A Multidisciplinary Translational Approach to Investigate the Mechanisms, Predictors, and Prevention of Persistent Post-Traumatic Headache

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Human Studies Protocol: Clinical Trial

August 2024

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Summary

This protocol describes the background, objectives, and methods for the Clinical Trial that is part of the Focused Program entitled "A Multidisciplinary Translational Approach to Investigate the Mechanisms, Predictors, and Prevention of Persistent Post-Traumatic Headache". Other Individual Projects that are part of this Focused Program are described in a separate protocol subtitled "Individual Projects Excluding Clinical Trial" and include: phenotyping and neurophysiology, neuroimaging, molecular biomarkers, and multivariate modeling.

Research Participant Flow Through the Human Studies

Individuals with post-traumatic headache (PTH) will be enrolled into the clinical trial. In total, up to 112 individuals with acute PTH attributed to mTBI will participate in the clinical trial that is part of this Focused Program.

Those with PTH who will be enrolled into the clinical trial will come from Paths A, C, and D as described:

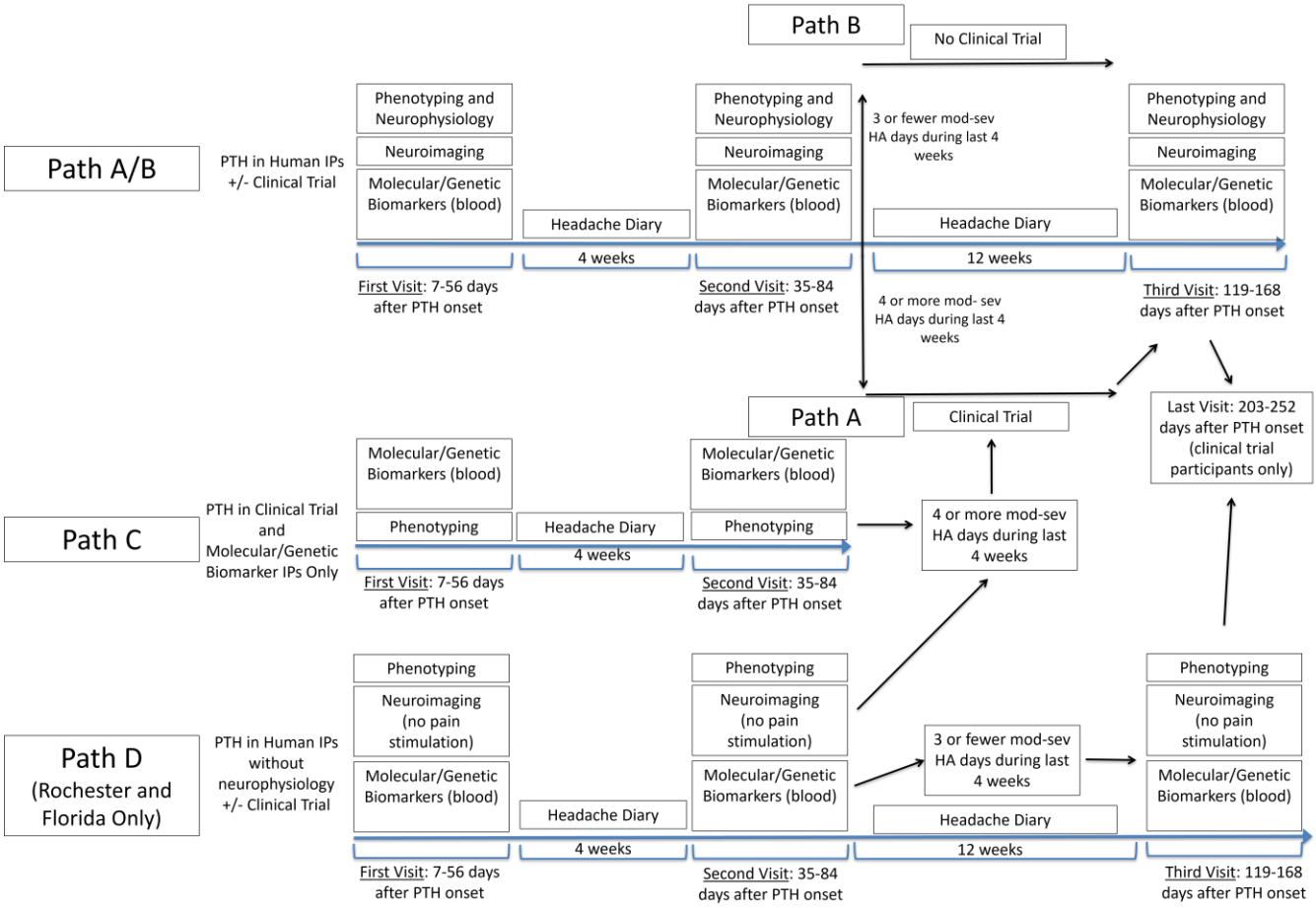
1) **Path A**: all of the human individual projects including phenotyping and neurophysiology, neuroimaging, molecular/genetic biomarker studies, and the **clinical trial** (n=82); or

2) **Path B** (this path will be carried out under a separate protocol subtitled "Individual Projects Excluding Clinical Trial"): each of the human individual projects including phenotyping and neurophysiology, neuroimaging, and molecular/genetic biomarker **but not the clinical trial** (n=82); or

3) **Path C**: only the phenotyping (but not neurophysiology or neuroimaging), molecular/genetic biomarker studies, and the **clinical trial** (n=60, half of which will qualify for the clinical trial); or

4) **Path D** (Rochester and Florida sites only): the human individual projects including phenotyping, neuroimaging, and molecular/genetic biomarker studies. Entry into the **clinical trial** will be dependent on headache diary entries. This path will not include neurophysiology testing (cutaneous and visual pain threshold testing) and will not include the event-related runs during fMRI.

Participant flow through this Focused Program is illustrated within the Figure inserted below.



It is anticipated that approximately 50% of patients with PTH who enter Path A/B or D will have 4 or more moderate-to-severe headache days during the 4-week run-in period and thus will qualify for the clinical trial. These individuals will continue down Path A/D, while those individuals not meeting eligibility criteria for the clinical trial will continue down Path B/D. If clinical trial enrollment goals are met, participants will still have the opportunity to participate in other research procedures as outlined in the flow diagram.

Participant Eligibility Criteria for those with PTH

Path A/D (all studies including the clinical trial)

Inclusion Criteria

- Have a diagnosis of acute PTH attributed to mild traumatic injury to the head as defined by the International Classification of Headache Disorders (ICHD-3).[1]

ICHD-3 Diagnostic Criteria for PTH Attributed to mTBI

A. Any headache fulfilling criteria C and D
B. Head Injury fulfilling both of the following:
  1. Associated with none of the following:
    a) Loss of consciousness for >30 minutes
    b) Glasgow Coma Scale (GCS) score <13
    c) Posttraumatic amnesia lasting >24 hours
    d) Altered level of awareness for >24 hours
    e) Imaging evidence of traumatic head injury
  2. Associated, immediately following the head injury, with at least one:
    a) Transient confusion, disorientation or impaired consciousness
    b) Loss of memory for events immediately before or after injury
    c) Two or more of: nausea, vomiting, visual disturbance, dizziness/ vertigo, impaired memory/concentration, gait instability
C. Headache is reported to have developed within 7 days after one of:
  1. The injury to the head
  2. Regaining consciousness following injury to the head
  3. Discontinuation of medication(s) that impair the ability to sense or report headache following injury to the head
D. If headache persists for >3 months following onset then it is "persistent" PTH. If headache resolved within 3 months of onset or 3 months have not yet passed, then it is "acute" PTH.
E. Not better accounted for by another ICHD-3 diagnosis

- PTH onset 7- 56 days prior to the time of enrollment
- Adults 18-70 years of age
- Willing to receive erenumab treatment
- Willing to maintain a headache diary
- Willing and able to return for follow-up visits

Additional Inclusion Criteria for the Clinical Trial (assessed after run-in phase)

- 4 or more moderate or severe headache days during the 4-week run-in phase

- An increase of at least 2 moderate to severe headache days compared to pre-TBI

- At least a 30% increase in moderate to severe headache days compared to pre-TBI

- At least 80% compliant with diary keeping during the 4-week run-in phase (i.e. provides data on at least 80% of days)

Exclusion Criteria

- Chronic headache (i.e. at least 15 headache days/month for more than 3 months) within 12 months prior to the mTBI that led to the current PTH, including PPTH, chronic migraine, medication overuse headache, new daily persistent headache, hemicrania continua, chronic tension-type headache.

- Diminished decision-making capacity that in the investigator's opinion would interfere with the person's ability to provide informed consent and complete study procedures

- Started or changed dose of a headache preventive medication within the 3 months prior to screening.

- Use of onabotulinumtoxinA in the head, neck or face region within 6 months of screening

- During the 6 months before screening, use of opioids or barbiturates on an average of at least 4 days per month

- Subjects who underwent an intervention or used a device (e.g., nerve blocks, transcranial magnetic stimulation, vagal nerve stimulation, or electrical trigeminal nerve stimulation) for headache within 3 months of screening.

- History of major psychiatric disorder such as schizophrenia and bipolar disorder

- History or evidence of any unstable or clinically significant medical condition, that in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

- History of positive neuroimaging findings that indicate a moderate or severe TBI

- Contraindications to magnetic resonance imaging, including, but not limited to:
    - Metal implants
    - Aneurysm clips
    - Severe claustrophobia
    - Implanted electronic devices
    - Insulin or infusion pump

    - Cochlear/otologic/ear implant
    - Non-removable prosthesis
    - Implanted shunts/catheters
    - Certain intrauterine devices
    - Tattooed makeup
    - Body piercings that cannot be removed
    - Metal fragments
    - Wire sutures or metal staples

- Factors that Reduce MR Image Quality and Interpretability
    - Dental braces or other non-removable devices (e.g. retainers)
    - Prior brain surgery
    - Known brain MRI abnormality that in the investigator's opinion will significantly impact MRI data

- Sensory disorders that in the investigator's opinion might affect perception of cutaneous thermal stimuli (e.g. peripheral neuropathy) *criteria not applicable for Rochester and Florida sites

- Pregnancy

- Breastfeeding

- History of myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening.

- Not willing to use a reliable form of contraception (for women of childbearing potential) through 16 weeks after the last dose of erenumab. Acceptable methods of birth control include not having intercourse, hormonal birth control methods, intrauterine devices, surgical contraceptive methods, or two barrier methods (each partner must use a barrier method) with spermicide. A reliable form of contraception must be started prior to or at the time of starting the run-in phase. Not being of childbearing potential is defined as any woman who:

    - Is post-menopausal by history, defined as:
        - At least 55 years of age with cessation of menses for 12 or more months, OR
        - Younger than 55 years of age but no spontaneous menses for at least 2 years, OR
        - Younger than 55 years of age and spontaneous menses within the past 1 year, but currently amenorrheic (e.g. spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels at least 40 IU/L) or postmenopausal estradiol level (less than 5 ng/dL) or

according to the definition of "postmenopausal range" for the laboratory involved.

OR

- Underwent bilateral oophorectomy OR
- Underwent hysterectomy OR
- Underwent bilateral salpingectomy

- Currently or within 90 days prior to screening: received treatment in another drug study or an investigational device study

- Has previously received any CGRP ligand or receptor targeted monoclonal antibody

Path C (phenotyping, molecular/genetic biomarker, clinical trial)

Inclusion Criteria

- Have a diagnosis of acute PTH attributed to mild traumatic injury to the head as defined by the International Classification of Headache Disorders (ICHD-3).[1]

ICHD-3 Diagnostic Criteria for PTH Attributed to mTBI

A. Any headache fulfilling criteria C and D
B. Head Injury fulfilling both of the following:
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    c) Posttraumatic amnesia lasting >24 hours
    d) Altered level of awareness for >24 hours
    e) Imaging evidence of traumatic head injury
  2. Associated, immediately following the head injury, with at least one:
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    b) Loss of memory for events immediately before or after injury
    c) Two or more of: nausea, vomiting, visual disturbance, dizziness/ vertigo, impaired memory/concentration, gait instability
C. Headache is reported to have developed within 7 days after one of:
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  2. Regaining consciousness following injury to the head
  3. Discontinuation of medication(s) that impair the ability to sense or report headache following injury to the head
D. If headache persists for >3 months following onset then it is "persistent" PTH. If headache resolved within 3 months of onset or 3 months have not yet passed, then it is "acute" PTH.
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- At least a 30% increase in moderate or severe headache days compared to pre-TBI
- At least 80% compliant with diary keeping during the 4-week run-in phase (i.e. provides data on at least 80% of days)

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- Chronic headache (i.e. at least 15 headache days/month for more than 3 months) within 12 months prior to the mTBI that led to the current PTH, including PPTH, chronic migraine, medication overuse headache, new daily persistent headache, hemicrania continua, chronic tension-type headache.
- Diminished decision-making capacity that in the investigator's opinion would interfere with the person's ability to provide informed consent and complete study procedures
- Started or changed dose of a headache preventive medication within the 3 months prior to screening.
- Use of onabotulinumtoxinA in the head, neck or face region within 6 months of screening
- During the 6 months before screening, use of opioids or barbiturates on average at least 4 days per month
- Subjects who underwent an intervention or used a device (e.g., nerve blocks, transcranial magnetic stimulation, vagal nerve stimulation, or electrical trigeminal nerve stimulation) for headache within 3 months of screening.
- History of major psychiatric disorder such as schizophrenia and bipolar disorder

- History or evidence of any unstable or clinically significant medical condition, that in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

- Pregnancy

- Breastfeeding

- History of myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening.

- Not willing to use a reliable form of contraception (for women of childbearing potential) through 16 weeks after the last dose of erenumab. Acceptable methods of birth control include not having intercourse, hormonal birth control methods, intrauterine devices, surgical contraceptive methods, or two barrier methods (each partner must use a barrier method) with spermicide. A reliable form of contraception must be started prior to or at the time of starting the run-in phase. Not being of childbearing potential is defined as any woman who:

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        - Younger than 55 years of age but no spontaneous menses for at least 2 years, OR
        - Younger than 55 years of age and spontaneous menses within the past 1 year, but currently amenorrheic (e.g. spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels at least 40 IU/L) or postmenopausal estradiol level (less than 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

      OR
    - Underwent bilateral oophorectomy OR
    - Underwent hysterectomy OR
    - Underwent bilateral salpingectomy

- Currently or within 90 days prior to screening: received treatment in another drug study or an investigational device study

- Has previously received any CGRP ligand or receptor targeted monoclonal antibody

Recruitment and Enrollment

Research participants will be recruited from the Mayo Clinic in Arizona, the Phoenix VA Healthcare System, Luke Air Force Base, Mayo Clinic in Rochester, and Mayo Clinic in Florida. Participants will be consented and enrolled from the Mayo Clinic in Arizona, the Phoenix VA Healthcare System, Mayo Clinic in Rochester, and Mayo Clinic in Florida. When Luke Air Force Base identifies a potentially eligible individual who may be interested in participating, they will refer the individual to the Mayo Clinic in Arizona for further discussion, determination of eligibility, and enrollment as appropriate. The Phoenix VA Healthcare System will identify and enroll research participants and will complete clinical phenotyping (i.e. study questionnaires). These research participants will then be referred to the Mayo Clinic in Arizona at which all clinical trial procedures will occur.

Participating Site Responsibilities

Mayo Clinic in Arizona: The Mayo Clinic in Arizona will be responsible for all clinical trial specific procedures including participant recruitment, consenting and enrollment, clinical phenotyping and neurophysiology, neuroimaging, collection of blood specimens, and conducting the clinical trial.

Phoenix VA Healthcare System: The Phoenix VA Healthcare system will be recruiting, consenting and enrolling research participants and then completing the clinical phenotyping. These patients will then be referred to the Mayo Clinic in Arizona for their participation in the other aspects of this Focused Program, including the clinical trial.

Luke Air Force Base: Luke Air Force Base will identify potentially eligible individuals for participation in this Focused Program. Such individuals will be referred to the Mayo Clinic in Arizona for further assessment, including participation in the clinical trial.

Mayo Clinic in Rochester and Mayo Clinic in Florida: The Mayo Clinic in Rochester and the Mayo Clinic in Florida will be responsible for all clinical trial specific procedures except for neurophysiology testing and the event-related fMRI runs.

Clinical Trial

Principal Investigator

Todd Schwedt, MD. Professor of Neurology. Mayo Clinic Arizona.

Brief Summary

There are currently no evidence-based or approved treatments for PTH. This clinical trial will determine whether intervention with a CGRP receptor mAb in a population of patients who have PTH for 35-84 days prevents the further persistence of PTH. In children, adults, athletes, civilian, and military populations, the most common phenotype of persistent PTH is migraine. CGRP has been demonstrated to play an integral role in the pathophysiology of migraine in humans and in preclinical animal models of PTH. Our group has shown that a single mTBI in a rodent animal model of PTH leads to a marked elevation in CGRP blood levels which when blocked with an anti-CGRP mAb, prevents the development of cephalic allodynia and headache-related behavior. Several anti-CGRP mAbs targeting the CGRP ligand or its receptor have been demonstrated to be effective and well tolerated for the preventive treatment of episodic and chronic migraine.[76,77] Erenumab is an anti-CGRP receptor mAb that was recently approved by the US FDA for the preventive treatment of migraine. This study will determine whether intervention with erenumab prevents the persistence of PTH in a group of individuals who have already demonstrated evidence for a high likelihood for PTH persistence (i.e. those who have had PTH for 35-84 days). Individuals with PTH will receive open-label monthly subcutaneous administration of erenumab 140 mg.[1] The primary endpoint will be the mean number of moderate-to-severe headache days between 9-12 weeks vs. the frequency during the 4 weeks prior to treatment (baseline diary phase).

Background

There are no evidence-based treatments for PTH. Specifically, there are no acute or preventive medications indicated for the treatment of PTH. The majority of military operators with persistent post-traumatic headache (PPTH) do not respond to first-line migraine preventive drugs.[78] PTH diagnosis and treatment are further complicated by the potential for analgesic overuse leading to a pattern of medication overuse headache.[79,80] Without established therapies for the treatment of PTH or other secondary headaches, it is common to try to match the treatment to the headache phenotype. In other words, drugs and other treatments that are typically used for migraine would be used in those with PTH that has a the characteristics of migraine (i.e. migraine-like phenotype).[81,82] However, limited clinical research is available investigating preventive treatments for PTH, and clinical experience suggests that these commonly used treatments are not effective.[79,81] Moreover, the symptoms that are often associated with concussion and accompany PTH, including those related to cognitive, vestibular, vegetative (fatigue, lethargy), mood and autonomic dysfunction, may be exacerbated by these medications and thus poorly tolerated by patients.[83] Other treatments that are used in the absence of controlled evidence and without significant clinical effect include trigger point injections, occipital nerve blocks, botulinum toxin

injections, and nonpharmacological treatments such as transcutaneous nerve stimulators, physical therapy, biofeedback, and cognitive behavioral therapy.[81] Given the gap in evidence for treating PTH and the large unmet medical need, there is an urgent need for well-designed clinical trials investigating treatments that target the pathophysiology of PTH. There is evidence that CGRP plays an integral role in the pathophysiology of PTH. In a preclinical mTBI rodent model, the development of headache pain-related behaviors appear to be mediated through a CGRP-dependent mechanism.[84] Our group has also shown in pre-clinical rodent models that a single mTBI induces cephalic allodynia that is accompanied by elevated CGRP blood levels, followed by a persistent period during which allodynia may be provoked by a brief period of stress - the most common trigger of migraine headache as well as other headache types. CGRP therefore induces a period of long-lasting latent trigeminal sensitization that may be responsible for the persistence of PTH.

Erenumab is a CGRP receptor mAb that has been demonstrated in phase 2 and phase 3 studies to be effective, safe, and well tolerated for the preventive treatment of episodic (< 15 headache days per month) and chronic migraine (≥ 15 headache days per month). Erenumab received FDA approval for the prevention of migraine in May 2018. In a phase 3 placebo-controlled trial in subjects with episodic migraine (STRIVE), 955 patients were randomized to receive monthly subcutaneous injections of erenumab 70mg, erenumab 140mg, or placebo over 6 months.[77] The primary endpoint (mean monthly migraine days; MMDs) and all secondary endpoints were achieved. The responder rates (> 50% reduction in MMDs) to erenumab 70mg (43%) and 140mg (50%) were superior to placebo (27%; p<0.001). Adverse events were experienced by 64% in the placebo group vs. 57% and 56% in the 70mg/140mg groups respectively. There were no treatment-related serious adverse events in either erenumab group. In another phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of erenumab 70mg in episodic migraine prevention (ARISE), 577 adults were randomized to subcutaneous, monthly placebo, or erenumab (70mg).[76] Erenumab significantly reduced MMD (primary endpoint) at weeks 9-12. A ≥50% reduction in MMDs was achieved by 40% and 30% in erenumab 70mg and placebo groups (odds ratio: 1.6; p=0.010). Erenumab-treated subjects also experienced a significant reduction in monthly use of acute migraine-specific medications compared to placebo (p=0.002). Similar to STRIVE, erenumab 70mg was well tolerated, and there were no treatment-related serious adverse events. In a recently conducted randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of erenumab 70mg and 140mg for the preventive treatment of chronic migraine, 667 patients were randomized to receive monthly subcutaneous injections over a 3-month period.[85]Erenumab was demonstrated to be superior for the primary endpoint of MMD reduction at weeks 9-12. Responder rates were also superior for erenumab 70mg (40%; p<0.001) and 140mg (40%; p<0.001) compared to placebo (24%). Similar to the episodic migraine trials, erenumab was demonstrated to be well tolerated, with an adverse event profile similar to placebo. In a long-term open-label extension study (total exposure of 555.4 patient-years), the safety and tolerability of erenumab was similar to that in the double-blind phase (25.9 and 34.1 patient-years for erenumab 70 mg and placebo, respectively).[86] At week 64, 65%, 42% and 26% of patients had response of ≥ 50%, ≥ 75% or 100%. Erenumab resulted in durable, clinically meaningful improvements across measures of disability, headache impact, and migraine-specific quality of life. Anti-AMG 334 antibodies occurred in 2.4% of the study population, but in all were transient except in one. Anti-AMG 334 antibodies did not impact efficacy or safety. With erenumab exposure of more than 2 years, safety and tolerability profiles

during the open label extension were similar to that observed in the double-blind phase and comparable to placebo.

Hypothesis/Objective

The objective of this study is to collect hypothesis generating data about whether intervention with erenumab is an effective treatment for PTH attributed to mTBI. Participants will receive erenumab when PTH has been present for 35-84 days. Once PTH has been persistent for this period of time, patients may be less likely to remit or improve spontaneously compared to if they were enrolled earlier after PTH onset. Thus, this population of individuals with PTH would be considered in high need of treatment.

Specific Aims/Study Endpoints

Primary endpoint

- Moderate-to-severe headache day frequency measured at weeks 9-12 after administration of first dose of erenumab 140mg vs. frequency of moderate-to-severe headache days during the 4-week baseline phase (BP). A moderate-to-severe headache day is defined as any headache lasting at least 2 hours and which at any point reaches at least moderate intensity.

Secondary endpoints

- Percentage of patients with at least a 50% reduction in headache days during weeks 9-12 after administration of first dose of erenumab 140 mg compared to BP.
- Percentage of patients with chronic headache defined as $\geq$15 headache days during weeks 9-12 after administration of first dose of erenumab 140mg compared to BP.
- Headache Impact Test (HIT-6) at weeks 9-12 after administration of first dose of erenumab 140 mg compared to BP.
- Acute treatment day frequency measured at weeks 9-12 after administration of first dose of erenumab 140mg compared to BP. (Acute treatment day is any day on which an analgesic, triptan, or ergotamine containing medication is taken, or device neuromodulation [e.g. vagal or trigeminal nerve electrical stimulation or single pulse transcranial magnetic stimulation] is administered to relieve headache)

Methods

This is a phase II prospective, open-label clinical trial of a CGRP receptor mAb for treatment of PTH. Of note, this was originally designed as a randomized, placebo-controlled clinical trial. However, recruitment into the clinical trial was slow. Since the estimated total enrollment would

be inadequate for making comparisons between the placebo and erenumab groups, the study was revised to an open-label design.

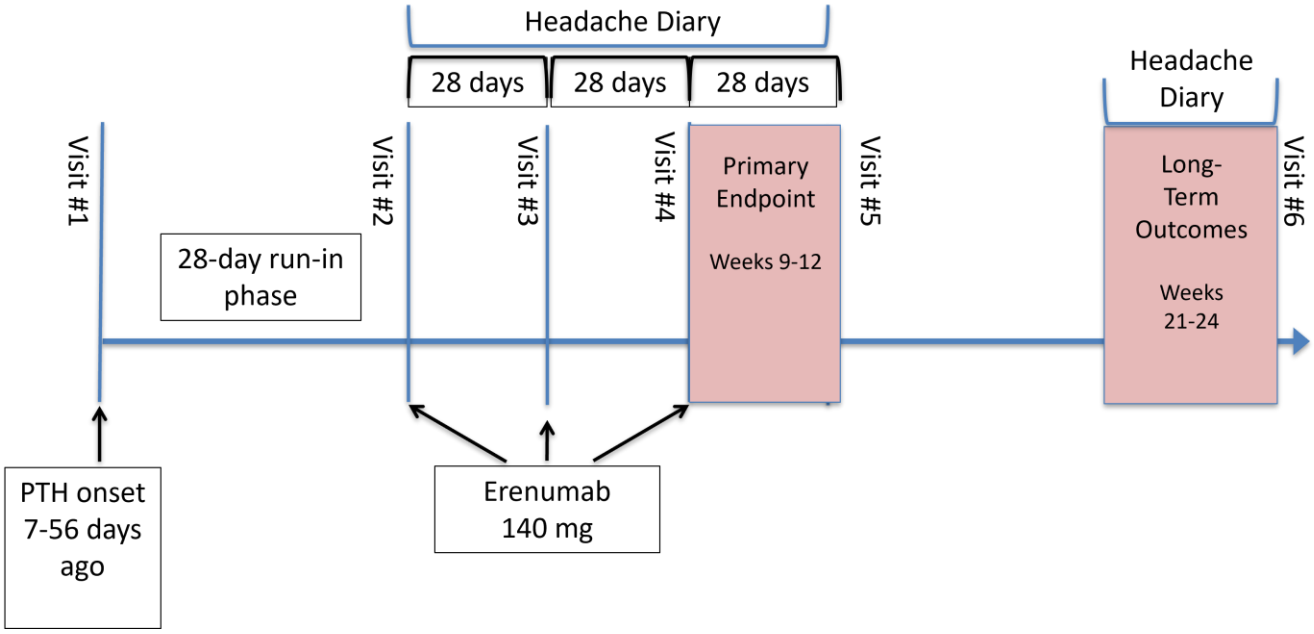
Individuals with PTH will be receive monthly subcutaneous administration of erenumab 140 mg over a 3-month period (total of 3 injections). The primary endpoint will be the mean number of moderate-to-severe headache days between 9-12 weeks after treatment vs. the number of moderate-to-severe headache days during the 4-week BP. Subjects will maintain an electronic daily diary during the 4-week BP, for the 12 weeks post-first treatment, and during weeks 21-24 post-first treatment.

All participants in this clinical trial will complete baseline and follow-up questionnaires described in detail in the separate human studies protocol subtitled "Individual Projects Excluding Clinical Trial" within the "Phenotyping and Neurophysiology" section. In brief, the following questionnaires will be used to collect baseline and follow-up data:

1) TBI and PTH characteristics
2) Post-TBI symptoms using the 22-item Symptom Evaluation Checklist from the Sport Concussion Assessment Tool (SCAT)
3) Headache Impact Test (HIT-6)
4) Self-Rating Questionnaire on Hypersensitivity to Sound
5) Photosensitivity Assessment Questionnaire
6) Allodynia Symptom Checklist (ASC-12)
7) State Trait Anxiety Inventory (STAI)
8) Beck Depression Inventory (BDI)
9) Posttraumatic Stress Disorder Checklist
10) Survey of Autonomic Symptoms
11) Pain Catastrophizing Questionnaire
12) Insomnia Severity Index
13) Cognitive Function
14) Dizziness Handicap Inventory
15) Trail Making Test A and B
16) Controlled Oral Word Association Test (COWAT)
17) Global Impression of Change
18) Follow-up Headache Characteristics
19) Adverse Events
20) Sensory Testing Results *not applicable for Rochester and Florida sites
21) Vital Signs
22) Pregnancy Test Results

In addition, all research participants will maintain a daily electronic headache and symptom diary to provide data on headaches, treatment, and presence and severity of associated symptoms. The diary will be maintained for the first 4 weeks, starting with enrollment (i.e. first research visit) and through week 16 (i.e. third research visit), and again during weeks 21-24 post-first treatment. The electronic diary requires individuals to record whether they did or did not have a headache each day, the severity of their pain, headache duration, level of functional disability due to the headache, and use of medication. To optimize compliance with diary maintenance, the amount of

time required to complete the daily entries has been minimized to less than 2 minutes. Subjects are asked to complete their headache diary at the end of each day. Data from the headache and symptom diary will be used to assess changes in symptoms over time, to prospectively determine who has persistence vs. resolution of PTH, to determine enrollment in the clinical trial depending on PTH persistence and frequency of moderate to severe headache days, and to track response to treatment for those individuals enrolled into the clinical trial.



Stratification, Randomization and Masking*:* This is an open-label study in which there is no stratification, randomization, or masking.

All study drugs will be prepared by a Mayo Clinic pharmacist who has no other role in the study. The drug will be delivered by pharmacy staff to the enrolling investigator clinician or research nurse, who will be responsible for delivering the injection. There will be strict adherence to inclusion and exclusion criteria. Participants will receive instructions and training from a study coordinator on how to use the electronic diary for daily reporting of headaches. A urine pregnancy test will be required for female participants prior to each of the erenumab treatments. Throughout the study, participants will record data in the daily diary for the previous 24 h period.

Treatment with Erenumab: Patients receive treatment with 140 mg of erenumab via subcutaneous injection. Treatment will be administered under research team observation. Injections will be administered using two 70 mg/1 mL prefilled syringes in the abdomen (except for a two-inch area right around the navel), thigh, or outer area of upper arm according to patient preference. If using the same body site for the two separate injections, the second injection is not to be given at the same spot used for the first injection.

Erenumab will be stored refrigerated at 2°C to 8°C (36°F to 46°F) until time of use. Once removed from the refrigerator, it will be kept at room temperature and used within 7 days. Prior to administration, erenumab will sit at room temperature for at least 30 minutes, protected from direct sunlight.

Concomitant Therapy

There are no restrictions on the use of as needed headache/pain therapies. Patients will record their use of such therapies within the headache diary and these data will be used when measuring patient outcomes.

For patients who are participating in the clinical trial, no preventive therapy for headache should be started. Preventive therapies include drugs, biologics, devices, procedures, and non-pharmacological modalities.

Statistical Plan:

Sample Size- all individuals who qualify for the clinical trial and are interested in participating will be enrolled, up to a maximum of 112 participants. This sample size is empirical and results will be used for hypothesis generation.

Headache Diary - Values for missing calendar day entries in a given month will be imputed by prorating scores of 4-week post-treatment periods with 20–27 days of diary data. For months with less than 10 days of diary data, scores will be estimated by the substitution of the patient's previous 28-day period mean score, multiplied by the ratio of the mean for all patients in the same period and divided by the mean for all patients in the previous period. For post-treatment periods with 10–19 days of diary data, scores were estimated using a mean of both methods.

Outcomes - Efficacy analyses will be conducted in the full analysis set, which includes all subjects (intent-to-treat population) who received at least one dose of study drug and have at least 10 days of efficacy assessments for the primary endpoint measured during weeks 9-12. Safety analyses will be performed in all subjects who receive at least one dose of study drug. The primary and secondary endpoints will be analyzed using a within-person one-sample t-test. Signed rank test will be used for the primary analysis if there is a deviation from normality assumption as assessed by Shapiro Wilk's test. Confidence intervals will be calculated. SAS version 9.4 (SAS Institute, Cary NC) will be used for all statistical analyses.

IRB Approvals and Informed Consent: IRB approvals will be obtained from the Mayo Clinic IRB, the Phoenix VA IRB and the DOD HRPO prior to starting any human study research. Written informed consent will be obtained from all subjects prior to their participation. The informed consent process will be based upon the Declaration of Helsinki principles and in accordance with US 21CFR. Applicable HIPAA privacy notifications will be included. Participants will be given ample time and opportunities to ask questions about this study. All consent forms will require IRB approval prior to their use. Patients will be informed of their right to withdraw from the study at any time. Enrolling clinicians will be made aware that the needs of their patients come first and thus the safety and wellbeing of study participants is of primary concern. The study will be done in accordance with the principles of Good Clinical Practice and with US Food and Drug Administration (FDA) and International Committee for Harmonization guidelines for safety

monitoring. Consent documents will be stored for a minimum of 3 years after conclusion of the study. The research participant will retain a copy of their signed consent document.

Study Materials: Study drug will be provided by Amgen, Inc, the manufacturer of erenumab.

Participant Compensation

Participants will be compensated $50 per research visit and $35 per month for headache diary completion at least 80% of the time for a total of up to $175.

Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial patient. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the patient 's record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

Definition of Serious Adverse Events
A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (eg, overnight stay). If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, hypersensitivity reaction, or events that necessitate an urgent intervention.

Reporting Procedures for Adverse Events That do not Meet Serious Criteria
The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the dose of investigational product through the end of the safety follow-up visit (12 weeks after administration of investigational product) are reported using the applicable case report form (CRF) (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- dates of onset and resolution (if resolved)
- severity
- assessment of relatedness to investigational product
- action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The investigator must assess whether the adverse event is possibly related to the investigational product and/or medical device. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?"

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events. If the severity of an adverse event changes from the date of onset to the date of resolution, the adverse event should be recorded as a single event with the worst severity on the Adverse Event Summary CRF.

Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the safety follow-up visit (12 weeks after the last dose of investigational product) are recorded in the subject's record and are submitted to Data Safety Monitoring Committee (DSMC). All serious adverse events must be submitted to the DSMC within 24 hours following the investigator's knowledge of the event via the applicable CRF. The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site in accordance with local procedures and statutes. Adverse events that occur during the clinical trial will be reported to Amgen according to the timelines described in the Appendix ("ISS – Timeframes for Submission of Safety Data to Amgen").

Data and Safety Monitoring and Annual Reporting to Regulatory Agency

IND safety reports. The DSMB will notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the DSMB determines that the information qualifies for reporting. Qualifications for reporting include:

- *Serious and unexpected suspected adverse reaction.* This includes a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome; one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug; an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the

underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

- *Findings from other studies.* Investigators will report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

- *Findings from animal or in vitro testing.* Investigators will report any findings from animal or in vitro testing, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

- *Increased rate of occurrence of serious suspected adverse reactions.* Investigators will report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

- *Submission of IND safety reports.* Investigators will annually submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Each notification to FDA will be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the investigators will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

- *Unexpected fatal or life-threatening suspected adverse reaction reports.* Investigators will notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Study Registration

The research program including the clinical trial will be registered at ClinicalTrials.gov.

Risks and Benefits of Participating in this Research Program

Possible Benefits:
It is possible that patients will have improvements in their PTH patterns following treatment with erenumab.

Possible Risks:

Erenumab has been shown to be well tolerated and associated with few side effects. The most common side effects are injection site reaction, constipation, muscle spasm, and pruritis. With the exception of injection site reaction (5.2%), these side effects were reported by less than 5% of patients in the phase II and III clinical trials of migraine. Constipation, sometimes with serious complications, was reported by approximately 3% of individuals receiving erenumab.

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of erenumab in the postmarketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalization. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration. In the majority of cases, the onset or worsening of hypertension was reported after the first dose.

The FDA has added a safety-related label change to erenumab to include a contraindication for patients with serious hypersensitivity to erenumab or to any of the excipients due to the risk of anaphylaxis and angioedema. Most hypersensitivity reactions were not serious and occurred within hours of administration, although some occurred more than one week after administration.

Additional risks that have been reported since erenumab was approved in May 2018 include mouth/lip sores and skin and subcutaneous tissue disorders such as alopecia and rash.

Potential risks associated with erenumab use during pregnancy and lactation are not established.

Protected health information (PHI) is being collected. Although measures are taken to reduce the risk, it is possible that there could be inappropriate access to the PHI by individuals not approved for such access.

There is a possibility that the stress and stimulation of participating in the research study could transiently exacerbate one's headache.

A research participant that indicates suicidal or homicidal intent on a study questionnaire will be referred to the Emergency Department for evaluation.

Protection Against Risks:

Individuals who are known to be pregnant or breastfeeding will be excluded from study participation.

Women of childbearing potential who are not known to be pregnant will have pregnancy testing at the baseline visit and prior to each treatment with study drug. Women found to be pregnant prior to treatment will not receive treatment. Women found to be pregnant after the initial treatment will not receive further study drug. Women of childbearing potential will be required to use a reliable form of contraception from the time of study enrollment through 16 weeks after the dose of erenumab.

Measures that will be taken to protect PHI: All information collected from study participants will be locked in a secure location. Identifying information will be removed from the data forms and replaced by unidentifiable codes. Electronic databases/spreadsheets will be password protected and only accessible to those with access rights.

Patient Retention

Subject retention and diary compliance will be essential for study success.

At the time of considering an individual for participation in this study, it will be ensured that the individual will be available for the duration of the study. The responsibilities of the subject will be clearly defined. Subjects will be contacted with reminders prior to each research appointment.

Diary compliance will be monitored on an ongoing basis. Subjects will be contacted immediately if non-compliance is observed.

Protocol Maintenance

Protocol modifications will be approved by the principal investigator and submitted to the IRB in accordance with IRB rules and regulations. Modifications will be documented separately and within the main protocol document with a newly assigned date and version number.

ISS – Timeframes for Submission of Safety Data to Amgen

For Interventional studies with Amgen IMP*:

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Sent to Amgen at time of regulatory submission
Serious Adverse Events (SAEs)	Not required, unless contractually specified per study
Adverse Events not meeting serious criteria	Not required, unless contractually specified per study

Events of Interest	Not required, unless contractually specified per study
Pregnancy/Lactation	Within 10 calendar days of Sponsor awareness
Event listing for reconciliation	As specified per contract

*Specific requirements are to be outlined in the Research Agreement

For all studies – aggregate reports*:

Safety Data	**Timeframe for submission to Amgen**
Annual Safety Report (eg, EU Clinical Trial Directive [CTD] **DSUR**, and US IND Annual Report)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc)
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion

*Specific requirements are to be outlined in the Research Agreement

Data Sharing

FITBIR (Federal Interagency Traumatic Brain Injury (FITBIR) informatics system):
FITBIR is a computer system run by the National Institutes of Health that allows researchers to share information with each other. Data from this study will be submitted to FITBIR. Before data are submitted, PHI will be replaced with a code number. Subjects will have the ability to opt out from having their data shared to FITBIR.

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