GORE® CARDIOFORM Septal Occluder Migraine Clinical Study: A Study to evaluate the safety and efficacy of transcatheter closure of patent foramen ovale for relief of migraine headaches

The Gore RELIEF Clinical Study

Protocol #: GSO 17-03

NCT # 04100135

Statistical Analysis Plan and Protocol

09FEB026

PROTOCOL SUMMARY

Study Title	GORE® CARDIOFORM Septal Occluder Migraine Clinical Study (RELIEF Clinical Study): A Study to evaluate the safety and efficacy of transcatheter closure of patent foramen ovale for relief of migraine headaches
Protocol Number	GSO 17-03
IDE or PMA Number	G190048
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 4250 West Kiltie Lane Flagstaff, AZ 86005 Telephone: 800-437-8181 Facsimile: 928-864-4957
Study Design	Multi-center, prospective, randomized, placebo- and sham-controlled study to evaluate the GORE® CARDIOFORM Septal Occluder for migraine headache relief
Study Objective	Evaluate PFO closure for migraine headache relief using the GORE® CARDIOFORM Septal Occluder
Study Endpoints	**Primary Efficacy Endpoint:** • Reduction in Migraine Headache Days: mean reduction in the number of migraine headache days per month from baseline to follow-up **Secondary Efficacy Endpoints:** • Treatment Responder Proportions (Percent Reduction in Migraine Headache Days): the proportions of subjects experiencing ≥50%, ≥75%, and ≥90% reduction in migraine headache day frequency from baseline to the post-procedure follow-up period • Change in Migraine Headache Disability as assessed by HIT-6 questionnaire comparing baseline to post-procedure months 6, 10, and 24 • Change in Migraine-Specific Quality of Life as assessed by MSQ v2.1 questionnaire comparing baseline to post-procedure months 6, 10, and 24 • Assessment of PFO closure at post-procedure month 10 as determined by the Echo Core Lab • Reduction in acute migraine medication days from baseline to - after thienopyridine discontinuation (during months 8-10) • Response to acute migraine medication (two-hour pain-free response) comparing baseline to after thienopyridine discontinuation (during months 8-10)

	Primary Safety Endpoint: • Proportion of subjects with any Serious Adverse Event (SAE) related to the study device or study procedure through 30 days post-procedure **Secondary Safety Endpoints:** • Incidence of bleeding by Bleeding Academic Research Consortium (BARC) type from enrichment through the primary endpoint visit (month 10) • Incidence of device events in the device arm (defined as post-procedure embolization or study device removal due to a device-related AE) from completion of the treatment procedure through the primary endpoint assessment at month 10 • Incidence of clinically significant new atrial arrhythmia from completion of the treatment procedure through the primary endpoint assessment at month 10 **Exploratory Endpoints:** • Assessment of differences in outcomes in migraineurs with aura versus migraineurs without aura • Assessment of differences in outcomes in episodic versus chronic migraineurs • Assessment of outcomes in subjects by shunt size • Assessment of the effectiveness of subject blinding • Assessment of migraine frequency in the 6 months following the treatment procedure
Test Arm	Thienopyridine-responsive migraineurs, per enrichment, randomized to PFO closure using the GORE® CARDIOFORM Septal Occluder
Control Arm	Thienopyridine-responsive migraineurs, per enrichment, randomized to a sham procedure (catheterization with no PFO closure)
Study Medications	Clopidogrel loading dose of 300 mg followed by a daily dose of 75 mg or Prasugrel 20 mg loading dose followed by a daily dose of 5 mg (Thienopyridines)
Control Drug	Placebo (applicable only in the enrichment phase)
Subject Population	Patients 18-55 years of age with a documented PFO who meet International Classification of Headache Disorders - 3 (ICHD-3) Diagnostic Criteria for migraine with or without aura and have more than one migraine headache day per week. Patients must also, by history, have tried at least two preventive migraine medications at adequate dosage for an adequate duration and exhibit stable dosage on their preventive migraine medication for at least two months prior to the screening visit.

Number of Subjects	• Approximately 150 thienopyridine-responsive migraineurs, per enrichment, will undergo randomization in the study procedure phase. • To attain that number, it is estimated that approximately 375 subjects with migraine headaches and confirmed PFO will need to be treated with thienopyridines (assuming 50% will exhibit responsiveness to thienopyridines), when randomized 4:1 against placebo. • To attain 375 subjects with both migraine and PFO screened for thienopyridine responsiveness (375 patients randomized to thienopyridine or placebo), approximately 1875 migraineurs will need to be screened for PFO (assuming the minimum prevalence of PFO (~25%) in the migraine population and that 20% of patients will not meet the minimum number of headache days in the baseline month). • Migraine headache subjects will continue to be screened until 150 subjects have been randomized for the study procedure phase (any subject active in the screening or enrichment phase at the time the 150th subject is randomized for the study procedure phase will be eligible for the study procedure phase if advancing through the enrichment phase; these are expected to add fewer than 10 subjects advancing through to the study procedure phase cohort).
Number of Sites	Up to 35 implanting study sites will be recruited in the U.S.
Coordination PI	National Neurology Principal Investigator: David W. Dodick, M.D. Professor Emeritus Department of Neurology Consultant, Mayo Clinic International Mayo Clinic Chair, Atria Academy of Science and Medicine National Cardiology Principal Investigator: Robert J. Sommer, M.D. Interventional Cardiology Director, Invasive Adult Congenital Heart Disease Columbia University Medical Center (CUMC) Associate Professor of Medicine, CUMC New York, New York
Inclusion Criteria	1. Subject is 18-55 years of age at the screening visit.

	2. Subject is willing and capable of complying with the study protocol requirements, including the specified follow-up period, and can be contacted by telephone. 3. Subject signed an Informed Consent Form prior to study participation. 4. **Subject's symptoms meet International Classification** of Headache Disorders - 3 (ICHD-3) Diagnostic Criteria for migraine with or without aura. 5. Subject has at least one year of migraine symptom duration. 6. Subject had migraine onset younger than 50 years of age. 7. Subject has more than one migraine headache day per week on average by history – headache day defined as: headache that meets ICHD-3 criteria for migraine or probable migraine with or without aura and lasts at least four hours or administration of acute medication before four hours (regardless of clinical response to acute medication). 8. Subject has tried and failed at least two preventive medications at adequate dosage for an adequate duration, in the judgement of the study site neurologist, and be from two separate classifications of the following classes of drugs: antidepressants, antihypertensive, anticonvulsant, onabotulinumtoxin A, CGRP inhibitors or other treatments with at least one positive randomized placebo-controlled trial (See APPENDIX A). 9. Subject must exhibit stable dosage on their preventive migraine medication for at least two months prior to the screening visit and agree to continue preventive medication at current dosage throughout the duration of the study. 10. Female subjects are currently not pregnant, breastfeeding or lactating and not planning pregnancy during their participation in the study. 11. Female subjects capable of becoming pregnant agree to use birth control or abstinence during their participation in the study. 12. Presence of Patent Foramen Ovale (PFO), as determined initially by positive bubble study utilizing Transthoracic Echocardiography (TTE) or transesophageal echocardiography (TEE), demonstrating right-to-left shunting.

	13. Subject is willing to complete daily electronic migraine headache log. 14. Subject is not planning surgery during their participation the study.
Exclusion Criteria	1. Subject is currently enrolled in any pre-approval investigational study. (Does not apply to long-term post-market studies unless participation might interfere clinically with the RELIEF endpoints.) 2. Subject has known organic issues which may cause headaches (e.g., temporo-mandibular joint, brain tumor, cervical spinal issues, known seizure disorder, etc.). 3. Subjects with hemicrania continua, post-traumatic headache, or other trigeminal autonomic cephalalgia secondary headache disorders. 4. Subject has known hypersensitivity or contraindication to thienopyridines. 5. Subject is currently taking a P2Y12 inhibitor (See APPENDIX B). 6. Subject has need for chronic oral anticoagulation therapy (e.g., atrial fibrillation, mechanical heart valve, etc.) (See APPENDIX B). 7. Subject has need for chronic antiplatelet therapy. 8. Subject has need for daily use of non-steroidal anti-inflammatory drugs (NSAIDs) (See APPENDIX B). 9. Subject has a history of thrombocytopenia within one year, or platelet count <100,000 mm^3 identified during the screening phase. 10. Subject has severe hepatic impairment with reduced synthetic function as documented by prolongation of PT/PTT or total bilirubin > 3.0 mg/dL identified during the screening phase. 11. Subject has any history of stroke, TIA, or intracranial hemorrhage. 12. Subject has previously implanted pacemaker, IVC filter, PFO closure device, ASD closure device, left atrial appendage closure device OR any cardiac surgical or interventional history which, in the investigator's opinion, would preclude them from study participation. 13. Subject has documented right-to-left shunt source in addition to PFO, such as pulmonary arteriovenous malformation. 14. Subject used opioids, marijuana (medical or recreational) or butalbital-containing medications for

	acute migraine headache treatment four or more times per month on average within the past six months. 15. Subject abuses alcohol and/or drugs in the opinion of the Investigator. 16. Subject is unable to understand the study requirements or has a history of non-compliance with medical advice. 17. Subject has a history of clinically significant bleeding within six months of the screening visit, any active bleeding, or active peptic ulcer disease. 18. Subject has an uncontrolled arrhythmia or, if on therapy, within the past 90 days has evidence of arrhythmia control failure (e.g., supraventricular tachycardia while under rate control or atrial fibrillation while under rhythm control). 19. Subject has elevated pulmonary vascular resistance (PVR) which, in the opinion of the implanting physician, precludes safe defect closure. 20. Subject has uncontrolled systemic hypertension at the time of screening, in the opinion of the investigator. 21. In the opinion of the Investigator, patient has anatomic criteria identified during the screening evaluation and/or the screening echocardiogram that are unfavorable for successful placement of the GORE® CARDIOFORM Septal Occluder. 22. Subject has active infection at the time of screening that cannot be treated.
Expected Time to Complete Enrollment	24-36 months
Expected Time of each Study Subject to Complete the Study	29 months
Total Expected Duration of the Study	5-6 years
Schedule of Events	**Screening Phase (Visit 1)** • Informed consent • Neurology determination / confirmation of migraine headaches meeting ICHD-3 criteria in addition to other entrance criteria required for the study • Demographics and medical history • Concomitant medication assessment • Physical exam (PE) • Echocardiogram for PFO determination (TEE or TTE with agitated saline injection)

	• Laboratory Testing:
	  o Platelet Count
	  o Total bilirubin
	  o Prothrombin time (PT)
	  o Partial Thromboplastin time (PTT)
	Screening Phase (Visit 2)
	• Echocardiogram and lab results
	• Initiation of electronic migraine headache diary for 8 weeks if confirmed PFO and no exclusionary labs
	• Concomitant medication assessment
	Enrichment Phase (Visit 3)
	• Eligibility determination of minimum of eight migraine headache days in weeks 5-8 of the 8-week headache screening period (this number cannot be discussed with the patient).
	• If eligible based on number of migraine headache days, PFO confirmation, and lab results, the following evaluations will be completed:
	  o Electrocardiogram (ECG)
	  o Urine or serum pregnancy test (for woman of child-bearing potential)
	  o HIT-6 Headache Impact Test Quality of Life Questionnaire
	  o MSQ 2.1 Migraine Specific Quality of Life Questionnaire
	  o Concomitant medication assessment
	• Eligible subjects will continue in the study and begin blinded study medication via 4:1 randomization to clopidogrel or placebo loading dose at study site followed by assigned treatment for at least 7 days
	Enrichment Phase (Visit 4)
	• Platelet Reactivity Units (PRU) lab testing between 7 and 10 days post-initiation of study medication
	• Concomitant medication and adverse event assessment
	• Continuation or adjustment of blinded study medication based on the reported PRU value:
	  o On Active Treatment and PRU < 140: Continue clopidogrel 75 mg (one 75 mg whole capsule plus three placebo whole capsules) loading dose, followed by one 75 mg whole capsule by mouth daily.

	○ **On Active Treatment and PRU ≥ 140:** Switch to prasugrel 20 mg (four 5 mg whole capsules) loading dose, followed by one 5 mg whole capsule by mouth daily. ○ On Placebo Treatment and Any PRU: Continue placebo (four whole capsules) loading dose, followed by one placebo whole capsule by mouth daily. • Resumption of electronic daily migraine headache diary until next study visit (5 weeks total – one week of medication stabilization and 4 weeks of headache monitoring) **Enrichment Phase (Visit 5)** • Determination of percent reduction in number of migraine headache days per month from baseline compared to the number of migraine headache days per month at the end of the enrichment phase • Each subject will be identified as a RESPONDER to study medication (≥ 50% reduction), a NON-RESPONDER to study medication (< 50% reduction), or a PLACEBO subject by the Clinical Data Management System (CDMS) • NON-RESPONDERS to study medication and PLACEBO subjects will be discontinued from further study participation • RESPONDERS to study medication will return within 4 weeks for the randomized study procedure. • Continue study medication now provided open label (either clopidogrel or prasugrel per previous PRU result) • Concomitant medication and adverse event assessment **Randomization / Study Procedure: 150 Responders (Visit 6 Week 0)** • Physical Exam (PE) • Urine or serum pregnancy test for women of childbearing potential • Pre-Procedure and Pre-Discharge ○ Electrocardiogram (ECG) • 1:1 randomization to device or sham to occur at time of procedure once successful guidewire crossing of the PFO takes place • Concomitant medication and adverse event assessment

	• Blinding Questionnaire • Continue open label study medication for 24 weeks **Post-Study Procedure Phase (Visit 7 Week 4)** • Physical exam (PE) • Electrocardiogram (ECG) • Concomitant medication and adverse event assessment • Continue open label study medication • Neurology visit for migraine headache review **Post-Study Procedure Phase (Monthly Telephone Contacts Weeks 8 through 20)** • Assessment of study medication compliance, adverse events, and concomitant medications **Post-Study Procedure Phase (Visit 8 Week 24)** • HIT-6 Headache Impact Test Quality of Life Questionnaire • MSQ 2.1 Migraine-Specific Quality of Life Questionnaire • Concomitant medication and adverse event assessment • Resume electronic daily migraine headache diary • Discontinue open label study medication **Post-Study Procedure Phase (Weekly Telephone Contacts Weeks 25 through 39)** • Diary compliance • Concomitant medication and adverse event assessment **Subject Procedure Unblinding (Visit 9 Week 40)** • HIT-6 Headache Impact Test Quality of Life Questionnaire • MSQ 2.1 Migraine-Specific Quality of Life Questionnaire • Blinding Questionnaire • Unblinded to study procedure received (device or sham) • PFO Evaluation by TTE with Valsalva maneuver and bubble study for closure assessment of device arm only • Sham arm subjects offered elective PFO closure • Considered study completion visit for sham subjects who do not elect to have PFO closure • Concomitant medication assessment

	• Final adverse event assessment for device arm and sham arm with no elective closure **Extended Post-Procedure (Sham arm elective closure subjects only)** • Physical exam (PE) • Urine or serum pregnancy test for women of childbearing potential • Elective PFO closure procedure • Pre-Procedure and Pre-Discharge o Electrocardiogram (ECG) • Concomitant medication and adverse event assessment **Extended Post-Procedure 30-Day Follow-up / Study Completion (Sham arm elective closure subjects only)** • Physical Exam (PE) • Electrocardiogram (ECG) • PFO Evaluation by TTE with Valsalva maneuver and bubble study for closure assessment • Concomitant medication and adverse event assessment • Considered study completion visit **Post-Study Procedure Phase (Randomized device arm subjects only) (Visit 10 Week 100 / Month 23)** • Resume electronic daily migraine headache diary **Study Completion (Randomized device arm subjects only) (Visit 11 Week 104 / Month 24)** • HIT-6 Headache Impact Test Quality of Life Questionnaire • MSQ 2.1 Migraine-Specific Quality of Life Questionnaire • Concomitant medication • Diary device retrieval
Additional Information	**Echocardiographic Core Laboratory:** Yale University 47 College Street Suite 203 New Haven, CT 06520 **Safety Review:** Data and Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC) Applied Clinical Intelligence, LLC (ACI) 225 City Avenue, Suite 15 Bala Cynwyd, PA 19004

	Clinical Monitoring: NAMSA Medical Research Organization 400 Highway 169 South, Suite 500 Minneapolis, MN 55426 **Randomization:** Medidata Solutions, Inc. 350 Hudson Street 9th Floor New York, NY 10014

Statistical Analysis Plan

GORE® CARDIOFORM Septal Occluder Migraine Clinical Study: A Study to evaluate the safety and efficacy of transcatheter closure of patent foramen ovale for relief of migraine headaches

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Protocol #: GSO 17-03

Table of Contents

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the RELIEF clinical trial. It details the analyses that will be performed to accomplish these objectives. This SAP defines endpoint variables and identifies methods and algorithms used to analyze the primary and secondary endpoints defined for this study.

2.0 Study Design

2.1 Primary Objective

The primary objective of the RELIEF Clinical Study is to evaluate PFO closure for migraine headache relief using the GORE® CARDIOFORM Septal Occluder.

2.2 Design Summary

The RELIEF Clinical Study is a multicenter, prospective, randomized, placebo- and sham-controlled study to evaluate the GORE® CARDIOFORM Septal Occluder for migraine headache (MHA) relief. This clinical trial is confirmatory: prespecified hypotheses on the primary efficacy endpoint will be tested with appropriate control of Type I and Type II errors.

Up to 35 investigative sites (referred to as "sites" in the remainder of this document) in the United States will participate in this study. Approximately 150 study medication responders from the enrichment phase will be randomized to the study closure procedure, defined as either actual closure with the study device or sham device closure. To attain 150 eligible subjects for the closure phase, it is estimated that approximately 375 subjects with migraine headaches and an imaging-confirmed PFO will need to be randomized 4:1 to active thienopyridine or placebo, respectively, assuming 50% will exhibit a satisfactory MHA reduction response to active thienopyridine (defined as at least 50% reduction in monthly MHA days from baseline to enrichment).

Patients may be enrolled into the study provided all pre-enrichment phase eligibility criteria are met, including documented presence of a PFO during screening and confirmation of at least 8.0 MHA days per month during weeks 5-8 (second month) of an 8-week (2-month) screening diary reporting period. Weeks 2-5 of the enrichment diary period will be used to calculate MHA days per month from enrichment and compared to baseline to determine thienopyridine responder status. At least 150 study medication responders from the enrichment phase will be randomized either to an actual or sham study closure procedure—per protocol, any subject active in the screening or enrichment phase at the time the 150th subject is randomized in the closure procedure phase will continue to be considered for the closure phase; these are expected to add fewer than 10 subjects to the study procedure phase cohort. Closure phase subjects will continue their thienopyridine for 24 weeks (6 months) postprocedure and will be evaluated through hospital discharge and will return for follow-up visits at 4 weeks (1 month), 24 weeks (6 months), and 40 weeks (10 months) postprocedure and will be followed by telephone contacts during weeks 8, 12, 16, 20 and 25-39 postprocedure. Total estimated duration of the primary endpoint assessment phase of the study is approximately 59 weeks, including 14 to 19 weeks for screening and enrichment prior to the randomized study procedure. All subjects randomized to actual closure with the study device will

have two additional visits at 100 and 104 weeks postprocedure for quality-of-life assessments and migraine headache diary collection.

Enrollment, Randomization and Blinding

A patient is considered an enrolled subject in the study when randomized to either active thienopyridine or placebo in Visit 3 of the enrichment phase. This is the first of two randomizations for eligible subjects. Enrichment randomization will be weighted 4:1 favoring active drug over placebo. Randomization schedules for each site will be produced and loaded into the [redacted] will be performed sequentially within the RTSM system by the site as subjects become eligible for randomization. The enrichment randomization plan stratifies by site, but not by any other baseline variables. This randomization will be double blind: both the subject and the site will be blind to the drug treatment allocation. The sole purpose of this randomization and double blinding is to control for a placebo effect while determining which subjects qualify as responders to active drug; as such, the enrichment phase is part of the screening process, and no formal between-group statistical analyses are planned.

[redacted]

Subjects will be randomized 1:1 either to the test arm (PFO closure using the GORE® CARDIOFORM Septal Occluder) or the control arm (sham procedure consisting of catheterization but no PFO closure). [redacted]

All subjects randomized into the closure phase will be followed, at a minimum, to the primary endpoint follow-up period, regardless of whether the intended treatment was accomplished successfully.

[redacted]

2.3 *Study Endpoints*

2.3.1 Primary Endpoints

The primary efficacy endpoint is **Reduction in Migraine Headache Days**, expressed as the mean reduction in the number of migraine headache days per month from baseline to follow-up.

The primary safety endpoint is **Procedural Serious Adverse Events (SAE)**, defined as onset of any SAE related to the study device or study procedure from index closure procedure through 30 days postprocedure.

[redacted]

[redacted]

2.4 Statistical Hypotheses

This study will test the null hypothesis that the mean reduction in monthly migraine headache (MHA) days in subjects treated with the study device (test arm) is less than or equal to the mean reduction in monthly MHA days in subjects treated with sham device PFO closure (control arm), versus the alternative hypothesis that the reduction in test arm subjects is greater than the reduction in control arm subjects. In statistical terms:

H_0: $\delta = \mu_T - \mu_C \leq 0$
H_1: $\delta = \mu_T - \mu_C > 0$

where:

δ is the true difference in means between the treatment arms (test – control)

μ_T is the true mean within-subject reduction (baseline – follow-up) in monthly MHA days in test arm subjects

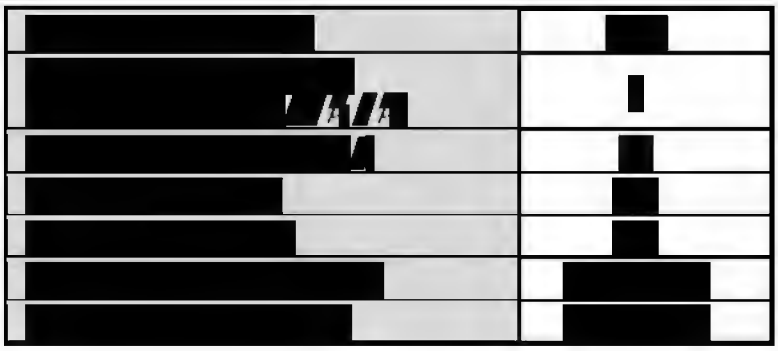
μ_C is the true mean within-subject reduction (baseline – follow-up) in monthly MHA days in control arm subjects

[redacted]

[redacted]

2.6 *Sample Size Calculations*

[redacted]



In summary, equal treatment group sample sizes of 63 subjects achieve 81% power to reject the null hypothesis of equal means when the difference in population means is 4 migraine headache days with a standard deviation for both groups of 7.8 migraine headache days and with a significance level (α) of 0.025 using a one-sided two-sample equal-variance t-test.

3.0 Study Treatment Arms

3.1 *Active Drug Arm*

The active drug arm will consist of subjects who were determined by the enrichment randomization process to receive the active drug treatment regimen (indicated as "Active Drug" in the RTMS system), which consists of protocol-specified administration of clopidogrel capsules with possible switch to prasugrel capsules depending on platelet reactivity units (PRU) lab assessment.

3.2 *Placebo Drug Arm*

The placebo drug arm will consist of subjects who were determined by the enrichment randomization process to receive the placebo drug treatment regimen (indicated as "Placebo" in the RTMS system), which consists of protocol-specified administration of capsules comprised of lactose monohydrate identical in appearance to the active drug capsules.

3.3 *Test Arm and Test Device*

The test arm will consist of active thienopyridine migraine headache reduction responders who were determined by the closure randomization process to receive the test treatment regimen (indicated as "Device" in the RTMS system), which consists of actual PFO closure with the test device. The test device is the GORE® CARDIOFORM Septal Occluder.

3.4 *Control Arm*

The control arm will consist of active thienopyridine migraine headache reduction responders who were determined by the closure randomization process to receive the control treatment regimen (indicated as "Sham" in the RTMS system), which consists of sham PFO closure (catheterization but no PFO closure).

4.0 Study Data Collection

4.1 *Study Data Collection Intervals*

Refer to Section 5.2, Schedule of Events, in the study protocol (MD171645, GSO 17-03 RELIEF Study Protocol).

4.2 *Study Interval Windows*

Subjects randomized in the closure phase will return for follow-up visits at completion of weeks 4, 24, 40 and 104. All intervals are calculated from the day of the index closure procedure, considered day 0 for this purpose. A week is defined as 7 calendar days, and a month is defined as 4 weeks or 28 days. The visit windows are calculated as the target day plus (or plus or minus for Week 4) the appropriate number of calendar days. Other than Week 4, these visit windows may or may not represent the actual target visit window or the acceptable analysis window for a given subject, since these visits depend on full completion of an MHA diary period immediately prior to the visit. This is especially true for the Week 104 visit, which is intended to occur at least 4 weeks from the Week 100 visit. The table below shows the "ideal" target days for visits based on the day of index closure procedure.

Week 4	Week 24	Week 40 (10 Months)	Week 104 (24 Months)
28 ± 7 days	168 + 7 days	280 + 7 days	728 + 7 days

[redacted]

[redacted]

[redacted]

5.0 Statistical Analyses

5.1 Analysis Sets

The primary and secondary endpoints will be analyzed under several different analysis set definitions, as described below. The primary analysis set for statistical testing of the primary efficacy endpoint is the intent-to-treat analysis set.

5.1.1 Intent-To-Treat (ITT) Analysis Set (Primary Analysis Set)

The ITT analysis set is defined as all subjects randomized to closure treatment and will be analyzed by treatment assigned at randomization, regardless of whether the correct treatment was administered.

5.1.2 Per-Protocol Analysis Set

For per protocol analysis, only subjects who were randomized, treated, and assessed according to protocol will be analyzed according to treatment assigned at randomization. Specifically, subjects randomized to test who receive successful PFO closure with the test device and retain the study device through completion of the primary endpoint follow-up, and subjects randomized to control who receive a successful sham PFO closure procedure and are not closed by any means before completion of the primary endpoint follow-up, will be analyzed according to treatment assigned at randomization.

Additionally, only subjects who had no major protocol deviations (PDs) will be included in the per-protocol analyses. Major PDs are defined as PDs with a level of seriousness such that inclusion of the subject(s) would unacceptably bias analyses of the primary endpoints. An example of a major PD might be failure to satisfy eligibility criteria to a degree where the subject does not fit the underlying scientific model for the treatment.

Protocol deviations that may be considered major and lead to exclusion of a subject from the per-protocol analysis set include (but are not limited to) eligibility criteria deviations, failure to obtain informed consent, any initiation, continuation, or resumption of antiplatelet therapy within, and prior to satisfactory completion of, the primary endpoint diary reporting period, and retention of more than one study device.

5.1.3 As-Treated Analysis Set

For as-treated analysis, subjects who were randomized, treated, and assessed will be analyzed by treatment received, regardless of treatment assigned at randomization. Specifically, randomized subjects who receive PFO closure by any means (test device, alternative device, or surgery) prior to start of the primary endpoint follow-up period (Month 8) will be analyzed in the "PFO Closure" group, and randomized subjects who receive no PFO closure by any means prior to completion of the primary endpoint follow-up will be analyzed in the "No PFO Closure" group. However, subjects with any initiation, continuation, or resumption of antiplatelet therapy within, and prior to satisfactory completion of, the primary endpoint diary reporting period will be excluded from this analysis set.

5.2 Timing of Analyses

5.2.1 Primary Endpoint Analysis

The primary endpoint analysis will occur when primary endpoint follow-up is complete for all subjects randomized into the closure phase (unless discontinued prior to follow-up).

5.2.2 Interim Analyses

No interim analyses involving formal statistical testing of the study hypotheses are planned.

5.3 Primary Endpoints Test Methods

5.3.1 Efficacy Endpoint

The primary efficacy endpoint, reduction in monthly MHA days, is subject-based and calculated within each subject as the difference in monthly MHA days from baseline to follow-up. Baseline is defined as the monthly MHA days calculated from the last 4 weeks (28 days) of the 8-week monitoring period immediately prior to Visit 3. Follow-up is defined as the monthly MHA days calculated from months 8-10 (total of 12 weeks or 84 days) of the 16-week monitoring period (i.e., months 7-10) that begins at week 24 post-treatment. At both time points, the monthly MHA days (a.k.a. MHA days per month) will be calculated as follows:

$MD_M = MD_R / DD_R \times D_M$, where

- MD_M is the monthly MHA days (a.k.a. MHA days per month)
- MD_R is the number of MHA days (i.e., days with a qualifying MHA) reported during the reporting period
- DD_R is the number of diary days (i.e., days with diary assessment) in the reporting period
- D_M is the number of days per standard month, equal to 28 days

The difference in means between treatment groups (test – control) will be assessed using a one-sided two-sample equal-variance t-test. If the observed difference in means is positive (>0) and the statistical test upper one-sided p-value is ≤ 0.025, then the null hypothesis will be rejected in favor of the alternative hypothesis of test arm superiority. The two-sided 95% t-distribution confidence interval of the difference in means will be reported.

In the primary analysis, subjects who are missing their evaluation of reduction in monthly MHA days will be excluded. Since all randomized subjects will have a valid baseline assessment of monthly MHA days, the only reasons for missing primary endpoint evaluation are discontinuation prior to the follow-up monitoring period (death, withdrawal, lost) or insufficient diary days completed during the follow-up monitoring period (<80% of total days in follow-up reporting period).

The 80% diary completion requirement translates to a minimum of 23 diary days for the 28-day baseline reporting period (and the 28-day enrichment reporting period as well) and a minimum of 68 diary days for the 84-day follow-up period. Patients with insufficient diary data at baseline (screening) will not be enrolled in the study, and subjects with insufficient diary data at enrichment will not be randomized to procedure. Subjects with insufficient diary data at follow-up will be considered missing observations and excluded from the primary analysis unless their diary data meets the following criteria:

- There are at least 4 weeks of diary data (with 80% completion) starting after the first week of month 7 (minimum drug washout period); and
- The calculated MHA days per month after the first week is at least 80% of the subject's baseline MHA days per month

The intent of this second tier of diary completion acceptability is to enable primary endpoint evaluation in subjects who experience a return of MHA frequency close to, or perhaps even greater than, their baseline frequency after having enjoyed a reduction in MHA frequency due to the thienopyridine. These subjects might choose to discontinue the protocol follow-up regimen prior to

completing months 8-10 in order to seek benefit from the thienopyridine medication from which they were withdrawn after 6 months.

[redacted]

5.3.2 Safety Endpoint

The primary safety endpoint, proportion of subjects with 30-day device- or procedure-related SAE, will be reported with descriptive statistics only, similar to the analysis of the secondary endpoints. Among subjects in the REDUCE trial who were randomized to PFO closure and closure was attempted with the study device, there were 14/413 (3.4%) with this outcome. With a planned randomization of 75 subjects to PFO closure in this study, statistical power is insufficient for statistical comparison to a meaningful and credible performance goal. The primary safety endpoint will, however, be adjudicated by an independent Clinical Events Committee that will evaluate seriousness and study relationship of all site-reported adverse events with onset within 30 days postprocedure.

[redacted]

5.5 *Adverse Events*

All site-reported AEs will be MedDRA coded and grouped by MedDRA System/Organ Class (SOC) and by MedDRA Preferred Term (or Lowest Level Term) within SOC. AEs will also be grouped by seriousness (SAE vs. nonserious AE) and primary relationship (study device, study procedure, study medication, and unrelated).

AEs will be summarized as subject-based binomial proportions. The numerator will be the count of subjects who experienced one or more episodes of the AE(s) of interest in the time period of interest. The denominator will be the count of subjects with clinical follow-up in the time period of

interest. Unless otherwise specified for a particular outcome measure, all enrolled subjects in the analysis set of interest will be considered evaluable and will contribute to the denominator.

AEs will be summarized separately for the enrichment phase.

5.6 [redacted]

[redacted]

[redacted]

6.0 Interim Analyses

No interim analyses involving formal statistical testing of the study hypotheses are planned.

[redacted]

[redacted]