nickel Patch Test

The purpose of the Nickel Patch Test is to detect subject allergy to the substance Nickel. The Nickel Patch Test will be completed using test kits provided by AGA Medical Corporation. The Nickel Patch Test kit should be distributed to the subject following confirmation of PFO.

Patch application to the subject's skin may be completed by the research center staff or subject. The patch should remain on the subject's skin for 48 hours and is then removed. Twenty-four (24) to 48 hours after patch removal (72-96 hours after initial application), the skin should be observed and graded according to the International Contact Dermatitis Research Group system:

- +? = doubtful reaction: mild redness only;
- + = weak, positive reaction: red and slightly thickened skin;
- ++ = strong positive reaction: red, swollen skin with individual small water blisters;
- +++ = extreme positive reaction: intense redness and swelling with coalesced large blisters or spreading reaction;
- IR = irritant reaction. Red skin improves once patch is removed;
- NT = not tested.

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A subject with a significant reaction to nickel on the Nickel Patch Test, grade ++ or grade +++, is excluded from further study participation.

4.5.9. Screen Failures

Subjects will undergo screening procedures in the recommended sequence until the point at which they fail to meet study inclusion/exclusion criteria. Complete a subject Discontinuation Form eCRF for all consented subjects who fail to meet all of the study inclusion/exclusion criteria. In most cases, screen failures will not be allowed to be rescreened. All rescreening must be approved by AGA in advance. If a subject is rescreened, the subject must sign a new consent form, and medical history and medications must be updated. Baseline labs and questionnaires (if previously completed) must be re-done. A repeat TTE/TCD or TEE is not required if previously completed. For consented screen failures, the reason for screen fail, study protocol related adverse events, shunt assessment, demographic data and patient history that is completed up to the time of screen failure will be collected. Data collected from patients who are not randomized may be used for future study design.

4.5.10. Screening Visit Windows

There are no defined visit windows for screening visits. Screening Visit 1 and 3 must be separated by a minimum of 90 days to allow for prospective headache diary completion during the 3-month baseline roll-in phase beginning at Screening Visit 1.

4.6. Randomization

4.6.1. Request for Randomization

Subjects who meet all inclusion/exclusion criteria after completing the screening phase will be eligible for randomization. To request a randomization assignment for a subject, submit signed headache diary with investigator assessments, confirm subject eligibility and complete the following eCRFs:

- Screening Visit 1 – Neurology Assessment
- Shunt Assessment
- Screening Visit 2 – Cardiology Assessment
- Nickel Patch Test
- Screening Visit 3 – Neurology Assessment

A designated AGA Medical Corporation representative will verify subject eligibility by eCRF review and contact the site with the outcome.

4.6.2. Randomization Scheme

Eligible subjects will be randomized to undergo:

- Percutaneous closure of the patent foramen ovale with an AMPLATZER® PFO Occluder, or
- Continue standard medical management

Randomization will take place according to the pre-defined algorithm described below.

Age and Gender

Randomization will be stratified according to age and gender

- Men: age < 30 years (subgroup M1), 30 to 40 year old (M2), > 40 years (M3)
- Women: age < 30 years (subgroup W1), 30 to 40 year old (W2), > 40 years (W3)

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In each subgroup, recruited subjects will be numbered consecutively (for example M2 (1), M2 (2), etc). According to their individual subject-number, subjects will be assigned to undergo PFO closure or not.

Men

| | |
|--|-----------------|
| M1: M1(n+1), M1(n+3), M1(n+5), M1(n+7), M1(n+9): | PFO closure |
| M1(n+2), M1(n+4), M1(n+6), M1(n+8), M1(n+10): | no intervention |
| M2: M2(n+1), M2(n+3), M2(n+5), M2(n+7), M2(n+9): | no intervention |
| M2 (n+2), M2(n+4), M2(n+6), M2(n+8), M2(n+10): | PFO closure |
| M3: M3(n+1), M3(n+3), M3(n+5), M3(n+7), M3(n+9): | PFO closure |
| M3(n+2), M3(n+4), M3(n+6), M3(n+8), M3(n+10): | no intervention |

Women

| | |
|--|-----------------|
| W1: W1(n+1), W1(n+3), W1(n+5), W1(n+7), W1(n+9): | no intervention |
| W1 (n+2), W1(n+4), W1(n+6), W1(n+8), W1(n+10): | PFO closure |
| W2: W2(n+1), W2(n+3), W2(n+5), W2(n+7), W2(n+9): | PFO closure |
| W2 (n+2), W2(n+4), W2(n+6), W2(n+8), W2(n+10): | no intervention |
| W3: W3(n+1), W3(n+3), W3(n+5), W3(n+7), W3(n+9): | no intervention |
| W3 (n+2), W3(n+4), W3(n+6), W3(n+8), W3(n+10): | PFO closure |

This simple plan for randomization is feasible because of different referring neurologists, each of them unaware of the current number of recruited subjects in every subgroup. This scheme has the advantage of providing roughly equal group sizes (controls vs. device), and a near equal distribution of men and women, and age stratum, in the two treatment arms, without the need to estimate the absolute subject numbers of the different subgroups.

4.6.3. Aspirin and Clopidogrel Regimen

After randomization, all subjects will be started on aspirin 75-100 mg for 6 months and Clopidogrel 75 mg for 3 months. Subjects should start aspirin and clopidogrel within 2 weeks of randomization.

The prescription of anti-thrombotic medication daily for a duration of 6 months for both the device and control group allows for investigation of the effects of an anti-thrombotic medication on headache frequency and intensity.

4.7. AMPLATZER® PFO Occluder Closure Procedure

In subjects randomized to undergo PFO closure, the PFO closure procedure should be performed within 2 weeks following randomization by a trained Investigator. Refer to the Instructions for Use (IFU) located in Attachment D for PFO closure procedure.

Device implant procedure data collection requirements include:

- Pregnancy test
- Cardiac catheterization information
- Product information
- Heparin administration and ACT data
- Post procedure assessment of device placement

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- Pre-discharge ECG
- Pre-discharge physical exam

Endocarditis prophylaxis will be carried out for 6 months according to standard of care at each institution.

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4.8. Follow-up

Follow-up visits will occur at 1, 3, 6, 9, and 12 months post-randomization. The Follow-up eCRF will be used to document data collected at each visit. The following table details data collection required at each visit.

If the TEE done at the 6 month follow-up visit does not show complete PFO closure as assessed by the Echo Core Lab, the procedure should be repeated at the 12 month follow-up visit.

Table 3. Follow-up Data Collection Requirements

| Data Collection Requirements for All Subjects | | | | | | |
|---|---------|---------|---------|---------|---------------|---|
| | 1 Month | 3 Month | 6 Month | 9 Month | 12 Month | Long Term Follow-up (Device Group Only) |
| Physical Exam | X | X | X | X | X | |
| Medication Use | X | X | X | X | X | X |
| Headache Diary Review | X | X | X | X | X | X |
| MIDAS Evaluation | | X | X | X | X | X |
| BECK Depression Inventory | X | X | X | X | X | |
| SF-12v2™ Quality of Life | X | X | X | X | X | |
| Adverse Event Assessment | X | X | X | X | X | X |
| Additional Data Collection Requirements for Device Group Subjects | | | | | | |
| | 1 Month | 3 Month | 6 Month | 9 Month | 12 Month | Long Term Follow-up |
| ECG | X | | X | | | |
| Transesophageal Echocardiography (TEE) | | | X | | X (if needed) | |

4.8.1. Follow-up Visit Schedule

Follow-up visit schedules are calculated based on the date of subject randomization. Day 1 will be defined as the day immediately following randomization. The following table details the follow-up visit schedule and visit window intervals.

Table 4. Follow-up Data Visit Schedule

| Scheduled Visit | Window Start* | Target Day* | Window End* |
|-----------------|---------------|---------------------------|-------------|
| 1 Month | 23 days | 30 days (+/- 7 days) | 37 days |
| 3 Month | 76 days | 90 days (+/- 14 days) | 104 days |
| 6 Month | 166 days | 180 days (+/- 14 days) | 194 days |
| 9 Month | 256 days | 270 days (+/- 14 days) | 284 days |
| 12 Month | 346 days | 360 days (+/- 14 days) | 374 days |

*Days post-randomization.

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4.8.2. Long Term Follow-Up

The device group will be required to have follow-up assessments annually until the final subject completes the 12 month post randomization visit. Subjects will have the option of an in-person visit, a phone follow-up, or completing a survey via mail. After the 12 month post randomization visit, only serious adverse events and adverse device effects will be collected. Subjects will also be asked to complete a headache diary for 3 months prior to the visit.

4.9. Unscheduled Visits

Unscheduled (or interim) visits are defined as office visits by consented subjects occurring between required study assessments.

For any unscheduled visit that occurs between Screening Visit 1 and the 12-month follow-up visit, an Unscheduled Visit eCRF must be completed. Additionally, if the visit is associated with an adverse event, an Adverse Event eCRF must be completed. If subject medication type, dose or frequency changes, update the Medication Log eCRF. A review of the subject's headache diary is also recommended at this time.

For any unscheduled visit associated with a serious adverse event or adverse device effect occurring after the 12-month follow-up visit and before the last follow-up, complete an Unscheduled Visit eCRF and an Adverse Event eCRF. During this visit, if subject medication type, dose or frequency changes, update the Medication Log.

5. Subject Discontinuation

A subject may be considered discontinued from the study after randomization if:

- Subject withdrew consent
- Subject lost to follow-up
- Death of a subject
- Subject completed study
- Premature study suspension or termination (Sponsor or site)
- Medical necessity per Investigator assessment

In such cases, complete and submit a Discontinuation eCRF.

If a subject's discontinuation from the study is related to an issue of safety or clinical performance of the device, or if the subject has an unresolved adverse device effect at the time of study discontinuation, the center must attempt to follow the subject according to the subject's follow-up schedule, until the event is resolved, or at study closure, whichever occurs first. For subjects who are lost to follow-up, attempts to contact subject will be documented on a Discontinuation eCRF. Subject discontinuations will be reported to the ethics committee or appropriate regulatory body per local requirements.

For all subjects discontinuing after randomization, the reason for discontinuation will be collected. All data will be captured up to the point of discontinuation. Data collected will be used as part of the final analysis.

6. Protocol Deviations

A protocol deviation is any deviation from the Clinical Investigational Plan, Instructions for Use, applicable laws or regulations, or the Clinical Trial Agreement. Complete a Protocol Deviation eCRF for each protocol deviation. When relevant, the ethics committees, competent authorities, or the appropriate regulatory bodies should be informed.

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7. Adverse Events

Beginning with Screening Visit 1 and prior to randomization, all study protocol-related adverse events will be collected. After randomization through the 12-month follow-up visit, all new and/or worsening adverse events will be collected. After the 12-month follow-up visit until the last 12 month follow-up visit is completed, all serious adverse events and adverse device effects will be collected for the device group.

The Investigator will report adverse events using an Adverse Event eCRF as soon as possible upon becoming aware of the event. Each adverse event will be reported on a separate Adverse Event eCRF.

All adverse events should be followed until resolution or study closure, whichever occurs first. For any changes in status, an Adverse Event Follow-up eCRF will be completed with information up to the time of discontinuation or study completion.

An independent Data Safety Monitoring Board (DSMB) composed of physicians with no affiliation to the PRIMA Trial will periodically review study progress with regard to safety. The DSMB will make the final determination on all adverse event categorizations. Details of adverse event adjudication processes can be found in the DSMB Manual of Operations.

7.1. Adverse Event Definitions

Table 5. Table Adverse Event Definitions

| Event | Definition |
|---|---|
| Adverse Event | An untoward medical occurrence in a subject NOTE: This definition does not imply that there is a relationship between the adverse event and the device under investigation. |
| Adverse Device Effect | An untoward and unintended response to a medical device NOTE 1 This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. NOTE 2 This definition includes any event that is a result of a user error. |
| Serious Adverse Event | An adverse event that a) led to a death, b) led to a serious deterioration in the health of the subject that 1) resulted in a life-threatening illness or injury, 2) resulted in a permanent impairment of a body structure or a body function, 3) required in-subject hospitalization or prolongation of existing hospitalization, 4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function. c) led to fetal distress, fetal death or a congenital abnormality or birth defect. |
| Serious/Near Serious Adverse Device Effect | An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune |

7.2. Foreseeable Adverse Events

- Air embolus – symptomatic event resulting from introduction of air into circulatory system

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- Allergic dye reaction – idiosyncratic reaction to dye used in imaging
- Allergic drug reaction – idiosyncratic reaction to drugs used
- Allergic reaction to the device – reaction to device material
- Anesthesia reactions – idiosyncratic reaction to anesthetic agent used
- Apnea – cessation of breathing
- Arrhythmia – cardiac rhythm disturbance
- Bacterial endocarditis – inflammation and infection of the heart
- Bleeding – loss of blood from vascular system requiring 1 unit of blood or >5 g/dl drop in Hgb.
- Brachial plexus injury –damage to brachial plexus
- Cardiac perforation – perforation of the heart wall
- Cardiac tamponade –constriction of the heart causing inefficient contraction resulting from accumulation of excess fluid in the pericardium
- Chest pain
- Death
- Device collapse due to structural failure
- Device embolization – detachment of a device or its part from intended location
- Device erosion-device wear on nearby tissues or cardiac structures
- Fever ≥ 38.6 °C
- Hypertension – sustained BP > 140/90 mmHg
- Hypotension – sustained BP < 90/60 mmHg
- Myocardial infarction – the death of heart muscle from the sudden blockage of a coronary artery by a blood clot, as characterized by 2 of the 3: increased troponin, ECG change, typical chest pain symptom
- New or different onset of migraine symptoms
- Pacemaker placement secondary to PFO device closure
- Palpitations
- Pericardial effusion – fluid collection around heart wall without hemodynamic compromise documented on 2D-echo.
- Pericarditis- A disorder caused by inflammation of the pericardium, which is the sac-like covering around the heart
- Peripheral embolism – symptom consistent with arterial embolism
- Pleural Effusion- An abnormal collection of fluid in the pleural space documented by Chest X-ray
- Pregnancy within 12 months post-randomization
- Pulmonary embolism – A blockage of an artery in the lungs by fat, air, clumped tumor cells, or a blood clot
- Stroke – acute focal neurological deficit presumed to be due to focal ischemia or hemorrhage , and either 1) symptoms persisting 24 hours or greater, or 2) symptoms persisting less than 24 hours, associated with MR or CT findings of a new, neuroanatomically relevant, cerebral infarct or bleed
- Thrombus – a blood clot
- 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, symptoms persisting greater than or equal to 5 minutes and less than 24 hours, which is not associated with MR or CT findings of a new cerebral infarct
- Valvular regurgitation – backflow of blood during contraction of the heart; caused by a defective heart valve, of more than “mild” severity defined by transthoracic color-flow echo.
- Vascular access site injury – damage at vascular access site (i.e. AV fistula, aneurysm)

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7.3. Reporting of Adverse Events

For any serious adverse event and any adverse device effect, the Investigator shall notify the Sponsor within 24 hours of the Investigator's awareness of the event and provide the Sponsor with all necessary documentation needed within 5 days of the Investigator's awareness of the event. The Investigator shall inform the ethics committee of any serious adverse device effect and any other adverse events per ethics committee requirements. The Investigator shall report adverse events to the competent authority per applicable local regulations.

Sponsor contact information for questions regarding adverse events can be found in Table 7 of Section 12.3 Sponsor Contact Information.

8. Device Accountability

All investigational product will be traced by serial number. All research sites must acknowledge receipt of devices and must return all unused product at the end of the investigation. Serial number of devices implanted will be recorded on eCRFs. Investigational devices stored at the center shall be located in a secure, locked location.

9. Hypothesis and Statistical Analysis Plan

The following section contains all statistical rationale used both in the design of this trial, and in the planned analysis of the data following the trial. All data will be analyzed in an intent-to-treat framework. No data imputations will be performed. When appropriate, if parametric methods are found to be inadequate, either non-parametric methods or data transformations will be employed. There are no interim analyses planned, and there will be no adjustments made for multiple comparisons, as there is a lone primary effectiveness endpoint. Unless otherwise specified, all p-values will be considered significant at a two-sided significance level of 0.05. Version 9.1 or higher of the SAS[®] statistical software package will be used to provide all statistical analyses.

The scope of the statistical analysis in this study is limited to subject data obtained up to and including the 12 month visit. The data from these visits compose the entire set of analysis data for primary and secondary endpoints. No formal statistical analyses will be performed on visit data beyond the 12 month visit.

9.1. Justification for Pooling Results

There are two major sources of variability among study centers that must be addressed by any multicenter trial: (1) the study population and (2) the practice of medicine. Differences in either of these can cause the results of the trial to differ among the study centers. In this case, the results are not strictly poolable. Therefore, the data analysis plan includes provisions for dealing with each source of non-poolability.

9.2. Variability in the Study Population

There is not a prior reason to believe that the practices of the participating study Investigators will include nearly identical subject populations. It is reasonable to assume that the practices of the Investigators in this study will reflect the populations that they serve. Therefore, rather than claim that the data will be poolable because all of the study centers have similar subjects, the analyses will be age, gender, and risk-factor adjusted if the demographic analysis shows that there are differences among the centers' subjects. The adjustor variables will accommodate the differences in the subjects. The effect is that like-subjects are compared to like. For example, the adjustments for age and gender assure that older females are compared to older females across centers. Thus the data are "pooled" into a single analysis of all the centers, but the safety and effectiveness results are not assumed to be identical among all types of subjects. The set of baseline variables that are found to be significantly different between the two groups will be referred to as significant adjustor variables (SAV).

9.3. Variability in the Practice of Medicine

Even if the subject populations are identical, it is possible for the results to vary among the centers due to differences in the practice of medicine. It is possible that mean reduction in migraine days may be affected by this variation. Therefore, rather than claim that the data will be poolable because all of the study centers have similar medical practices, the analyses will be center-adjusted (i.e., a "center effect" will be included in the analytic model via the inclusion of $k(\text{number of centers}) - 1$ dummy variables). This method will accomplish two things: (1) it will provide a statistical test for the equivalence of results across centers, and (2) it will adjust for the differences if any exist. If no differences are detected, the center effect may be dropped from the analytic model. In either case, the data are "pooled" into a single analysis of all the centers, but the safety and effectiveness results are *not* assumed to be identical among all centers. The results can be presented either as an average across all centers, or by center.

9.4. Comparison of Demographic Variables and Other Baseline Information

Baseline measures collected at the time of enrollment will be compared between the two treatment groups. A two-sided significance level of 0.05 will be used for all comparisons to assess significance. The Chi-Square test will be used to compare all categorical variables, and the two-sample t-test will be used for all continuous variables. When significant differences are discovered between baseline variables and those variables are judged to be of high clinical significance, those variables will be entered into the SAV matrix for use in subsequent analyses.

9.5. Analysis of Primary Endpoint

Primary effectiveness is the reduction in migraine days at the one year follow-up.

The null hypothesis for testing this endpoint can be stated as: in subjects undergoing percutaneous PFO closure (device group), there will not be a reduction in migraine days at the end of follow-up, relative to the control group. This can be expressed mathematically as:

$$H_0: d_{\text{CLOSURE}} = d_{\text{CONTROL}}$$

$$H_a: d_{\text{CLOSURE}} > d_{\text{CONTROL}}, \text{ where}$$

d_{CLOSURE} = the mean reduction in migraine days in the device group, and

d_{CONTROL} = the mean reduction in migraine days in the control group.

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The basic analysis will be a two-sample t-test comparing the device and control groups in the change from the mean baseline headache days to the final three 30 day periods' headache days. In addition to the basic analysis, Generalized Estimating Equation (GEE) methods will be used to analyze the set of all longitudinal monthly measurements. The specific GEE formulation will assume either negative binomial or Poisson measurements (depending on deviance criterion and over-dispersion) and use the standard log link. The effect of device group will be assessed at $\alpha=0.05$. Any SAV identified during the demographic analysis will be included in the GEE as well as the (k-1) center effects.

It is hoped that the two approaches above will yield similar conclusions. If the statistical conclusions reached from the basic t-test differ with those reached by the GEE methods, the GEE model will be examined to determine the relation of the reduction in migraine days with time in order to decide which conclusions to use.

9.6. Analysis of Secondary Endpoints

All endpoints will be calculated for both treatment arms. Comparisons will be made between the device group and control group using the appropriate statistical methodology defined in Section 9: Hypothesis and Statistical Analysis Plan. When appropriate, some comparisons may also be made within a treatment arm (i.e. follow-up vs. baseline). However, all such comparisons will be considered secondary and ad hoc.

9.6.1. Change in Responder Rate

In addition to the primary endpoint assessing the reduction in the number of migraine days, this secondary endpoint will assess reduction on the subject level. The responder rate will be defined as the proportion of subjects who have a 50% or greater reduction in the number of migraine days relative to baseline.

The null and alternative hypotheses for this rate will be stated as follows:

$$\begin{aligned} H_0: & \square_{\text{CLOSURE}} = \square_{\text{CONTROL}} \\ H_a: & \square_{\text{CLOSURE}} > \square_{\text{CONTROL}}, \text{ where} \\ & \square_{\text{CLOSURE}} = \text{the responder rate in the device group, while} \\ & \square_{\text{CONTROL}} = \text{the responder rate in the control group.} \end{aligned}$$

The null hypothesis can be stated for this comparison as: there will be no difference in the responder rate between the two treatment groups.

Statistical Analysis

The statistical analysis for responder rate will be completed via logistic regression, modeling each subject's odds of achieving a 50% reduction in mean headache days over the 9 through 12 months of the study period as a function of treatment, the (k-1) center effects, and any SAV identified in the analyses of baseline and demographic variables. If there is no effect of center found, the matrix of fixed effects will be removed from the model, and the model re-estimated. The trial will be considered successful if the p-value attached to the device group coefficient is less than 0.05.

A second analysis will be completed modeling the responder rates across the 12 months of the study. In order to test for treatment differences in a repeated measures framework with categorical responses (responder/no responder), a Generalized Estimating Equation (GEE) will be used employing a logit link. Center effects and SAV will enter the model in the usual fashion. This analysis will merely be used to support the primary analysis presented above and to ascertain the effects of treatment on responder rates over time.

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It is hoped that, like the primary endpoint, the two approaches above will yield similar conclusions. If the statistical conclusions reached from the logistic regression differ with those reached by the GEE methods, the GEE model will be examined to determine the relation of the reduction in migraine days with time in order to decide which conclusions to use.

9.6.2. Change in Number of Migraine Attacks and Attacks with Aura

It has been hypothesized that the distribution of subject's migraine attacks may differ from their distribution of migraine days. Thus, an analysis of attacks will be performed in a similar manner to the analysis of migraine days.

The null hypothesis for testing this endpoint can be stated as: in subjects undergoing percutaneous PFO closure (device group), there will not be a reduction in migraine attacks at the end of follow-up, relative to the control group. This can be expressed as:

$$H_0: d_{\text{CLOSURE}} = d_{\text{CONTROL}}$$

$$H_a: d_{\text{CLOSURE}} > d_{\text{CONTROL}}, \text{ where}$$

d_{CLOSURE} is the mean reduction in attacks in the device group, and
 d_{CONTROL} is the mean reduction in attacks in the control group.

In addition, an analysis will be performed on the number of migraine attacks with aura. The corresponding null hypothesis is similar to the hypothesis for migraine attacks:

$$H_0: d_{\text{CLOSURE}} = d_{\text{CONTROL}}$$

$$H_a: d_{\text{CLOSURE}} > d_{\text{CONTROL}}, \text{ where}$$

d_{CLOSURE} is the mean reduction in attacks with aura in the device group, and
 d_{CONTROL} is the mean reduction in attacks with aura in the control group.

Migraine attacks and attacks with aura will be recorded from the headache diary. The number of migraine attacks, as well as attacks with aura, is taken from the Screen Visit 3 – Neurology Assessment form and the Follow-Up Visit – Neurology form, as adjudicated by a headache diary endpoint committee, and recorded on the adjudication eCRF.

The basic analysis for each will be a two-sample t-test comparing the device and control groups in the change from the mean baseline migraine attacks to the attacks in the 9 through 12 month period. In addition to the basic analysis, Generalized Estimating Equation (GEE) methods will be used to analyze the set of all longitudinal monthly measurements. The specific GEE formulation will assume either negative binomial or Poisson measurements (depending on deviance criterion and over-dispersion) and use the standard log link. The effect of treatment group will be assessed at $\alpha=0.05$. Any SAV identified during the demographic analysis will be included in the GEE as well as the (k-1) center effects.

As with migraine days, it is hoped that the two approaches above will yield similar conclusions. If the statistical conclusions reached from the basic t-test differ with those reached by the GEE methods, the analysis will proceed as described above for migraine days.

9.6.3. Change in Use of Acute Migraine Medications

It is believed that PFO closure may result in a subsequent decrease in the use of acute migraine medications relative to the control group. Separate analyses will be performed for acute medications.

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For each analysis, the null and alternative hypotheses will be stated as follows:

$$H_0: D_{\text{CLOSURE}} = D_{\text{CONTROL}}$$

$$H_a: D_{\text{CLOSURE}} > D_{\text{CONTROL}}, \text{ where}$$

D_{CLOSURE} = the mean reduction of acute migraine medication days during the follow-up phase relative to the baseline phase for the device group, and

D_{CONTROL} = the mean reduction of acute medication days during the follow-up phase relative to the baseline phase for the control group

If necessary, medication use for each group will be adjusted to reflect differing lengths of the baseline and treatment phases.

9.6.4. Change in MIDAS score

The null hypotheses for the analysis of MIDAS scores are:

$$H_0: M_{\text{CLOSURE}} = M_{\text{CONTROL}}$$

$$H_a: M_{\text{CLOSURE}} > M_{\text{CONTROL}}, \text{ where}$$

M_{CLOSURE} = the mean reduction of MIDAS score during the follow-up phase relative to the baseline phase for the device group, and

M_{CONTROL} = the mean reduction of MIDAS score during the follow-up phase relative to the baseline phase for the control group

9.6.5. Change in Quality of Life

PFO closure may also result in improvement in quality of life as measured by the QOL Questionnaire. This will be tested using the following hypotheses:

$$H_0: Q_{\text{TREATMENT}} = Q_{\text{BASELINE}}$$

$$H_a: Q_{\text{TREATMENT}} < Q_{\text{BASELINE}}, \text{ where}$$

$Q_{\text{TREATMENT}}$ = the average QOL score when assessed during the treatment phase, and

Q_{BASELINE} = the average QOL score for subjects undergoing PFO closure, when assessed during the baseline phase

This hypothesis will only be tested for subjects undergoing PFO closure.

9.6.6. Change in Beck Depression Scores

Change in the Beck Depression Inventory (BDI) will be analyzed in a similar manner to the MIDAS Evaluation. The null hypotheses for the BDI analysis are:

$$H_0: B_{\text{CLOSURE}} = B_{\text{CONTROL}}$$

$$H_a: B_{\text{CLOSURE}} > B_{\text{CONTROL}}, \text{ where}$$

B_{CLOSURE} = the mean reduction of the total BDI score during the follow-up phase relative to the baseline phase for the device group, and

B_{CONTROL} = the mean reduction of the total BDI score during the follow-up phase relative to the baseline phase for the control group

It is anticipated that repeated-measures general linear models will be used to test the above hypotheses for acute medications, MIDAS, QOL, and BDI. If appropriate, this analysis will be completed by utilizing Generalized Estimating Equation (GEE) methods to analyze the set of all longitudinal measurements as collected. The specific GEE formulation will assume Poisson or negative binomial measurements (counts of medications used, inventory scores) and use the standard log link. For either model, the effect of treatment group will be assessed

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at $\alpha=0.05$. Any SAV identified during the demographic analysis will be included in the GEE as well as the (k-1) center effects.

9.6.7. Effects of Anti-Thrombotic Medication

The main analysis of the effects of anti-thrombotic medication (aspirin and clopidogrel) will be assessed by comparing the number of headache days from baseline until the 6 month visit, when medication is taken, against the number of headache days during screening and between the 9 and 12 month visits, when medication is not taken.

For this analysis, the date of the six month visit will separate the medication and non-medication time periods. A simple hypothesis test will be performed to determine if a significant difference exists between the mean headache days for the “medication period” (baseline to 6 months) versus the “no medication period” (0, and 9 to 12 months). However, even with a significant difference this may not be the best fitting model. This is because of a potential longitudinal effect of time on headache days, and because aspirin and Clopidogrel are not taken uniformly at the medication timepoints. As a result, quadratic and cubic contrasts, as well as potentially a repeated measures analysis, will be included in the models explored to determine the best fitting model, if any.

9.6.8. Adverse Event Classification

The type, seriousness, relatedness, and resolution of all adverse events recorded in the study will be tabulated and presented. Differences between the device and control group in types of adverse events through 12-months of follow-up will be assessed via chi-square tests.

9.6.9. PFO Closure

Incidence of complete foramen ovale closure by 12 months in device group subjects will be assessed by TEE.

9.7. Treatment Failure

A subject who either (1) increases or (2) changes his/her prophylactic/preventative migraine medication to an alternative agent secondary to migraine headaches (rather than due to medication intolerance) will be considered a treatment failure. Medication increases or changes should be symptom driven and under the control of the treating neurologist. Any improvement accompanied by a decision to increase medications cannot indicate a treatment success.

A subject who changes or adds a medication used for another purpose, but with the incidental effect of treating migraines, will not necessarily be considered a treatment failure. Rather, the effect of this medication will be assessed by a blinded Endpoint Review Committee to determine if the subject has failed the study.

9.8. Power Analysis and Sample Size

In one of the largest randomized trials of migraineurs to date, Silberstein et. al.¹⁹ enrolled subjects into four groups to receive either a placebo, or one of three dose levels of Topiramate. The average number of migraine attacks for all groups was near 5.6 ± 2.6 , and the average number of migraine days was 6.4 ± 2.8 . The placebo group experienced an 18% reduction in the number of attacks from 5.6 ± 2.3 to 4.6 ± 3.0 . The placebo group is an

Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)

appropriate benchmark for the control arm in this study as they will continue on with their established medical management of migraine, and no large reductions are expected beyond those that typically occur when a subject is aware they are participating in a trial (Hawthorne effect). Assuming a correlation between paired measurement of 0.5, we can estimate the standard deviation of the paired differences in migraine attacks to be 2.72 (nQuery 5.0, Statistical Solutions, USA). We can then estimate the standard deviation of the paired differences in migraine days to be 3.1 [$\text{var}(bX) = b^2 \text{var}(X)$, where $b = 6.4/5.6 = 1.14$].

In a recent publication²⁰, 80% of subjects with migraine plus aura who had closure of a PFO experienced complete resolution of their migraines. Therefore, it can be conservatively estimated that there would be at least a 50% reduction in the number of migraine days in this group. In addition, it will be conservatively estimated that the control group will experience a 25% reduction in migraine days, greater than the 18% reduction found in the literature. In order to show a difference between a 25% reduction from 6.4 (4.8) and a 50% reduction from 6.4 (3.2), where both groups are assumed to have a common standard deviation of paired differences of 3.1, with 80% power and at a two-sided significance level of 0.05, a minimum of 60 subjects are required per group (nQuery 5.0, Statistical Solutions, USA). In order to account for a 20% loss-to-follow-up rate, a minimum of 72 subjects will be randomized into each treatment group.

9.9. Sensitivity Analysis

Subjects who do not complete 12 months of therapy will have incomplete treatment phases. Consequently, they will not be evaluated with regard to the primary endpoint. However, this primary analysis will be supplemented by a sensitivity analysis to determine the effect of these missing subjects.

In this analysis, subjects who completed less than 12 months of treatment will first have their recorded migraine days included in this analysis. After these days are included, suppose there are N_t missing days of therapy in the device group, and N_c missing days of therapy in the control group. Then there are 0, 1, 2, . . . N_t potential additional migraine days in the device group and 0, 1, 2, . . . N_c potential additional migraine days in the control group. This can be expressed as an N_t by N_c matrix of migraine days.

Each entry in this matrix will be calculated to determine if the null hypothesis for the primary endpoint, as evaluated by the basic t-test, would have been rejected had this combination of migraine days been obtained. Combinations where the null is rejected will be recorded as study successes, while combinations where the null is not rejected will be recorded as study failures. The total percentage of these study successes will be reported in order to gauge the likelihood of these missing headache days influencing the overall conclusions of the trial.

In addition to this analysis, an analysis will be performed where each entry in the N_t by N_c matrix is weighted by the probability of obtaining that particular result. The weights used will be based on the relative frequencies of migraine days from the reported observations. The probabilities of study success for each entry, multiplied by the probability of each entry, will be added to determine the overall probability of study success in this analysis.

10. Risk/Benefit Analysis

10.1. Risk/Benefit Assessment For the Device Group

10.1.1. Interventional Risks

The risks of percutaneous PFO closure consist of the risk of the implantation procedure and the long-term risk of the device itself. The implantation risks are similar to those of other interventional cardiac procedures. They include, but are not limited to, arrhythmias, vascular or cardiac perforation, and air embolus. The risks of cerebral vascular accidents and myocardial infarction are expected to be lower than other cardiac catheterization requiring arterial access. The risk of death is minimal. See section 7.2 for a complete list of foreseeable adverse events.

10.1.2. Risk/Benefit Assessment of the AMPLATZER® PFO Occluder

The subjects who are randomized to receive the AMPLATZER® PFO Occluder will be exposed to the risks outlined above. In addition, the subjects who receive the device will be exposed to potential risks of this permanent implant. The device has been designed so that it can be securely positioned across the septum before its final release with a screw mechanism. In case of misplacement, recapturing of the device is performed in the mid-left or right atria where it can be collapsed and retrieved inside the delivery catheter for repositioning.

The common risks associated with the AMPLATZER® PFO Occluder include cardiac perforation, bacterial infection on the device, and thrombus formation on the device surface with the risk of subsequent embolization, arrhythmias and device collapse due to structural failure.

- *Cardiac perforation* - This complication could require open-heart surgery to correct the problem. The ethical justification for implanting a permanent device in these subjects is that the quality of life produced by frequent migraine headaches is seriously diminished and could be significantly improved if this study confirms prior observations of the reduction in frequency of migraine headaches in subjects who have had their PFO closed.
- *Bacterial infection of the device* - Since this is a permanent implant of a foreign body, there is a potential risk of bacterial contamination, especially when the subject is exposed such as during dental cleaning. To diminish this risk, the subjects will be instructed to use standard antibiotic prophylactic procedures.
- *Atrial arrhythmias* - Increased palpitations following implantation of this device have been reported which were often diagnosed as either isolated or premature atrial contractions (PACs).
- *Allergy to nickel* - The AMPLATZER® PFO Occluder is made of Nitinol which is an alloy of nickel and titanium. Approximately 10 to 20 of the population demonstrate an allergic skin reaction to nickel. Despite this incidence of potential allergy, the AMPLATZER® PFO and ASD Occluders have been implanted in approximately 100,000 patients worldwide with only one reported patient who had an apparent allergic reaction to the device manifested by pericardial effusion and atrial fibrillation.

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- To decrease the potential risk of this occurrence, subjects will be screened with a nickel allergy patch test. Any subject who has a significant reaction to nickel will be excluded from participating in this trial.
- *Thrombus on the device* - Implantation of this device in the atrial chambers has potential for formation of thrombus which could embolize from the left side to the cerebral circulation or anywhere else in the body. To prevent this possibility, the subjects will be treated with antiplatelet medications for six months.
- *Radiation Risks* - The risks of radiation are identical to diagnostic catheterization and are well within permissible limits. The risks are comparable to procedures like balloon valvuloplasty and angioplasty, which are routinely performed in neonates, children and adults.

The minimally invasive nature of this procedure, shorter hospitalization stay, and considerable financial savings are strong reasons to consider the AMPLATZER® PFO Occluder a potential treatment modality of choice in such subjects.

10.1.3. Potential Benefit for the Device Group

A potential benefit of having the AMPLATZER® PFO Occluder implanted is that the PFO may be closed without open-heart surgery. Usually the pain after the implant procedure is less than open-heart surgery. The stay in the hospital is usually shorter. The recovery time may be faster and there is little scarring. However, it is not known how effective the AMPLATZER® PFO Occluder will be to reduce the frequency and severity of migraines in humans and is to be evaluated in this study.

10.2. Risk/Benefit Assessment for Both Device and Control Groups

10.2.1. Risks with Aspirin and Clopidogrel

Both subject groups will receive the same medications of aspirin and clopidogrel. These medications are commonly used in subjects who receive coronary artery stents. The most common risk of these antiplatelet agents is superficial skin ecchymosis. These usually resolve especially when the dose of the medications is decreased, as will be allowed in this clinical trial. Gastritis or exacerbation of intestinal bleeding, such as from an ulcer, may occur but the incidence of these complications has been diminished dramatically with the concomitant use of agents to decrease the production of hydrochloric acid in the stomach.

10.2.2. Risks with Transcranial Doppler

There is a potential of having a migraine headache after shunt assessment by the transcranial ultrasound, which may be induced by the saline injection during the procedure.

10.2.3. Risks associated with TEE

The procedure is generally safe, and serious complications such as esophageal injury or bleeding, vocal cord paralysis, cardiac arrhythmias, hypotension, seizures, cardiac arrest occur in less than 3% of TEE examinations. The reported mortality rate associated with TEE is 0.0 1-0.03%; but in most cases a causal link with TEE has not been established

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and is likely due to the underlying pathology. Agitated saline bubble studies to assess right to left shunts have been associated with induction of migraine headache in susceptible patients.

10.2.4. Potential Benefit for the Control Group

The potential benefits of having the current standard of care treatment are that subject's condition will be treated without any invasive procedures, the subject will be closely followed, and data from this study may change future treatments for migraine subjects.

In addition, upon CE mark approval of the device for the migraine indication, subjects who were randomized to the control group will be offered PFO closure. The AMPLATZER® PFO Occluder will be available at no charge.

10.3. Alternative Forms of Treatments for Migraine and Associated Risks

Many therapies are available for the treatment of migraine. Many only work in approximately 50% of subjects. Of those treatments approved by the FDA, divalproex can cause pancreatitis and fatal hepatitis; methysergide can cause retroperitoneal fibrosis and beta-blockers can exacerbate depression and angina. No medication for migraine prevention has been proven safe in pregnancy and divalproex is a known teratogen.

11. Device Description

11.1. Product Description

The AMPLATZER® PFO Occluder is a self-expandable, double disc device made from a Nitinol wire mesh. The two discs are linked together by a short connecting waist. In order to increase its closing ability, the discs contain polyester fabric. The polyester fabric is securely sewn to each disc by a polyester thread. The delivery system consists of a delivery sheath with Touhy-Borst adapter, dilator, loader, plastic vise and delivery cable. The following table lists available device sizes.

Table 6. Device Description

| Part Number | Right Atrial Disc Diameter | Left Atrial Disc Diameter |
|-----------------------|-----------------------------------|----------------------------------|
| 9-PFOPRIMA-018 | 18 mm | 18 mm |
| 9-PFOPRIMA-025 | 25 mm | 18 mm |
| 9-PFOPRIMA-030 | 30 mm | 30 mm |
| 9-PFOPRIMA-035 | 35 mm | 25 mm |


11.2. Product Labeling

- A copy of the Instructions for Use can be found in this Investigational Plan.
- Subject ID card - All subjects will be assigned a subject identification number at the time of signing consent. All subjects who are randomized in the PRIMA Trial will be given a Subject Identification Card. Draft ID cards are provided on the following page.

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For Device Group

Front of card


| SUBJECT IDENTIFICATION CARD | |
|-----------------------------|---|
| Subject Initials: |  |
| Subject ID: | |
| Procedure Date: | |
| Cardiologist: | |
| Phone: | |
| Neurologist: | |
| Phone: | |
| Product Number: | |
| Lot Number: | |
| Serial Number: | |

Back of Card

| |
|---|
| <p>The carrier of this card is participating in a randomized, controlled study and has been treated with an implantable patent foramen ovale closure device.</p> <p>Device is NON-FERROMAGNETIC / MR COMPATIBLE UP TO 3.0T.</p> <p>Notify your doctor if there is any change in your medical condition or address. Remember to take Clopidogrel for three months and Aspirin for six months following randomization (insert date).</p> <p>If you experience shortness of breath or chest pain: Seek medical attention immediately. An echocardiogram may be required.</p> |
| <p>Manufactured by: AGA Medical Corporation 5050 Nathan Lane North Plymouth, MN 55442 USA Tel: +1.763.531.2748</p> |

For Control Group

Front of Card


| SUBJECT IDENTIFICATION CARD | |
|-----------------------------|--|
| Subject Initials: |  |
| Subject ID: | |
| Randomization Date: | |
| Cardiologist: | |
| Phone: | |
| Neurologist: | |
| Phone: | |
| | |
| | |
| | |

Back of Card

| |
|---|
| <p>The carrier of this card is participating in a randomized, controlled study and has been randomized to current medical management.</p> <p>Notify your doctor if there is any change in your medical condition or address. Remember to take Clopidogrel for three months and Aspirin for six months following randomization (insert date here).</p> |
| <p>Manufactured by: AGA Medical Corporation 5050 Nathan Lane North Plymouth, MN 55442 USA Tel: +1.763.531.2748</p> |

For Both Groups

Front of Card

| | |
|--|---|
| <p>The card holder is participating in the Prima Trial sponsored by AGA Medical Corporation</p> |  |
| <p>Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study</p> | |
| Subject Initials: | |
| Subject ID: | |
| Randomization Date: 00-00-0000 (dd-mm-yyyy) | |
| Investigator Name: | |
| Phone: | |
| | |
| | |
| | |

Back of Card

| |
|--|
| <p style="text-align: center;">FOLLOW-UP SCHEDULE (dd-mm-yyyy)</p> <p style="text-align: center;">1 Month (22-09-2010 - 06-10-2010)</p> <p style="text-align: center;">3 Month (14-11-2010 - 12-12-2010)</p> <p style="text-align: center;">6 Month (12-02-2011 - 12-03-2011)</p> <p style="text-align: center;">9 Month (13-05-2011 - 10-06-2011)</p> <p style="text-align: center;">12 Month (11-08-2011 - 08-09-2011)</p> <p>Follow-up visits will include physical, MIDAS evaluation, BECK Depression Inventory, and Quality of Life Assessment</p> <p>Please be certain to bring your Headache Diary to each follow-up visit. Additionally, for device subjects, an ECG will be required at the 1 month visit, as well as a TEE at the 6 month visit.</p> <p>Follow-up assessments will also be conducted annually for device subjects until the last device subject completes the 12-month follow-up visit.</p> |
|--|

Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)

The AMPLATZER® PFO Occluder device packaging labels are provided below and on the following page.

| | | |
|---|-------------------------------|---|
| EXCLUSIVELY FOR CLINICAL INVESTIGATIONS Exclusivement pour les investigations cliniques Ausschließlich für klinische Überprüfung Esclusivamente per ricerca cliniche Wylączne dla Badań Klinicznych | 220036-006 (01) 600036-006 |  |
| Investigational Device To be Used by Qualified Investigators Only Instrument de recherche Réservé uniquement à l'usage de chercheurs compétents | | |

Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)



Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)

11.3. Preclinical Testing

Please refer to the Investigational Brochure to obtain details on pre-clinical testing.

12. Study Management

12.1. Monitoring Procedures

Monitoring for the PRIMA study will be performed by AGA Medical Corporation and authorized designees according to ISO 14155, the Monitoring Plan for the study, and applicable AGA Medical Corporation standard operating procedures and work instructions. Qualified monitors will be designated to assure that both the Sponsor and Investigators comply with protocol and ISO 14155 requirements.

During the pre-investigational assessment, the monitor will assess the adequacy of the facilities, the availability of the Investigator, the potential number of study participants, and the provisions for staff support.

The monitor will communicate with each investigational site prior to the onset of the study to review relevant ISO regulations, the Clinical Investigational Plan, ethics committee review and approval, completion and submission of applicable forms, record keeping requirements, and administrative reports.

To ensure that the Investigators and their staff understand and accept their defined responsibilities, the monitor will maintain regular correspondence and perform periodic site visits during the course of the study. This will verify the continued acceptability of the facilities, compliance with the Investigational Plan and relevant competent authority regulations, and the maintenance of complete records.

Monitoring will include review and resolution of missing or inconsistent results and source document checks (i.e. comparison of submitted study results to original reports) to assure the accuracy of the reported data.

The monitor will evaluate and summarize the results of each site visit in written reports, identify any repeated data issues with the Investigator and specify recommendations for resolution of noted deficiencies. Investigative sites will be provided with summaries of the reports from each monitoring visit.

12.2. Auditing Procedures

The sponsor or regulatory authority may audit the study center to evaluate the conduct of the study. The Investigator and institution shall allow trial-related audits, ethics committee review, and regulatory inspection by providing direct access to source data and documents.

**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study (PRIMA Trial)**

12.3. Sponsor Contact Information

The following table lists Sponsor contact information for this clinical study.

Table 7. Sponsor Contact Information

| | |
|--|--|
| Sponsor Offices | AGA Medical Corporation 5050 Nathan Lane North Plymouth, MN 55442 USA International Clinical Research Telephone: +1 (763) 531-2748 Main Company Telephone: +1 (763) 513-9227 Fax: +1 (763) 647-5903 |
| Worldwide Study Manager and Monitor | Michele Davies, MBA AGA Medical Corporation 5050 Nathan Lane North Plymouth, MN 55442 USA Telephone: +1 (763) 531-2732 Mobile: +1 (612) 245-3028 Fax: +1 (763) 647-5903 E-mail: mdavies@amplatzer.com |
| Statistician | Brian Van Dorn AGA Medical Corporation 5050 Nathan Lane North Plymouth, MN 55442 USA Telephone: +1 (763) 531-2708 |
| Country Representative (Europe) | AGA Medical Ltd Shane Brown Suite 1 3500 Parkside Birmingham Business Park Birmingham B37 7YG |

12.4. Protocol Changes

No changes in the study procedure shall be affected without mutual-agreement of the Investigator and the Sponsor. All changes must be documented by signed protocol amendments. All changes require notification to ethics committees and competent authorities.

12.5. Data Management

12.5.1. Source Data and Documentation

All study findings must be documented as source data. Source data is all information in original records (or certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, recorded data from automated instruments, subject files).

Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)

12.5.2. Data Collection and Processing

The Investigator shall be responsible for the accuracy, legibility, and security of all Prima Trial data, documents, and subject records at the Site. The Investigator, or an individual designated by him/her, is responsible for entering the data from source documentation to electronic case report forms (eCRFs) in the Remote Data Entry (RDE) system. Attachment C contains draft eCRFs for this study. eCRF data will be reviewed and verified by the authorized Investigator and promptly submitted to the Sponsor. Any alteration of the data shall be made by only authorized personnel through the remote data entry system.

Required source documents will be sent to AGA Medical by the sites in a timely manner where the data will be reviewed. Subject's information should be de-identified prior to sending any related data set or information to AGA Medical Corporation.

12.6. Regulatory

This study will be conducted according to the Clinical Investigational Plan, ISO 14155, the guidelines established in the most recent version of the Declaration of Helsinki, and applicable local and national regulations. ISO regulations, as well as AGA Medical Corporation policies, require that certifications and other regulatory documents be kept up-to-date at all times during the conduct of a clinical investigation. The ethics committee must review and approve the continuation of the study per local requirements until the study is officially closed out at the site.

12.7. Advisory Committees

The following Advisory committees for the PRIMA Trial will be established: Steering Committee, Data Safety Monitoring Board, Echo Review Core Lab, Endpoint Review Committee. Detailed information on each board can be found in the respective Manual of Operations governing each committee.

12.7.1. Steering Committee

The Steering Committee for the PRIMA trial will consist of clinical study Investigators who will serve as an advisory board for AGA Medical Corporation from the development stage throughout the course of the clinical investigation. Some responsibilities of Steering Committee members include but are not limited to: identifying inclusion/exclusion criterion, study objectives and other functions as required during the course of the investigation. Additionally, the Steering Committee may act as an advisory panel for questions regarding informed consent, subject entry, protocol implementation, study endpoints, Investigator discrepancies, and other issues that may present during the course of the study.

12.7.2. Data Safety Monitoring Board

An independent Data Safety and Monitoring Board (DSMB) will regularly review study progress with regard to safety.

The DSMB will consist of cardiologists and neurologists that have no affiliation with the study sponsor, nor will they be participating Investigators in the study. A biostatistician will be available to the committee if they have questions concerning the significance of the data.

The primary responsibilities of the DSMB are to:

- Review and refine adverse event definitions (and refine definitions as necessary during the conduct of the study).
- Review and adjudicate adverse events as they occur over the course of the study.
- Rigorous review of all failure criteria.
- Review and validate the subject sample (i.e., review inclusion/exclusion deviation and other protocol deviations).
- Provide oversight for issues affecting general subject welfare.

At any time during the course of the study, the DSMB may offer opinions or make formal recommendations concerning aspects of the study impacting subject safety (e.g., safety related protocol changes or input regarding adverse event rates associated with the study). Additionally, the DSMB may act as an advisory panel for questions regarding Informed Consent, subject entry, protocol implementation, study endpoints, Investigator discrepancies, and other issues that may present during the course of the study.

12.7.3. Echo Review Core Lab

An echo core lab with no affiliation with the study sponsor, or participating Investigators in the study will review 6-month or later TEE data to provide an objective assessment of PFO closure status post-implant. Screening TEEs may also be reviewed by the core lab.

12.7.4. Endpoint Review Committee

The Endpoint Committee will consist of neurologists that have no affiliation with the study sponsor, nor will they be participating Investigators in the study. Responsibilities will include review of headache diaries that contribute to primary endpoint data. Committee members will be masked to the assigned study arm when performing its assessments, even though the trial itself is not conducted in a blinded manner. Additionally, the Endpoint Review Committee may act as an advisory panel for questions regarding informed consent, subject entry, protocol implementation, study endpoints, Investigator discrepancies, and other issues that may present during the course of the study.

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12.8. Insurance and Indemnity

Each subject is insured against any health impairment occurring as a result of participation in the investigation in accordance with laws and regulations of the country in which the investigation is performed. Details concerning the insurance, such as the insurance company and the insurance number, will be filed in the Trial Master File and in the Investigator's File and submitted upon request to the Ethics Committee(s). The Investigator must report immediately to the Sponsor any claim made by a subject that may be related to participation in the investigation.

12.9. Subject Compensation

Subjects will not receive any payment for participating in this study.

Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)

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A Randomized Prospective Study (PRIMA Trial)**

14. Attachments

Attachment A. List of Institutions and Principal Clinical Investigators

| Institution | Cardiologist | Neurologist |
|--|---|--|
| Royal Sussex County Hospital Cardiology Research Unit Room 108, Sussex House Eastern Road Brighton BN2 1ES, United Kingdom | David Hildick-Smith, MD Royal Sussex County Hospital Eastern Road Brighton BN2 5BE, United Kingdom Tel: +44 1273664494 | Anirban Romi Saha, MD Royal Sussex County Hospital Department of Neurology, C/O Neurology Secretaries Brighton BN2 5BE, United Kingdom Tel: +44 1273696955 x4305 |
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**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study (PRIMA Trial)**

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**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study (PRIMA Trial)**

Attachment B. Informed Consent Template

**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study (PRIMA Trial)**

Attachment C. Electronic Case Report Forms

- Pre-Screening Questionnaire
- Screen Visit 1
- Medication Log
- Shunt Assessment
- Screen Visit 2
- Nickel Patch Test
- Screen Visit 3
- Unscheduled Screening Visit
- SF-12v2™ Quality of Life
- Randomization
- Device Implant Procedure
- Follow-up Visit - Neurology
- Follow-up Visit – Cardiology
- Long Term Follow-Up
- Protocol Deviation
- Adverse Event
- Adverse Event Follow-Up
- Discontinuation
- Technical Incident report

**Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura -
A Randomized Prospective Study (PRIMA Trial)**

Attachment D. AMPLATZER® PFO Occluder Instructions for Use

Percutaneous Closure of Patent Foramen Ovale In Migraine with Aura - A Randomized Prospective Study (PRIMA Trial)

Attachment E. Recommended TEE Protocol

- Seven separate recordings need to be made onto CD or tape for analysis by the Echo Core Lab. Each recording should be labelled 1-7 on the CD or tape.
- The bubble contrast mixture should consist of 7mls saline, 2mls blood, 1ml air, fully agitated using 2 Luer lock syringes and a three-way tap.

Recordings to be made

1. Mid-esophageal view of the device without color flow, to examine for device migration or related anatomical abnormalities.
2. Mid-esophageal view of the device with color flow, to examine for anatomical abnormalities associated with abnormal flows.
3. Optimal view (mid-esophageal 50-70 degree or bicaval 100-120 degree) of the right and left atria with bubble contrast mixture injected at rest. Record from the time the injection is made and for 10 cardiac cycles after the contrast appears in the right atrium
4. Optimal view of the right and left atria with bubble contrast mixture injected during and after Valsalva maneuver. The Valsalva maneuver in sedated patients may be replicated by firm abdominal pressure and release. Record from the time the injection is made and for 10 cardiac cycles after the contrast appears in the right atrium
5. Optimal view of the right and left atria with bubble contrast mixture injected during and after Valsalva maneuver. The Valsalva maneuver in sedated patients may be replicated by firm abdominal pressure and release. Record from the time the injection is made and for 10 cardiac cycles after the contrast appears in the right atrium
6. Optimal view of the right and left atria with bubble contrast mixture injected during and after other provocative maneuvers. For unsedated patients, cough or sniff are the preferred maneuvers. For sedated patients, maneuvers may include raising the arms or legs to increase venous return, or induction of gastric heave by manipulation of the probe. Record from the time the injection is made and for 10 cardiac cycles after the contrast appears in the right atrium
7. Pulmonary vein sweep with bubble contrast mixture injected at rest. Record from the time the injection is made and for 20 cardiac cycles after the contrast appears in the right atrium, sweeping across from the left to right pulmonary veins to assess for pulmonary shunting.

Once the study is complete, further images can be obtained and added to the tape as necessary according to any abnormalities detected.