
Ticagrelor Therapy for RefrACTORy Migraines – Pilot (TRACTOR Migraine Pilot Study)

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ABSTRACT:

We recently demonstrated a dramatic reduction/elimination of migraine symptoms in 13 of 15 patients with right to left shunt treated with clopidogrel (off-label, unblinded) for one month. We have treated an additional 50 patients since the publication of the initial cohort.

Some of the patients who have not responded to clopidogrel therapy have proven to be clopidogrel “resistant”. Common genetic differences of the CYP2C19 enzymes preclude both the break down of the clopidogrel thiophene ring and the conversion of the pro-drug to its active metabolite. PRU blood testing while taking clopidogrel (Platelet Reactivity Testing) in some of the headache-non-responders has proven a failure to inhibit platelet reactivity.

In some of these non-responders, we tried prasugrel, another thienopyridine which is metabolized differently than clopidogrel. Four of five prasugrel patients had a reduction/elimination of headache symptoms similar to that seen in the initial clopidogrel responders, with PRU-proven platelet inhibition, confirming an unspecified role of P2Y12 inhibition.

Brilinta/ticagrelor, a newer P2Y12 inhibitor, is not a thienopyridine and is therefore metabolized independently of the CYP2C19 pathway. Because Brilinta/ticagrelor has a lower reported bleeding risk than prasugrel, we are preparing a multi-center, randomized, blinded trial with Brilinta/ticagrelor for refractory migraineurs. However, before investing in this large trial, we must ensure that Brilinta/ticagrelor’s P2Y12 inhibition has a similar headache effect to that of the thienopyridines. For that reason, we propose a pilot study using Brilinta/ticagrelor in 40 patients with right to left shunts, 20 of whom have refractory episodic migraine and 20 of whom have refractory chronic migraine, according to International Headache definitions.

STUDY PURPOSE AND RATIONALE:

More than 40 million Americans ≥ 12 years of age suffer with migraine headache (MHA).¹ Current therapies include analgesics and preventative medications with limited efficacy and frequent side effects. In the subset of MHA patients with preceding aura (MHA+), 40% have a patent foramen ovale (PFO), an open flap in the atrial septum that allows right to left shunting (RLS).^{2,3}

PFO, which is a remnant of the normal fetal circulation, has also been associated with thromboembolic stroke, and can be closed with transcatheter devices to prevent stroke recurrence. In the stroke population, closure of the PFO has resulted in unanticipated and dramatic improvement of concurrent MHA in some patients, perhaps by eliminating the RLS that in some way triggers MHA.⁴⁻¹¹ But since the mechanism linking PFO to migraine is poorly understood, as is our ability to predict which MHA patient will benefit (demonstrated in the MIST Trial¹²), there is yet no justification for PFO closure as a therapeutic option for MHA.

The underlying difficulty is that there has been no diagnostic method for separating patients in whom the PFO is causative from those in whom it is incidental of the headaches. Our best current theories involve a central role of activated platelets, which contribute to paradoxical embolization of micro-clots or platelet-released vasoactive substances.¹³

Recently, we demonstrated a dramatic reduction or elimination of migraine headache symptoms in 13/15 severe migraineurs, with RLS, using clopidogrel (a P2Y12 thienopyridine platelet inhibitor).¹⁴ In subsequent clinical (off-label) use of the drug, we have seen efficacy in over 70% of patients. A large, multicenter randomized clinical trial is planned and will be required to prove that this effect is reproducible, and not the result of a placebo effect.

One difficulty in using clopidogrel for such a randomized trial, is the nearly 25% incidence of patients who are unable to metabolize clopidogrel. This is due to genetic polymorphisms in the Cytochrome P450 enzymes, which are required to break down clopidogrel from pro-drug to its active metabolite.¹⁵ Some of our MHA non-responders had normal platelet function while taking clopidogrel, proven with platelet reactivity testing (VerifyNow PRU Test – Accumetrics Inc. San Diego, CA)).

Five of these patients were subsequently treated with prasugrel (another P2Y12 thienopyridine platelet inhibitor, metabolized via a different pathway than clopidogrel) with complete elimination of headache symptoms in four (unpublished data). While prasugrel is also used frequently in patients with coronary artery disease who are clopidogrel resistant, it has a higher risk of bleeding complications, which makes it less attractive for a headache study.¹⁶

Brilinta/ticagrelor is a third P2Y12 inhibiting agent, which is not a thienopyridine drug and does not require in vivo metabolism to be active.¹⁷ We are currently in the process of establishing a multi-center, randomized, double-blinded, placebo-controlled, cross-over trial (The TRACTOR Migraine Trial) using Brilinta/ticagrelor, to establish the principle that P2Y12 inhibition will treat headaches in patients with RLS. However, we have yet to treat any migraine patients with this drug. Therefore, before undertaking this large study, our goal is to provide evidence that P2Y12 inhibition with a non-thienopyridine agent will yield the same headache relief.

BACKGROUND:

In 2000, in a seminal paper, Wilmshurst et al.⁴ reported unanticipated improvement or elimination of MHA symptoms after transcatheter device closure of an atrial communication (PFO or atrial septal defect) in a group of divers who had previously suffered decompression illness and/or stroke. Subsequent worldwide observational (retrospective) studies reported significant improvement or elimination of migraine symptoms in at least 70% of patients who had had a PFO closed for prevention of recurrent embolic stroke⁴⁻¹¹.

At that time it was proposed that the RLS, common to all of these patients, was in some way triggering the headaches. This tied in nicely to observations of increased migraine prevalence in patients with cyanotic congenital heart disease^{18, 19} and in patients with the Hereditary Hemorrhagic Telangiectasia syndrome²⁰, both of which also have chronic RLS due to congenital malformations or to pulmonary arteriovenous malformations (PAVMs)

respectively. In the latter group, it was noted that the incidence of migraines also decreased after transcatheter embolization of the PAVMs and elimination of the RLS.

As a result of this observational data, the MIST Trial¹² was undertaken in Great Britain. MIST was a double blinded, randomized, sham-controlled study of PFO closure in 147 patients with severe episodic MHA+ and a documented PFO with moderate or large RLS. MHA- patients, those with chronic daily migraine and those with a history of stroke, were excluded. The results of this controversial study ultimately showed no benefit to PFO closure, casting uncertainty on the causative role of the PFO.

Wilmshurst et al.²¹, noted an increased frequency of MHA+ symptoms in the first few weeks after PFO closure. This effect was mitigated by the concurrent use of clopidogrel with aspirin. The development of MHA after PFO closure in patients with no prior history of headache, and the elimination of those symptoms with clopidogrel, strongly suggested a mechanistic role for platelet activation in the pathogenesis of MHA in some patients. The authors speculated that the observed benefit of using clopidogrel might be based on clopidogrel's blockade of ADP binding to its platelet surface receptor (P2Y₁₂), a mechanism different from that of aspirin.

Nozari et al.¹³, studied the impact of cerebral microembolization in mice, using PET scan imaging to demonstrate cortical-spreading depression (CSD), after carotid artery injections of air and particulate matter. CSD has been strongly linked to symptoms of MHA+ in humans²²⁻²⁴. Their work clearly demonstrated the potential of cerebral microembolization, from a right to left shunt, to trigger migraine without causing stroke.

A group from the Netherlands noted that there was an improvement of migraine symptoms, and a reduction in rescue medication use on warfarin,^{25, 26} but there has been no further investigation of this relationship since 2004.²⁷

We formulated our study hypothesis, in part, based upon our experience with a handful of stroke patients treated with clopidogrel, due to aspirin sensitivity. Several returned reporting reduction/elimination of migraine symptoms.

As a result, 15 patients with frequent severe episodic MHA and documented RLS, were treated with a one-month trial of clopidogrel.¹⁴ None of the patients had prior stroke or TIA. All remained on baseline migraine medication throughout the month. There was a dramatic reduction or elimination of MHA symptoms in 13 of the 15 patients. Subsequently, some of the responders have been able to decrease or eliminate other migraine prophylactic agents (i.e. topiramate). Four responders have continued on clopidogrel therapy with persistent benefit, while the other 9 responders went on to have PFO closure. Of these, 8 of 9 continue to be headache-free even after discontinuation of clopidogrel. Although the preliminary results were positive, there were insufficient numbers to detect statistical significance of the results/adverse events, and a placebo effect could not be ruled out. As discussed above, headache elimination was seen in four of five patients on prasugrel who were unresponsive to clopidogrel, and proven by PRU testing to be unable to metabolize/utilize the clopidogrel.

STUDY DESIGN AND STATISTICAL PROCEDURES:

We propose a prospective, open-label, single-arm pilot study treating 40 subjects to assess the hypothesis that P2Y₁₂ inhibition with Brilinta/ticagrelor (90 mg PO twice a day) reduces episodic and/or chronic migraine headache symptoms in patients with right to left shunt. There will be no randomization or blinding of therapy. The study drug will be provided, free of charge, by the manufacturer, Astra-Zeneca. All subjects will be treated with the same medical regimen, and will be treated at Columbia University Medical Center or one of Principal Investigators external offices. All subjects will have an initial visit that will include the completion of a screening questionnaire (inclusion/exclusion criteria), informed consent, transcranial Doppler screening, laboratory blood testing by venipuncture (approximately 15 cc of blood = 1 tablespoon), and instruction on the use of the daily headache log (see Appendix 1, Appendix 2). Over the next 28 days, the subjects will receive an e-mail/text reminder daily with a link to complete the headache log (see below). At a second study visit, following completion of the first baseline month, the study staff will review the subject's headache log material, will release those subjects with insufficient headache days in the screening month, will assign the remaining/eligible subjects to either the episodic or chronic migraine cohort, will distribute the study drug, will administer the Brilinta/ticagrelor loading dose, and will review the medication's proper use. After 7 days of treatment with Brilinta/ticagrelor, while still on therapy, subjects will be sent for additional laboratory testing (PRU test < 10 cc of blood by venipuncture). At the completion of the 28 days (+7 days) on Brilinta/ticagrelor, each subject will have a follow-up study visit within 7 days, before discontinuing medication. At the third study visit, headache logs will be reviewed with the study staff, results will be discussed, remaining medications and empty bottles will be returned, and adverse events will be reviewed. Headache frequency while on Brilinta/ticagrelor will be compared with the documented baseline for each subject. If the Brilinta/ticagrelor therapy was effective (> 50% reduction in monthly headache days), the subject could elect to continue therapy for an additional two months, while continuing to complete daily headache logs.

Data collected from these 40 subjects will be evaluated to assess the feasibility of conducting a randomized, placebo-controlled, double blinded study in this population.

TRACTOR Migraine Trial Definitions

Headache Definitions:

(From: the International Classification of Headache Disorders (ICHD-II)

<http://www.ihc-classification.org/en/>)

- **Migraine without aura:** Requires all of the following symptoms: a) recurrent headaches (at least 5 lifetime attacks); b) untreated or unsuccessfully treated headache duration of 4 to 72 h; and c) at least two of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are associated with at least one of nausea/vomiting, photophobia, or phonophobia. Finally, other causes of headache must be excluded.
- **Migraine with aura:** Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last

for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

- Acephalgic Migraine: Migraine aura without subsequent head pain.
- Episodic migraine: migraine headaches as defined above, with history of 0 to 14 headache days per month.
- Chronic migraine: migraine headaches as defined above, with history of 15 or more headache days per month.

Adverse Events Definitions:

- Adverse Event: Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study including intercurrent illnesses or injuries, whether or not it is considered therapy related. Adverse events will be reviewed by the Principal Investigator and the Executive Committee and will be defined as serious, or non-serious. Any adverse event will be considered “study-related” if it occurs in the time between the first dose of the study medication and 30 days after the last dose of the medication.
- Serious Adverse Event: Any adverse event that:
 - is fatal
 - is life-threatening requiring immediate intervention
 - requires or prolongs existing hospital stay
 - results in persistent or significant disability or incapacitation
 - requires intervention to prevent the above and/or permanent impairment or damage

Non-serious Adverse Event: any other adverse event that does not meet criteria for a serious adverse event.

Definitions of bleeding events are based on the PLATO Trial protocol²⁸, a previously published study comparing Brilinta/ticagrelor to clopidogrel.

- Major Life-Threatening Bleeding includes:
 - Any Fatal Bleed
 - Intracranial Hemorrhage
 - Intrapericardial bleed with cardiac tamponade
 - Bleeding resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
 - Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
 - Bleeding requiring transfusion of ≥4 U whole blood or PRBCs
- Other Major Bleeding includes:
 - Bleed causing clinically significant disability (e.g., intraocular bleed with permanent vision loss)

- Clinically overt or apparent bleeding associated with decrease in hemoglobin >3 g/dL, but < 5 g/dl
 - Bleeding requiring transfusion of ≥ 2 , but < 4 U whole blood or PRBCs
- Minor Bleeding includes any bleeding requiring medical intervention but not meeting the criteria for major bleeding

Working Study Definitions:

- Migraine Headache Day: any study day in which headache symptoms occur. If a single headache lasts from the end of a calendar day into the beginning of the next, it would be considered a single headache day provided the event lasted less than 24 hours. If headache symptoms last more than 24 hours, it would be considered 2 Headache Days; more than 48 hours would be considered to be three days, etc. Aura alone (“Acephalgic migraine”) will not be considered a headache. The subject must experience headache pain.
- “Responder” to Therapy: $\geq 50\%$ reduction in the average number of monthly headache days during the month of therapy compared with participant’s own baseline.
- “Non-responder” to Therapy: $< 50\%$ reduction in the number of monthly headache days during the month of therapy compared with participant’s own baseline.
- Platelet Inhibition: This is a functional definition based on Platelet Reactivity. PRU Test Result (VerifyNow PRU Test, Accumetrics Inc. San Diego CA) of < 140 , while on therapy, will be considered a “positive” inhibitory effect of the medication. PRU results of 141 – 160 will be considered a borderline response. PRU results > 161 will be considered a negative response.

Primary Study Endpoints:

- Primary Efficacy Endpoint: A subject will be considered to have achieved the primary efficacy endpoint (a “Responder”) if she/he has $\geq 50\%$ reduction in the number of monthly headache days during the month of therapy compared with participant’s own baseline. If there is $< 50\%$ reduction in the number of migraine days, she/he will be considered a Non-Responder.
- Primary Safety Endpoint: Major bleeding episode (as defined above) or other life-threatening adverse event (see below), while taking the Brilinta/ticagrelor.

Secondary Study Endpoints:

- Secondary Efficacy Endpoints will be assessed as follows:
 - Absolute reduction in headache days as a continuous response variable.
 - Absolute reduction in headache intensity as a continuous response variable.

- Quantitative comparison of the number of monthly uses of rescue medications in the roll-in versus the treatment phase
- Comparison of time to headache resolution after rescue medications. If < 2 hours to resolution, will be considered a “successful” intervention. Will compare the percentage of successful interventions in the baseline and treatment phases.
- Secondary Safety endpoints: Non-life threatening adverse events to Brilinta/ticagrelor, including:
 - Minor bleeding
 - Allergic reactions
 - Shortness of Breath
 - Rash
 - Extreme fatigue
 - Any other symptom requiring the participant to withdraw from the study prior to completion of the one month medication administration

Subject Recruitment, Eligibility and Screening:

Study subjects will be recruited from hospital-based cardiology and headache clinic at Columbia University Medical Center, and through the private offices of the study physicians.

Preliminary Inclusion Criteria:

- Subject age 18 – 65 years
- Symptoms meet International Headache Society Criteria for Episodic Migraine or Chronic Migraine
- At least one year history of Episodic or Chronic migraine headache symptoms
- At least 6 headache days per month
- Subject agrees to use two forms of birth control or abstinence throughout duration of the study
- Subject able to complete online daily headache log
- Right to left shunt >grade 1 as determined by Transcranial Doppler evaluation

Preliminary Exclusion Criteria:

- Inability to understand the study or history of non-compliance with medical advice
- Currently taking a P2Y12 inhibitor
- Known hypersensitivity to Brilinta/ticagrelor
- History of stroke/transient ischemic attack (TIA) in the previous 6 months
- Active bleeding from any site
- Active peptic ulcer disease or upper gastrointestinal (GI) bleeding within six (6) months
- Migraine onset after 50 years of age
- Renal impairment: Creatinine Clearance < 60 cc/min
- Severe hepatic impairment with total bilirubin > 3.0 mg/dL
- Thrombocytopenia with platelet count < 100,000 / μ l
- History of intracranial hemorrhage
- Contraindications to blood thinner therapy or history of major bleeding episode while taking blood thinner therapy

- Need for chronic oral anti-coagulation therapy (i.e. Atrial Fibrillation)
- Need for chronic anti-platelet therapy (i.e. DE Stent), including daily aspirin use
- Need for daily NSAID use
 - Need for daily carbamazepine therapy or other strong CYP3A inhibitors or potent CYP3A inducers (see Reference Medication Form).
 - Need for simvastatin or lovastatin greater than 40 mg daily
 - Symptomatic bradycardia or syncope
- Pregnancy or currently breast-feeding, or plan to become pregnant during the study period
- Planned surgery during the study time-frame
- Previously implanted PFO, ASD, pacemaker, inferior vena cava filter, or left atrial appendage closure device
- Subject is unwilling to sign the Informed Consent Form
- Subject is currently enrolled in another investigational study that has not met the primary endpoint.

Transcranial Doppler Screening:

The presence of a right to left shunt, as defined by transcranial Doppler screening (described below) is a requirement for receiving the study drug under the TRACTOR Migraine protocol. As the incidence of a right to left shunt is ~ 25% in the migraine population, in order to find 40 subjects for treatment who fulfill all of the migraine definitions, the preliminary inclusion and exclusion criteria, and who have a right to left shunt, approximately 160 subjects will need to be screened. It is anticipated that few, if any of those identified with a right to left shunt will be excluded on the basis of subsequent laboratory testing or baseline migraine screening.

Transcranial Doppler Screening:

When a participant meets basic inclusion/exclusion criteria, she/he will be screened with a Power M-Mode Transcranial Doppler (TCD) examination as described by Spencer et al.²⁹ An ultrasound probe will be placed over the patient's temple and an arterial tracing will be obtained. She/he will receive a small intravenous line, through which two boluses of normal saline will be injected. Each participant will undergo initial testing in a supine position, with the head of the bed at a 30° incline, breathing normally. Secondary testing will be done with the patient in the same position, but the bolus will occur following release of a forced Valsalva, noting a reduction in cerebral blood flow velocity as an indicator of adequacy of the Valsalva strain.

All studies will be recorded electronically, and will be saved for potential review at a later time. Each participant will receive two scores, according to the Spencer Scale, one at rest and one with Valsalva. These results of the transcranial Doppler exam will be described as follows:

- *Grade 0: No embolic events.*
- *Grade 1: 1–10 cerebral embolic events.*
- *Grade 2: 11–30 cerebral embolic events.*
- *Grade 3: 31–100 cerebral embolic events.*
- *Grade 4: 101–300 cerebral embolic events.*
- *Grade 5: Greater than 300 countable discrete events.*
- *Grade 5+: Overwhelming events (“curtain” effect).*

A Spencer Grade ≥ 2 , either at rest or with Valsalva release, will be used as criteria for the presence of a right to left shunt.

Any participant without a documented right to left shunt by Transcranial Doppler will have completed her/his participation in the study and will be referred back to her/his referring physician for on-going conventional treatment of migraines.

Those participants identified with a right to left shunt will be assigned a Patient Study Number. This number will be used for maintaining participant confidentiality and as identification for entering demographic and baseline headache log information in the TRACTOR Migraine Trial Database. This number will continue with the participant throughout her/his participation in the trial, and will be used in any correspondence, Executive Committee meetings, or reports of adverse events.

Once assigned a Patient Study Number, the subject will undergo baseline laboratory screening, consisting of:

- Complete Blood Count: Hemoglobin/Hematocrit, White Blood Count
- Platelet Count
- Chemistry panel, including Na⁺, K⁺, Cl⁻, HCO₃⁻, BUN, creatinine and creatinine clearance, and total bilirubin
- Urine pregnancy test for women of childbearing potential to be done at the time of enrollment (or within one week prior to enrollment)

Laboratory work must be completed within 60 days of the enrollment date, and demonstrate the following:

- Negative urine pregnancy test
- Platelet count > 100,000 / μ L
- Normal renal function with creatinine clearance ≥ 60 cc/min
- Total bilirubin < 3.0

All participants must demonstrate the ability to complete a daily headache questionnaire online.

Both women and men of child-bearing potential must document two methods of birth control or agree to abstinence while participating in the study. Males will need to document use of birth control to eliminate the possibility of impregnating a partner while on the medication.

Subject must agree that she/he will continue all baseline headache and non-headache medications without change for the two months duration of the study (see below). Rescue/abortive headache therapy will be allowed as needed (see below).

Once all of the above criteria have been fulfilled, the subject will continue to the baseline-monitoring phase of the clinical trial (Phase 1).

All participants will complete a Quality of Life Survey (MSQ 2.1) at the outset of the study, upon completion of study visit 3, and upon completion of the continued access phase (if applicable).

Allowed Headache Medications:

Most of the participants who will be eligible for the TRACTOR Trial will already have tried, or will be taking prophylactic migraine headache medication. During the TRACTOR Trial, to best isolate the effect of the Brilinta/ticagrelor, all participants will be asked to continue their headache medications at baseline dosage, throughout the duration of the trial. This would include any of the drugs in the following categories:

- *Beta Blockers*
- *Calcium Channel Blockers*
- *Carbonic Anhydrase Inhibitors*
- *Skeletal Muscle Relaxants*
- *Fatty Acid Derivative Anticonvulsants*
- *Anti-adrenergic agents*
- *Angiotensin Converting Enzyme Inhibitors*
- *Vitamin Supplements*

Should the need arise to change the dose, or discontinue one of the medications for any reason, a protocol deviation report will be filed. All medications for non-headache indications should be continued as well.

Participants who are treated with Botox injections, may be considered for the TRACTOR Migraine Trial, but should be warned of the small additional risk of bleeding at the site of the injection while on blood thinner therapy. This should be discussed with the potential participant, as part of the informed consent process. The study coordinator will be responsible for documentation of these discussions.

During the TRACTOR Trial, there will be no restrictions on abortive/rescue medications for migraine episodes, among the categories of drugs as follows:

- *Opiates*
- *Benzodiazepines*
- *Non-steroidal anti-inflammatories*
- *Aspirin*
- *Tylenol*
- *Triptans*
- *Caffeine*
- *Ergotamines*
- *Butalbital*
- *Anti-emetics*
- *Muscle Relaxants*

The use of abortive/rescue therapy will be documented in the daily headache log.

Headache Tracking and Treatment Phases:

Baseline-Monitoring Phase (Phase 1): The subject will track her/his headaches daily for 28 days through an online survey tool (REDCap, licensed through Columbia University), to establish a baseline headache frequency. Each day, the subject will receive a text message/e-mail reminder to complete the daily headache log. The message will contain a link to log into the survey tool. During this phase, subjects will answer questions including presence or absence of headache symptoms, severity of headache symptoms, duration of symptoms, impact on daily activities, and use of rescue medication. Any headache lasting more than 24 hours will be counted as a second headache day. After 28 days of monitoring, the study coordinator will assess the subject's data to make sure the subject meets criteria for minimum headache days, and has been consistently performing the daily log. If the number of headache days is insufficient, the subject's participation will be completed. If the subject logs at least 6 headache days in the month, she/he will continue in the study. If the participant has been assigned to the Episodic arm of the study, but has >14 headache days in the screening month, or if the participant has been assigned to the Chronic arm of the study, but has <15 headache days in the screening month, she/he will NOT be reassigned, but will remain in the assigned group for analysis. The subject will then be treated with Brilinta/ticagrelor for a 28-35 day test period (Phase 2). The length of the test period will depend on the timing of the participant's follow-up visit after beginning treatment. The protocol window is 28+7 days.

Treatment Phase (Phase 2): The subject will return for a follow-up visit to receive her/his medication within 1 week of completing the 28 day headache log. A loading dose of Brilinta/ticagrelor 180 mg will be administered in the office. Thereafter, for 28-35 days, a Brilinta/ticagrelor 90 mg tablet will be taken once in the morning and once in the evening, as close to 12 hours apart as possible. Each day, the subject will receive a text message reminder to login to the website, to record her/his headache activity. If she/he fails to login for two consecutive days, the study coordinator will place a follow-up phone call. PRU testing will be done a minimum of 7 days after the initiation of treatment, but before the medication is completed. A follow-up visit will be arranged between day 28 and day 35 days of monitoring to review efficacy, compliance, and side effects, to return unused medication, and to allow continued access to Brilinta/ticagrelor if indicated. A second Quality of Life survey will be completed.

Continued Access Phase (Phase 3): If the subject has a beneficial response to the Brilinta/ticagrelor (> 50% reduction in the average number of monthly headache days compared with the baseline), she/he will be offered continued access to the medication to complete an additional 2 months of therapy with on-going headache monitoring. A final office visit and Quality of Life Survey will be completed within 7 days of the 56th day of Phase 3 for return of unused medication, empty medication bottles and discussion about future therapeutic options. If the subject fails to have a beneficial response following the first month of treatment (Phase 2), the medication will be discontinued and participation in the study will be completed. If the subject elects to discontinue the Brilinta/ticagrelor, despite a beneficial response, participation in the study will be completed.

Outcomes Assessment/Statistical Analysis

Information from this study will be assessed to determine the feasibility of performing a larger randomized, blinded, placebo-controlled multi-center trial. We will assess not only our therapeutic drug response rate in order to estimate a required sample size for the future trial, but also our ability to recruit patients from local referring sources to estimate the time frame of such a trial. Subject compliance rate with use of daily online questionnaires will be determined. Drop-out rates, related to medication side effects will also be assessed.

1. Statistical Considerations and Analysis Plan:

This is a prospective, open label single-armed trial designed to evaluate the safety and efficacy of Brilinta/ticagrelor (90 mg twice daily) used off-label, in a young healthy population, for the treatment refractory migraine headache. The primary endpoints are:

- Efficacy – Response to treatment defined as a $\geq 50\%$ reduction in chronic headache during a three month period of therapy, compared with baseline.
- Safety – Bleeding events and adverse medication reactions measured over the 3 month treatment period.

Only 40 subjects will be treated in this initial feasibility trial, 20 with episodic migraine, 20 with chronic migraine. We will assess the number of “Responders” in each study group. Responsiveness will be compared with the measured PRU while on therapy. The results of this trial will be descriptive only. It is not anticipated that the number of subjects enrolled will provide statistically analyzable results.

However, if treatment were to be seemingly beneficial, these data could form the foundation for the development of a pivotal randomized, blinded, prospective trial in a larger cohort as mentioned above.

The safety analysis set will include all subjects who receive at least one dose of study medication. This will be the primary analysis set for all safety endpoints which will include major bleeding complications, and adverse drug reactions. Bleeding outcomes, in this younger, healthier cohort will be compared with the previously published PLATO Trial²¹.

Any participant who completes her/his daily headache logs for at least two weeks, but not the full month of the study period, will be classified according to her/his current response status (LOCF), regardless of whether or not he/she completed the required therapy.

2. Analysis of Secondary Endpoints

The secondary endpoints, which will be reported, are as follows:

- Absolute reduction in headache days as a continuous response variable.
- Comparison of the use of rescue medications in the roll-in versus the treatment phase and “successful” interruption of MHA (< 2 hours to resolution) with rescue therapy.
- Non-major bleeding side effects of the medication

STUDY PROCEDURES:

All potential subjects must have migraine headache documented by a Neurologist. All potential subjects must have a documented RLS by transcranial Doppler (see details above) prior to being a candidate for inclusion into the treatment group. All potential subjects will undergo baseline blood work testing and a urine pregnancy test if indicated. All subjects will take a migraine specific Quality of Life Survey (see below) at the start of the study and at visit #3 and at the conclusion of the continued access phase of the study (if applicable). All subjects will complete a daily headache log (see below), using the REDCap Survey Tool. Each subject will monitor headaches for the first month (28 days) while on her/his baseline medication, and will monitor headaches while also taking Brilinta/ticagrelor 90 mg twice daily for the second month (28-35 days). All subjects will undergo PRU blood testing a minimum of 7 days after the start of the Brilinta/ticagrelor therapy (but prior to its completion). A subject may be eligible for two additional months of Brilinta/ticagrelor therapy, with on-going headache monitoring, if she/he has a positive response to the medication.

STUDY DRUG:

Description:

Brilinta/ticagrelor, the first of a new class of oral anti-platelet agents (cyclopentyltriazolopyrimidines), is a non-competitive, P2Y₁₂ receptor antagonist. Following a loading dose of 180 mg, the drug will be administered in its current FDA approved (2011) dosage of 90 mg twice daily.

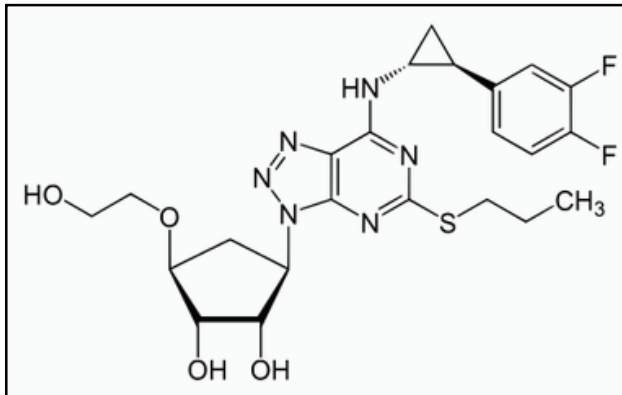


Figure 1

Approved Uses:

Brilinta/ticagrelor is currently FDA approved as a prescription medicine for patients who:

- Have had a recent heart attack or severe chest pain that happened because their heart wasn't getting enough oxygen
- Have had a heart attack or chest pain and are being treated with medicines or procedures to open blocked arteries in the heart

Formulation/Dosage to be Used:

Brilinta tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasiccalcium phosphate, sodium starch glycolate, hydroxypropyl

cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

Dose Rationale and Risk/Benefits:

Based on the known safety profiles of the clinically approved medication, Brilinta/ticagrelor will be given by mouth, in a dose of 90 mg twice daily. There are small, but known risks of this medication, particularly related to bruising and bleeding (see package insert). Since the potential benefits of the therapy is unknown in this application, the standard clinical dosing was selected.

There are several important pharmacologic differences between Brilinta/ticagrelor and the thienopyridines:

- Unlike the thienopyridines, Brilinta/ticagrelor binds reversibly to P2Y₁₂
- Unlike the thienopyridines, in vivo metabolism is not required to have this effect.
- In pharmacodynamics studies, Brilinta/ticagrelor provided more potent and faster onset of platelet inhibition than clopidogrel, without a significant increase in the overall risk of major bleeding.²⁸

Several side effects, not seen with clopidogrel or prasugrel, were seen with the use of Brilinta/ticagrelor.

- Dyspnea³⁰⁻³² was usually mild and self-limiting with no change in pulmonary function tests. In PLATO it was seen in 14% of patients, compared with 8% of patients on clopidogrel.²⁸
- Bradyarrhythmia, particularly sinus pauses occurred in 5.8% of patients on Brilinta/ticagrelor and on 3.6% of patients on clopidogrel²⁸ with no clinically reported dizziness, syncope, pacemaker need or cardiac arrest. This effect is likely related to the drug's delay of adenosine metabolism and re-uptake.
- Increased serum levels of uric acid: as uric acid is a break-down product of adenosine, this is also likely related to higher levels of adenosine.
- Increased serum creatinine: These changes were not clinically apparent. Elevated adenosine levels also may explain this effect. Adenosine alters renal hemodynamics by decreasing tension in the afferent arteriole, and lowering the glomerular filtration pressure.

Packaging of Study Drug:

Brilinta/ticagrelor will be provided to the study by the manufacturer in its FDA approved packaging. The receipt, storage and dispensing of the investigational medication will be handled by the Research Pharmacy at Columbia University Medical Center. Medication bottles will be labeled as per federal and state regulations.

Storage and Distribution:

The Clinical Trials materials will be distributed at controlled room temperature, in an insulated shipper with a temperature monitor by AstraZeneca. The Research Pharmacy at Columbia University Medical Center will store all materials at controlled room temperature (15°C to 25°C) in a secured limited access area.

Return/Destruction of Study Drug:

Unless the study is stopped early due to side effects, it is anticipated that subjects will use all drugs supplied by the trial. Any unused drug will be returned at Study Visit #3. Any

returned drug will be collected by the Columbia University Medical Center Research Pharmacy for appropriate disposal.

STUDY INSTRUMENTS:

Quality of Life Survey:

The MSQ – 2.1 Survey (Migraine Specific Quality of Life Questionnaire – Version 2.1) will be used as an assessment of the impact of the headaches on participants' lives at the outset of the TRACTOR Migraine Trial, and at the completion of the medication month (Phase 2). This survey will be completed with the study coordinator at the initial visit, at the completion of Phase 2, and at the completion of the continued access phase if applicable. MSQ-2.1 is a validated tool for the assessment of migraine participants to medical therapy²³.

Headache Log Recordings:

Participants will be responsible for tracking headache symptoms daily. The daily headache log is a simple questionnaire adapted from the validated Migraine Disability Assessment (MIDAS) questionnaire²⁴ and the validated 24 hour period migraine-specific quality of life questionnaire (24-h MQoLQ)²⁵. The first question will determine if the participant has had headache symptoms within the previous 24 hours. If no headache symptoms were present, the participant will have completed the headache log for the day. If headache symptoms were present, additional questions will determine the duration of the symptoms, their severity, the response to rescue medication (if used), and the degree of disability related to the headache.

Participants will receive a daily text message/e-mail reminder, with a link to the Headache Log via the REDCap Survey tool. When clicked, the link will take the subject directly to the daily log questions (either through a computer or through a smart phone). Each link is valid for only one use. All headache log data will be stored on a HIPAA compliant, secure server at Columbia University Medical Center, for later analysis.

STUDY SUBJECTS:

Patients ages 18 – 65 years with a history of at least one year of migraine headache with at least 6 headache days per month, confirmed by a neurologist. All patients must meet all Preliminary Inclusion and Preliminary Exclusion criteria and will then be offered participation in the trial. Once identified, all potential participants will be consented by the Principal Investigator/Research team at Columbia University Medical Center. Subjects will then be screened with a transcranial Doppler study to determine the presence or absence of a right to left shunt. All subjects with right to left shunt, who meet subsequent laboratory criteria will proceed with the protocol until a total of 20 episodic subjects are treated with Brilinta/ticagrelor and 20 subjects with chronic headaches are treated with Brilinta/ticagrelor.

RECRUITMENT:

Subjects will be recruited from the investigators' clinic and private patient populations. Study information, which will be pre-approved by the Institutional Review Board, will be available to both referring physicians and to the subjects in printed format and on-line. Local physicians interested in referring subjects to the study will be able to set up appointments for their patients directly through the office of the Principal Investigator.

Patients will be approached for participation by the Study Investigators at the time of her/his office visit at Columbia University Medical Center or the external office of the Principal Investigator. The investigator will discuss the study with her/him in order to ascertain whether or not she/he might be interested in participation.

A member of the research team will review patient information to see if she/he meets the initial inclusion/exclusion criteria for the study. All of the information the treatment team member reviews to screen potential participants has been obtained by the clinical staff (NP's, PA's and physicians) for clinical purposes. Some examples of the type of information reviewed include the patient's age, their medication list, drug allergies, length of migraine history, migraine frequency, etc. If the patient is found to fit study criteria, the consent process begins.

INFORMED CONSENT PROCESS:

Patients who meet Preliminary criteria will be consented by a member of the treatment team. At the first screening visit, patients will sign a Screening Consent, which will give the investigators permission to perform the Transcranial Doppler Study and blood work to assure their eligibility. Once it is determined that a right to left shunt is present, the complete consent for the TRACTOR Migraine Headache Study will be completed. All questions regarding the study will be answered and the patient will have the opportunity to discuss any research related issues. No time limit will be defined and sufficient time will be given to the patient to consider participation. The patient will be given the opportunity to consult with others including family members, referring physician, etc. If she/he is interested in participating, written consent will be obtained either at that time or at any subsequent date.

SAFETY AND ADVERSE EVENTS:**Definitions of Adverse Events (see above):****Recording of Adverse Events:**

The Principal Investigator will review all adverse events and immediately be notified of any Serious Adverse Event (SAE); an electronic Adverse Event Report Form will be completed.

Adverse Event Reporting Period:

Serious Adverse Events, after assessment by the study investigator, are to be reported to all other investigators (Executive Committee) within 48 hours. The Investigator will convene the Executive Committee to review/adjudicate the event, with reporting to the IRB/FDA/AstraZeneca as required. Non-serious adverse events will be recorded in the participant study record, reviewed by the study investigator, and will be reported to the IRB/AstraZeneca as required.

Reporting of Serious Adverse Events:

The Principal Investigator is responsible for concurrently informing AstraZeneca, as well as the local authorities and ethical committees, of any serious adverse events as per local requirements. Serious adverse events that do not require expedited reporting need to be reported to AstraZeneca quarterly either as individual case reports or as line-listings.

Any SAE that is unexpected and for which there is a reasonable possibility that the drug caused the adverse event will be considered a “Suspected Unexpected Serious Adverse Reaction (SUSAR), and will be reported to the FDA in accordance with 21 CFR 312.32. This report will be submitted to the FDA as soon as possible, but no later than 15 calendar days from participant notification, and unexpected fatal or life-threatening serious adverse reactions (SARs) will be submitted no later than 7 calendar days from the initial notification. Events that are considered to be “Unanticipated Problems” or UPs, will be submitted promptly to CUMC IRB, but no later than 7 calendar days following the occurrence of the UP or first knowledge of the UP.

All Serious Adverse Event reports will be reviewed/adjudicated by the Executive Committee with reporting to the IRB/FDA as required. The Principal Investigator will be responsible for the dissemination of all serious adverse event (SAE) information to each of the study investigators.

Adverse Event Reporting forms will be used to identify and track each Adverse Event during the study. The form will capture the nature of the event (e.g. Bleeding, Shortness of Breath, etc.), the likelihood that the AE was related to the study medication, the need for treatment related to the AE, the type of treatment required, and the clinical outcome of the AE. Each AE will be classified as an anticipated or unanticipated issue with the study medication. Any bleeding AE will be further characterized (separate report form) as a major life-threatening bleed, major non-life threatening bleed or minor bleed. Additional separate report forms are available in the event of a subject mortality during the study. All AE’s will be reported as safety endpoints in the final study report.

If a participant, or the female partner of a male participant should become pregnant during the study (with or without an adverse event), the pregnancy will be followed to delivery (no matter how the pregnancy ends, spontaneous abortion, elective abortion, pre or term delivery etc.) and the outcome of the pregnancy will be documented and reported as appropriate (to both FDA and to AstraZeneca). Any congenital anomaly or birth defect, in the offspring of a patient (male or female) who was taking the study drug when pregnancy occurred, will be reported to the IRB, to the FDA and to AstraZeneca as an SAE.

If a patient should take a dose of a drug in excess of that specified in the protocol (overdose), the patient should be evaluated for any AE or SAE. The outcomes of any such overdose will be reported to the FDA and AstraZeneca as appropriate. Note that overdoses with or without associated symptoms should be collected and sent to AstraZeneca alone.

CONFIDENTIALITY OF STUDY DATA:

Any information collected during this study that could identify the subject by name will be kept confidential. All research study information will be kept in the form of electronic files, which will be password protected and stored on an encrypted server. A code will be used to identify subjects but this code will be linked to the subjects' identity. The code and the subjects' identity will be included in the same password protected electronic file and stored on an encrypted server.

PRIVACY PROTECTIONS:

Measures such as those described in the confidentiality section will be taken to keep subject data secure, however, complete confidentiality cannot be promised. Despite all of our efforts, unanticipated problems, such as a stolen computer may occur, although it is highly unlikely. We will not share any identifiable data outside of the research team.

POTENTIAL RISKS:

Brilinta/ticagrelor will be used off-label. There is no prior report of its use in the migraine headache population. Risks are extrapolated from the well- studied acute coronary syndrome population.

	BRILINTA N=9235	Clopidogrel N=9186
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

Table 1 - Non-CABG related bleeds (%)

Bleeding Risks:

From the PLATO Trial²⁸ annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days. This suggests that if the TRACTOR population were the same as the PLATO Trial, a risk of a major bleeding event would be expected in ~ 2.2% of patients on a 30 day course of the medication, with a potential life-threatening bleed occurring in ~ 1%.

However, PLATO included only patients with acute coronary syndromes. As a result, the average patient age was 62 years. The average patient age for the TRACTOR Migraine Pilot Study cohort should be around 30 years. Historically, blood-thinning agents have a much higher propensity for causing bleeding in the older population. In addition, all patients in the PLATO trial were on dual antiplatelet therapy (with aspirin), which also increases the bleeding risk. In the TRACTOR Migraine Trial subjects will not be taking aspirin concurrently. The bleeding risks in PLATO were statistically higher, but not clinically different from that in the clopidogrel population. We had no bleeding complications in a similar migraine population, in our published clopidogrel trial.¹⁴

Other Potential Risks:

In PLATO²⁸ there were no serious clinical risks associated with the other observed side effects of the drug. Dyspnea was self-limited and mild in most. Elevation of serum uric acid and creatinine was not a clinically important issue, and in the TRACTOR Migraine Pilot will

be less important in a younger, healthier population. The bradyarrhythmic episodes noted in PLATO were also not clinically important or apparent.

Outcomes in the TRACTOR Migraine Trial will be compared to historical data from prior studies and drug manufacturing data to identify any new, unexpected adverse events or outcomes. The Executive Committee of the Trial will review all reports of adverse events.

POTENTIAL BENEFITS:

This is an observational study of the off-label use of Brilinta/ticagrelor as a primary therapy for treatment of migraine headache. In a previous study of 15 patients with severe migraine treated with clopidogrel¹⁴, >80% had improvement or complete resolution of symptoms. It is unknown if Brilinta/ticagrelor will benefit any individual subject.

ALTERNATIVES:

Subjects may choose not to participate in this study. Subjects may continue to work with their Neurologist using other preventive headache therapies such as Onabotulinumtoxin A, beta-blockers, topiramate, divalproex/sodium valproate, calcium channel blockers, and others including non-medication management.^{33,34}

WITHDRAWAL OF SUBJECTS:

There may be circumstances in which a participant may need to withdraw from the TRACTOR Migraine Trial. These may include either Serious or Important Adverse Events (as listed above), a change in health status (including need for urgent surgical or medical intervention, or unanticipated pregnancy), or non-compliance with the protocol. Non-compliance would be defined as recurrent failure to take the medication as directed, failure to keep protocol appointments, or repeated failure to enter headache log information despite reminders from the local study coordinator.

Any other serious adverse event, which might require discontinuation of the study drug, would require documentation of the issue by the local study team, with formal consultation with the Principal Investigator. An electronic Patient Withdrawal Form would need to be completed by the Principal Investigator. Any adverse event leading to subject withdrawal will require documented discussion by the Executive Committee, and a follow-up assessment by the local study team, to confirm the participant's return to baseline health status.

Once withdrawn from the TRACTOR Migraine Trial for medical reasons, all efficacy data collected to date will be maintained, but no further data will be collected. Any participant who completes the daily headache logs for at least two weeks while on treatment, but who does not complete the full four weeks of the study period, will be classified according to their current response status (LOCF), regardless of whether or not they completed the required therapy (see Outcomes Assessment).

Should a participant choose to withdraw consent for the TRACTOR Migraine Trial, at any time during the monitoring period, for reasons other than an adverse event, the participant must contact the principal investigator, who will complete an electronic Patient Withdrawal

Form. In such a circumstance, efficacy data already collected will no longer be eligible for review. However, safety data up to the point of participant withdrawal will be reviewable for the final data analysis.

MEDICAL MONITORING

The Principal Investigator and his designees will have the primary responsibility of monitoring participant safety. All potential issues of participant safety will be reported to the Executive Committee, which will be comprised of all of the TRACTOR Migraine study Investigators. The Executive Committee will serve the function of the Data and Safety Monitoring Board for the TRACTOR Migraine Trial. This group will meet monthly, after enrollment of the first patient, and will review all safety data on an on-going basis and all SAE's within 48 hours. Enrollment, clinical outcomes and safety data will be reviewed for all patients after 20 patients have been enrolled.

DATA HANDLING AND RECORD KEEPING

Confidentiality:

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Source Documents:

All source data, whether participant demographic information, notes from participant office visits, or participant entered headache log information will be stored in a database on a HIPAA compliant, secure server at Columbia University Medical Center. Transcranial Doppler studies will be recorded and stored in both .pdf and original format. Pharmacy records covering distribution medication will be kept at the Study Research Pharmacy. Baseline laboratory results and PRU testing results will be entered into the study database, and copies of the original documentation will be scanned into a file on the Columbia University Server.

Study Data:

All participant/study related information will be stored in a database on secure server at Columbia University Medical Center. At the time of enrollment, the Study Coordinator will

assist the participant in entering her/his personal demographic information into the database, through a data entry page on the TRACTOR Migraine Trial Website. This webpage will also be housed on the Columbia University Server.

All daily headache log data will be entered (e-CRF's) directly by the participant via computer, smartphone, or on paper through the REDCap Survey Tool, housed on the Columbia University Server.

Record Retention:

The local study investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

STUDY MONITORING, AUDITING AND INSPECTING

Monitoring Plan:

The Principal Investigator/IND Sponsor (PI) will ensure that the study protocol is followed, the data is accurate and the research subjects are safe. Safety data will be reviewed by the PI, or by his designee, as soon as it is received. Safety data will also be monitored by the Executive Committee (EC), which will review safety data and make recommendations regarding continuation, termination, or modification of the study. The EC will formally review the safety data, enrollment, and clinical outcome data after the first 20 subjects have been treated and will review all serious adverse events within 48 hours.

A dedicated Study Coordinator will review 100% of source documentation/data collected for accuracy, including all safety data. The regulatory binder, along with other essential study documents, will also be reviewed to ensure that it is complete and up to date. The first review will occur after the first subject is enrolled and will continue weekly with new enrollments. Any discrepancies will be discussed with relevant study personnel for clarification and/or correction.

The Study Coordinator will be responsible for the monitoring and day-to-day running of the trial. Her/his responsibilities will include:

- scheduling all appointments for Transcranial Doppler
- obtaining consent for participants on the day of their initial visit
- checking the data against source documentation for all participants to ensure data accuracy and integrity
- tracking blood test results for baseline evaluation and entering laboratory data into the study database
- scheduling additional study visits
- tracking participant compliance with the daily headache logs
- contacting participants who are not up-to-date on their headache log entries
- acting as central contact for any adverse events which will need to be reviewed by the Principal Investigator and the Executive Committee

Auditing and Inspecting:

The principal investigator will permit study-related monitoring, audits, and inspections by the Executive Committee and the IRB, the sponsor, government regulatory bodies, and

University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

References:

1. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache* 1998; 38:497-506.
2. Del Sette M, Angeli S, Leandri M, Ferriero G, Bruzzzone GL, Finocchi C, Gandolfo C. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. *Cerebrovasc Dis.* 1998;8:327-30.
3. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology.* 1999;52:1622-5.
4. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* 2000; 356:1648-51.
5. Schwerzmann M, Wiher S, Nedeltchev K, Mattle HP, Wahl A, Seiler C, Meier B, Windecker S. Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology* 2004; 62:1399-401.
6. Giardini A, Donti A, Formigari R, Salomone L, Palareti G, Guidetti D, Picchio FM. Long-term efficacy of transcatheter patent foramen ovale closure on migraine headache with aura and recurrent stroke. *Catheter Cardiovasc Interv* 2006; 67:625-9.
7. Reisman M, Christofferson RD, Jesurum J, Olsen JV, Spencer MP, Krabill KA, Diehl L, Aurora S, Gray WA. Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol* 2005;45:493-5.
8. Slavin L, Tobis JM, Rangarajan K, Dao C, Krivokapich J, Liebeskind DS. Five-year experience with percutaneous closure of patent foramen ovale. *Am J Cardiol* 2007; 99:1316-20.
9. Kimmelstiel C, Gange C, Thaler D. Is patent foramen ovale closure effective in reducing migraine symptoms? A controlled study. *Catheter Cardiovasc Interv* 2007; 69:740-6.
10. Wahl A, Praz F, Tai T, Findling O, Walpoth N, Nedeltchev K, Schwerzmann M, Windecker S, Mattle HP, Meier B. Improvement of migraine headaches after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* 2010; 96:967-73.
11. Khessali H, Mojadidi MK, Gevorgyan R, Levinson R, Tobis J. The effect of patent foramen ovale closure on visual aura without headache or typical aura with migraine headache. *J Am Coll Cardiology CV Interventions* 2012; 5:682-7.
12. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation* 2008; 117:1397-404.
13. Nozari A, Dilekoz E, Sukhotinsky I, Stein T, Eikermann-Haerter K, Liu C, Wang Y, Frosch MP, Waeber C, Ayata C, Moskowitz MA. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. *Ann Neurol* 2010; 67:221-9.
14. Spencer BT, Qureshi Y, Sommer RJ. A retrospective review of clopidogrel as primary therapy for migraineurs with right to left shunt. *Cephalalgia.* 2014;34:933-37.
15. Mega JL, Simon T, Collet J, et al. Reduced-Function CYP2C19 Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI: A Meta-analysis. *JAMA.* 2010;304(16):1821-1830.
16. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndrome. *N Engl J Med* 2007; 357:2001-2015.

17. Dobesh PP, Oestreich JH. Review of Therapeutics. Ticagrelor: Pharmacokinetics, Pharmacodynamics, Clinical Efficacy and Safety. *Pharmacotherapy*. 2014 (August 28, Epub ahead of print).
18. Hirth A, Nightingale S, Wilmschurst P, Disney P, Thorne S. Prevalence of migraine in adults with cyanotic congenital heart disease. *Congenit Heart Dis* 2008; 3:124-7.
19. Truong T, Slavin L, Kashani R, Higgins J, Puri A, Chowdhry M, Cheung P, Tanious A, Child JS, Perloff JK, Tobis JM. Prevalence of migraine headaches in patients with congenital heart disease. *Am J Cardiol* 2008; 101:396-400.
20. Post MC, Thijs V, Schonewille WJ, Budts W, Snijder RJ, Plokker HW, Westermann CJ. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. *Neurology* 2006; 66:202-5.
21. Wilmschurst PT, Nightingale S, Walsh KP, Morrison WL. Clopidogrel reduces migraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects. *Heart* 2005; 91:1173-5.
22. Hadjikhani, Nouchine, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proceedings of the National Academy of Sciences* 2001; 98: 4687-4692.
23. Woods, Roger P., Marco Iacoboni, and John C. Mazziotta. Bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. *New England Journal of Medicine* 1994; 331: 1689-1692.
24. Cao, Y., Welch, K.M., Aurora, S. & Vikingstad, E.M. Functional MRI-BOLD of visually triggered headache in patients with migraine. *Arch. Neurol* 1999; 56: 548-554.
25. Rahimtoola H, Egberts ACG, Buurma H, Tijssen CC, Luefkens HG. Reduction in the intensity of abortive migraine drug use during coumarin therapy. *Headache* 2001;41:768-773.
26. Wammes-van der Heijden EA, Tijssen CC, van't Hoff AR, Egberts ACG. A thromboembolic predisposition and the effect of anticoagulation on migraine. *Headache* 2004;44:399-402.
27. Maggioni F, Bruno M, Mainardi F, Lisotto C, Zanchin G. Migraine responsive to warfarin: an update on anticoagulant possible role in migraine prophylaxis. *Neurol Sci* 2012;33:1447-1449.
28. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-57.
29. Spencer MP, Moehring MA, Jesurum J, et al. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging* 2004;14:342-349.
30. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006;27:1038-47.
31. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 2007;50:1844-51.
32. Gurbel PA, Bliden KP, Butler K, et al. Randomized doubleblind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120:2577-85.
33. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache: The Journal of Head and Face Pain* 2012; 52: 930-945.
34. Joshi SG, Mathew PG, Markley HG. New daily persistent headache and potential new therapeutic agents. *Curr Neurol Neurosci Rep* 2014;14:425-31.

Appendix 1:

Trial Schedule: (see attached TRACTOR Migraine Trial Flow Sheet in Appendix 2)

Study Visit #1: At the time of the first visit, study coordinator/investigators will discuss trial and subject eligibility for participation based on migraine headache frequency. The coordinator will collect all demographic information required for the study. Participant will receive explanation of the additional testing required for trial participation. After patient has been given an opportunity to ask questions, a screening consent will be signed to perform this testing. Participant will receive a Patient Study Number. Transcranial Doppler study will be performed. If negative for right to left shunt, participant will be sent back to the referring physician for on-going clinical care. If positive for right to left shunt (Spencer Grade ≥ 2) participant will be eligible to continue in the trial. The trial will be explained in detail, including participant responsibilities, and the patient will receive written study materials. A complete TRACTOR Migraine Headache Trial consent will be signed. The participant will receive a test e-mail/text message and must demonstrate the ability to answer the headache log questions. A Quality of Life Survey will be taken. Laboratory screening is done. End of visit.

**Study Phase 1:
(28 Days)** Within 72 hours of the laboratory evaluation, participant will be notified of results of laboratory testing and ability to continue participation. She/he will begin to receive daily reminders (e-mail/text message) to log-in to answer the headache log questions. A follow-up appointment will be scheduled within 7 days of the completion of 28 days of headache monitoring.

Study Day 29: Headache log entries will be reviewed by the Study Coordinator to determine final eligibility for trial based on the number of headache days documented.

Study Visit #2: Must occur within seven days of completion of baseline headache log. Participant will return to receive her/his medication. She/he will receive a loading dose of 180 mg of Brilinta/ticagrelor and an additional 70 tablets and will again review the responsibilities for participation with the coordinator. The participant will be observed for 30 minutes after taking the first medication dose.

**Study Phase 2:
(28-35 Days)** Participant will receive reminder text message/e-mail to take daily study medication, and to log-in to answer the headache log questions. Participant will take Brilinta/ticagrelor 90 mg twice daily for 28-35 days. Participant will receive instructions for PRU testing.

PRU Testing: (> 7 days on drug)	Participant will go to local laboratory or to study center for blood testing of platelet inhibition.
Study Visit #3:	Within 7 days of completion the 28 th day of the study medication participant will return to meet with the study coordinator to review the results of the therapy, to return unused medication, and to review any adverse events. If no perceived benefit, participation is completed. If subject has had a clinical benefit, options for on-going therapy with additional headache log entries will be discussed. Participant will complete a follow-up Quality of Life questionnaire.
Continued Access (56-63 days):	If eligible, participant will continue to take Brilinta/ticagrelor for an additional 2 months. She/he will continue to receive daily e-mail/text message reminders to log-in to record headache data.
Study Visit #4:	Within 7 days of the 56 th day of study medication, participant will return to meet with the study coordinator to review the results of the therapy, to return unused medication, and to review any adverse events. Participant will complete a follow-up Quality of life questionnaire. Study is complete.

Appendix 2:

TRACTOR Migraine Flow Chart: Events and responsibilities are described for each phase of the trial.

Events	Study Visit #1	Phase 1 (28 Days)	Day 29	Study Visit #2	Phase 2 (28-35 Days)	PRU visit	Study Visit #3	Continued Access (56-63 Days)	Study Visit #4
Time Window		After completion of all screening	Day after completion of Baseline Headache logs	Within 1 week of completing headache logs	Day after Study Visit #2	> 7 days after starting, but still on medication	Within 7 days of 28 th day of Phase 2 monitoring	After Study Visit #3	Within 7 days of 56 th day of continued access phase meds
Meet Study Investigator/ Coordinator	Yes			Yes			Yes		Yes
Sign Consent	Yes								
Transcranial Doppler Exam	Yes								
Complete Quality of Life Survey	Yes						Yes		Yes
Blood Testing	Yes					Yes			
Receive Daily Reminder		Yes			Yes			Yes	
Record Daily Headache Log		Yes			Yes			Yes	
Receive Study Medication				Yes			Yes (if continuing)		
Take Study Drug					Yes			Yes	
Coordinator Reviews logs for compliance		Yes			Yes			Yes	
Coordinator Reviews Logs and Contacts Participant			Yes				Yes		Yes
Clinical Research Forms to be completed during visit (see Appendix 1)	Form 2-7 Form 8, 9 (if R to L shunt proven by TCD)	Form 10 (daily)	--	Form 11	Form 10 (Daily)	Complete Form 9 (PRU Result)	Form 12	Form 10 (Daily)	--