Imaging the migraine brain pre-and post-erenumab: an MRI study to identify functional and structural changes that correlate with patient improvement

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Summary

Compared to healthy people without migraine, migraine is associated with alterations in brain structure and function. This is a prospective, longitudinal, open-label study that will investigate brain magnetic resonance imaging changes amongst individuals with migraine following treatment with erenumab.

The Specific Aims of this study are to:

1. **Identify changes in brain function and structure that correlate with response to erenumab.**

2. **Develop models using imaging data to predict which patients will respond to erenumab**. Pre-treatment and early post-treatment imaging data will be used separately for predictive modeling.

The study will include 50 subjects with migraine aged 18-65 years who have 6-25 migraine days per month at baseline. Following a 4-week run-in phase, subjects will be treated twice with once monthly subcutaneous injections of erenumab 140 mg. Questionnaires, structured interviews, cognitive tests, quantitative sensory testing and brain imaging will be performed prior to and following erenumab treatment. These data will be collected at early time points after the first treatment as well as at eight weeks following the first treatment to allow for identification of early and late effects of erenumab on clinical, physiologic, and imaging outcomes and to determine if early physiologic and imaging outcomes predict clinical outcomes at eight weeks. Physiologic and imaging data will be compared to already collected data from healthy controls so as to interpret changes that are seen following treatment with erenumab.

The primary hypothesis is that improvements in migraine patterns associated with erenumab treatment will be associated with "normalization" of brain function. Secondarily, it is hypothesized that improvements in migraine patterns associated with erenumab treatment will be associated with "normalization" of brain structure, pain thresholds, and cognitive performance. Finally, it is hypothesized that exploratory analyses will demonstrate that there are early changes in brain function following the first treatment with erenumab and that these early changes will be predictive of longer-term clinical responsiveness to erenumab.

Research Team

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Background

Migraine is a highly prevalent disorder that affects 38 million people in the US and is associated with moderate to severe pain, hypersensitivities to sensory stimuli, nausea, vomiting, and reduced quality of life. (1-3) Annual costs from migraine are estimated at $20 billion in the United States and €27 billion in Europe. (4, 5) Migraine remains poorly treated and there are currently few options for the preventive treatment of migraine. The release of erenumab to the market represents a substantial improvement in the landscape of migraine preventive treatment.

Phase 2 and 3 randomized, double-blind, placebo-controlled studies have demonstrated that erenumab is safe and effective for the prevention of episodic and chronic migraine. (6-8) Erenumab received US Food and Drug Administration approval for the prevention of migraine in May 2018. Structural and functional neuroimaging could provide important insights into central mechanisms of treatment response and imaging biomarkers that track treatment response or are indicators for early treatment response. A few studies have demonstrated normalization of functional activation patterns, reorganization of functional connectivity, and normalization of brain metabolism following migraine treatment with external trigeminal neurostimulation, topiramate, and precision ophthalmic tints. (9-12) However, the effects of erenumab on brain function and structure, including the processing of painful stimuli, have been inadequately investigated. Furthermore, it is possible that measures of brain function and structure could serve as predictors for clinical response to erenumab, either prior to treatment or early after the first treatment. It is of clinical interest to interrogate whether neuroimaging is a useful technique for establishing a brain biomarker for predicting treatment response and measuring treatment responses earlier than is possible using clinical measures alone.

This study will investigate longitudinal changes in brain structure and function in high frequency episodic migraine and chronic migraine patients who are responding to erenumab treatment compared to those patients who are non-responders. In addition, pre-treatment and early post-treatment brain imaging data will be used to build models that predict which individual migraine patients will respond to erenumab treatment.

The Specific Aims of this study are to:

1. **Identify changes in brain function and structure that correlate with response to erenumab.** This objective of this aim is to investigate effects of treatment with erenumab on brain function and structure in patients who respond to treatment with erenumab and in patients who do not respond to treatment with erenumab.

2. **Develop models to predict which patients will respond to erenumab**. The goal of this aim is to identify structural and functional brain magnetic resonance imaging predictors of response to erenumab in patients with migraine. Specifically, this aim seeks to identify those migraine patients who are going to have a positive response to erenumab treatment versus those who will not respond to treatment. Pre-treatment and early post-treatment imaging data will be used separately, and in combination, for predictive modeling.

Published Work and Preliminary Data

Our team has performed multiple studies that are directly relevant to the goals of this project and serve as evidence of our ability to successfully conduct this study. We have completed studies comparing noxious heat-induced brain activation patterns in people with migraine vs. healthy controls. (13) These studies showed that migraineurs have greater pain-induced activation in several brain regions, many of which participate in cognitive aspects of pain processing. For several of these regions, the extent of greater activation correlated with the frequency of headaches, serving as strong evidence for a direct relationship between having migraine and greater activation of these pain-processing brain regions and at least suggesting that reductions in headache frequency would correlate with reductions in pain-induced activation. Our resting-state functional connectivity studies have investigated functional connectivity of affective-emotional pain processing regions and of descending pain modulatory brainstem regions. (14, 15) These studies demonstrated that migraineurs have atypical functional connectivity and the extent of atypical connectivity correlates with measures of migraine disease burden such as number of years with migraine and allodynia symptoms. Our structural MRI studies have shown migraineurs to have atypical structure of the brainstem and abnormal cortical thinning with age, aberrant correlations between brain cortical thickness and cutaneous pain thresholds, atypical cortical thickness correlations, and abnormal white matter tract integrity. (16-18) Furthermore, our work has shown migraineurs with interictal photosensitivity to have thicker cerebral cortex in parieto-occipital and fronto-parietal regions. (19) Finally, our machine-learning multivariate pattern analyses have yielded migraine classifiers that use brain structural data to differentiate the brain of an individual chronic migraineur from that of a healthy control (see Figure 1) or episodic migraineur (see Figure 2) with high accuracy (American Headache Society Wolff Award winning paper). (20) Our classifiers based on resting state functional connectivity data differentiate the brain of an individual migraineur from a healthy control with high accuracy (American Academy of Neurology Harold Wolff – John Graham Award winning research, see Figure 3). (20, 21) In addition, we developed a decision support system using multi-modality imaging data to interrogate the utility of combining structural and functional imaging data for migraine patient discrimination and the accuracy of such discrimination. (see Figure 4) (22) Results showed better classification accuracy when combining structural and functional data than using either data type alone.

Figure 1: Regions that allow for accurate discrimination of the chronic migraine brain from that of a healthy control. (20) Structural measures (i.e. cortical thickness, volume, surface area) of the colored brain regions allow for classification of the individual brain MRI as belonging to a person with chronic migraine vs. a healthy control with 86.3% average accuracy. Similar model-building techniques can be used to construct classifiers that predict response to erenumab.

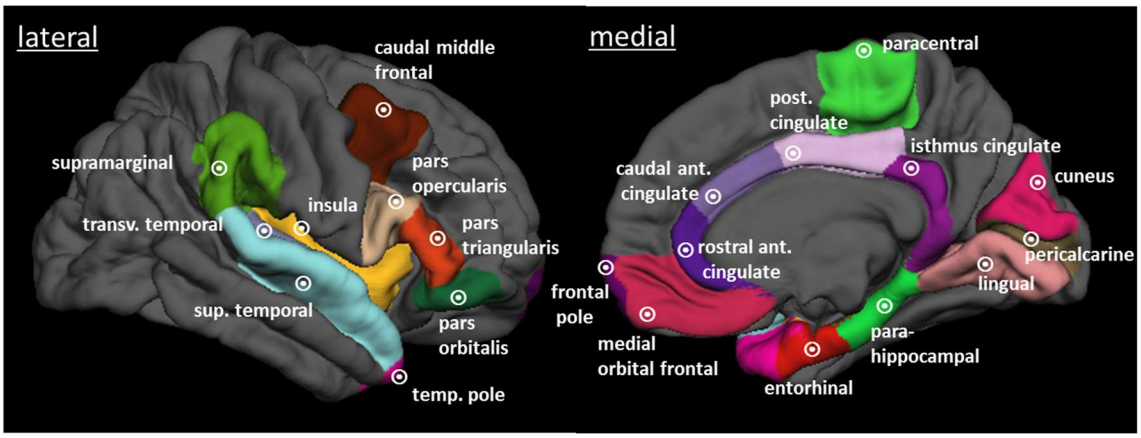


Figure 2: Regions that allow for accurate discrimination of the chronic migraine brain from that of an episodic migraineur. (20) Structural measures (i.e. cortical thickness, volume, surface area) of the colored brain regions allow for classification of the individual brain MRI as belonging to a person with chronic migraine vs. episodic migraine with 84.2% average accuracy. Similar model-building techniques can be used to construct classifiers that predict response to erenumab.

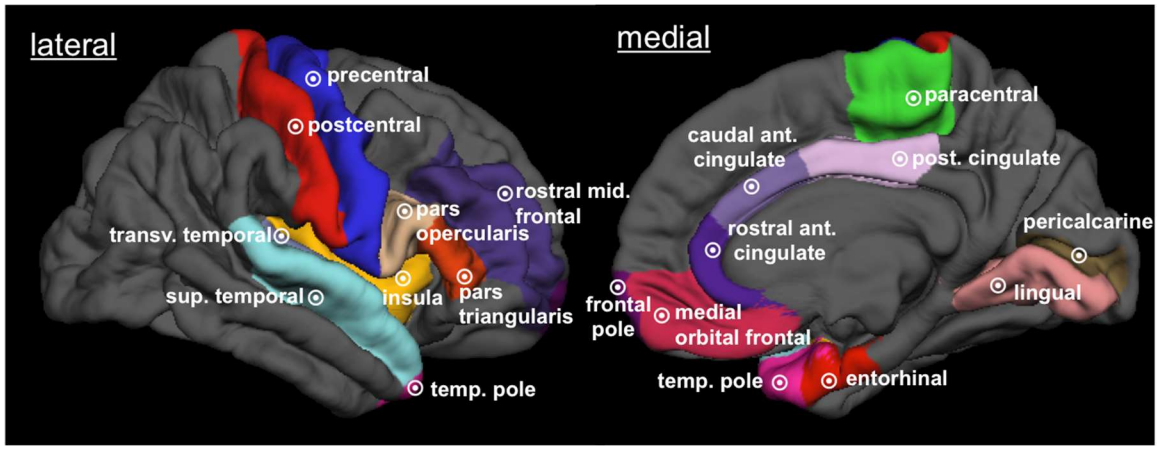


Figure 3: Functional connectivity patterns for the left and right amygdala that contribute to the classification accuracy of distinguishing between individual migraine patients and individual healthy controls. (21) Whole-brain functional connectivity patterns of 6 regions distinguished migraine patients from healthy controls with a best classification accuracy of 86.1%. Migraineurs with longer disease durations were more accurately classified than migraine patients with shorter disease durations. Similar model building techniques could be used to track and predict response to erenumab treatment.

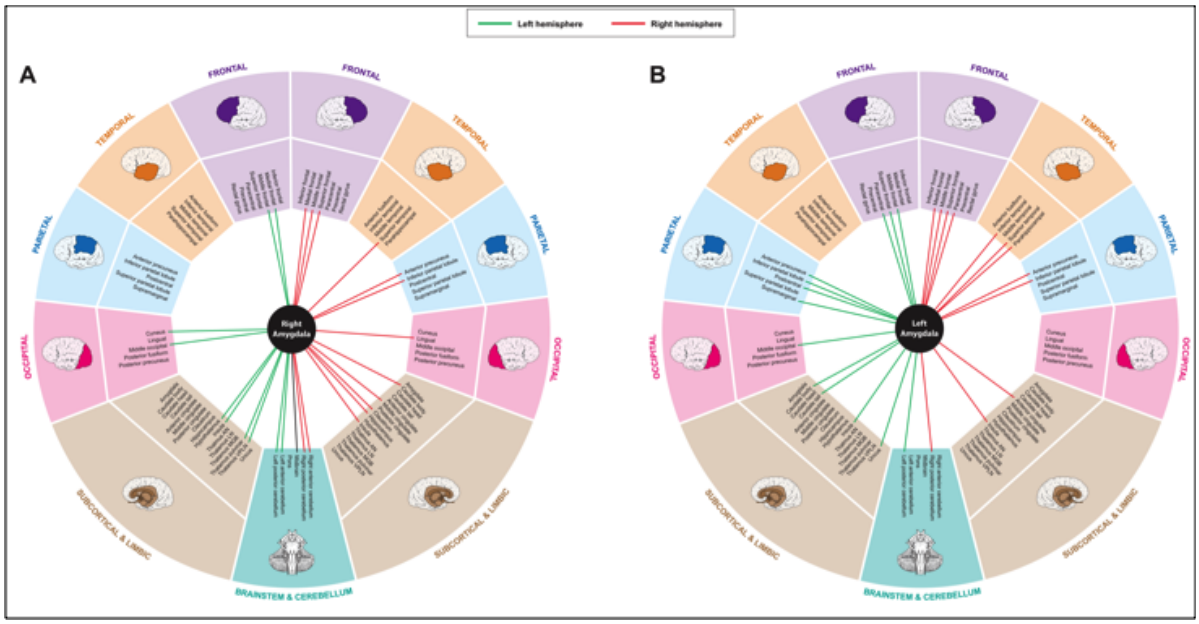
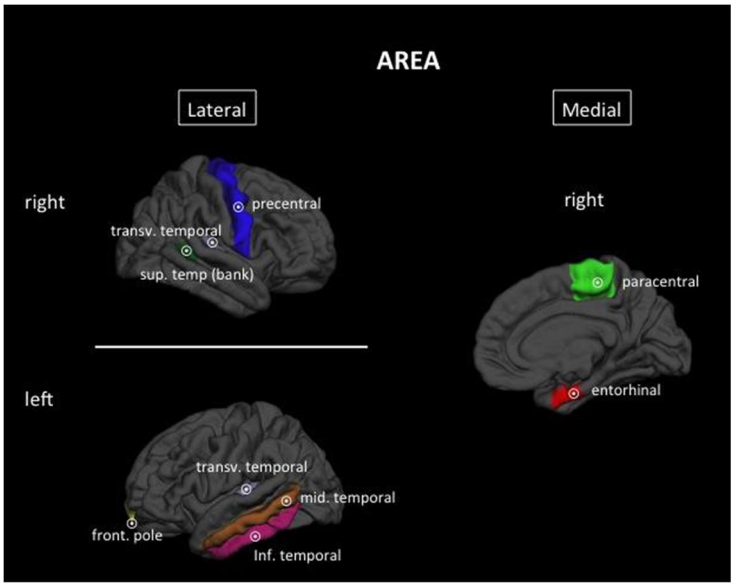
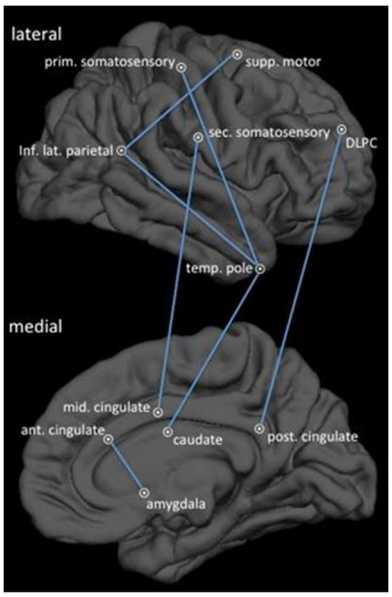


Figure 4: Key brain areas (based on brain structural imaging) and functional connections (based on resting-state imaging) that contribute to distinguishing migraine patients from healthy controls. (22) The combined model that included structural and functional data provided greater accuracy (83%) compared to the model based on structural data alone (80%) and the model built on functional connectivity data alone (75%). The combination of structural and functional brain imaging data may increase the classification accuracy for predicting/determining treatment response to erenumab.





Specific Aims

1. **Identify changes in brain function and structure that correlate with response to erenumab.** The objective of this aim is to investigate effects of treatment with erenumab on brain function and structure in patients who respond to treatment with erenumab and in patients who do not respond to treatment with erenumab. Specifically, this aim will assess changes in brain structure (cortical thickness, volume, area, white matter integrity), brain perfusion, resting-state functional connectivity, and pain-induced brain activation patterns in treatment responders and in treatment non-responders. This aim will identify structural and functional brain biomarkers for treatment response with erenumab.

2. **Develop models to predict which patients will respond to erenumab**. The goal of this aim is to identify structural and functional brain magnetic resonance imaging predictors of response to erenumab in patients with migraine. Specifically, this aim seeks to identify those migraine patients who are going to have a positive response to erenumab treatment versus those who will not respond to treatment. Pre-treatment and early post-treatment imaging data will be used separately, and also in combination, for predictive modeling.

Methods

Study Design: This is a prospective, open-label, longitudinal, pre- and post-treatment magnetic resonance imaging (MRI) study of patients treated with erenumab. A summary of the study flow is presented in Table 1.

Table 1- Study Flow.

	Run in Phase (time: -4 wks)	Baseline (time: 0)	First Follow-up (time: 2 wks)	Second Follow-up (time: 4 wks)	Third Follow-up (time: 8 wks)	Fourth Follow-up (time: 12 wks)
Determine Eligibility	X	X				
Questionnaires	X	X	X	X	X	X
QST		X	X		X	
MR Imaging		X	X		X	
Cognitive Testing		X	X		X	
Vital Signs		X	X	X	X	X
Urine Pregnancy Test		X		X		
Erenumab Treatment		X		X		
Headache Diary	X	X	X	X	X	X

Participants: Up to 67 adult patients who are at least 18 years of age but younger than 66 years of age with high frequency episodic migraine or chronic migraine with and/or without aura will be enrolled into the run-in phase of this study at Mayo Clinic Arizona. Enrollment will stop once 50 subjects provide headache diary during the run-in phase that meets eligibility criteria (i.e. documented 6-25 migraine days per 28 days). Previously collected data of healthy control subjects (n=50) will be used for data comparison. Exclusion and inclusion criteria will be modeled after those used in the phase 2 and 3 trials of erenumab for the prevention of migraine. (6, 8) In addition, patients who have contraindications to MRI (e.g. metal implants, aneurysm clips, severe claustrophobia) will be excluded from study participation. Potential participants will be excluded if they have active chronic pain conditions other than migraine (e.g. chronic pelvic pain) or acute pain conditions (e.g. recent surgery). Potential participants who have sensory disorders that might affect the perception of cutaneous thermal stimuli will also be excluded (e.g. peripheral neuropathy).

Subject Eligibility

Inclusion Criteria

- Adults 18-65 years of age

- Episodic migraine (with or without aura) or chronic migraine according to the diagnostic criteria included within the International Classification of Headache Disorders 3 (ICHD-3) (23)

    - Episodic Migraine
        A. At least 5 attacks fulfilling criteria B-D
        B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)
        C. Headache has at least two of the following four characteristics:
            a. Unilateral location
            b. Pulsating quality
            c. Moderate or severe pain intensity
            d. Aggravation or causing avoidance of routine physical activity
        D. During headache at least one of the following:
            a. Nausea and/or vomiting
            b. Photophobia and phonophobia
        E. Not better accounted for by another ICHD-3 diagnosis

    - Chronic Migraine
        A. Headache (migraine-like or tension-type like) on at least 15 days per month for longer than 3 months, and fulfilling criteria B and C
        B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for "episodic migraine" (above)
        C. On at least 8 days per month for longer than 3 months, fulfilling any of the following:
            a. Criteria C and D for migraine without aura
            b. Criteria B and C for migraine with aura
            c. Believed by the patient to be a migraine at onset and relieved by a triptan or ergot derivative
        D. Not better accounted for by another ICHD-3 diagnosis

- 6-25 migraine days per month on average over the 3 months prior to screening, confirmed by run-in phase prospective data collection

- Duration since migraine onset of at least 12 months prior to screening based on medical records and/or patient self-report

Exclusion Criteria

- Older than 50 years of age at migraine onset

- History of cluster headache or hemiplegic migraine

- Continuous headache pain (i.e. no pain-free periods of any duration during the one month before screening)

- Opioid- or butalbital-containing analgesics on 6 or more days per month during the 2 months prior to the start of the baseline phase

- 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

- No therapeutic response in migraine prevention after an adequate therapeutic trial of 4 or more of the following medication categories:
    - Category 1: divalproex sodium, sodium valproate
    - Category 2: topiramate
    - Category 3: beta-blockers
    - Category 4: tricyclic antidepressants
    - Category 5: venlafaxine or desvenlafaxine, duloxetine or milnacipran
    - Category 6: flunarizine, verapamil
    - Category 7: lisinopril, candesartan
    - Category 8: botulinum toxin

  No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment. Lack of sustained response to a medication and failure to tolerate a therapeutic dose are not considered to be "no therapeutic response".

- Concomitant use of 3 or more of the following medications for migraine prevention within 2 months before the start of the baseline phase or throughout the study: divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin, beta-blockers, tricyclic antidepressants, venlafaxine, desvenlafaxine, duloxetine, milnacipran, flunarizine, verapamil, lomerizine, lisinopril, candesartan, clonidine, guanfacine, cyproheptadine, methysergide, pizotifen, butterbur, feverfew, magnesium (at least 600 mg per day), riboflavin (at least 100 mg per day).

  Use of up to two medications is permitted as long as the dose has been stable for at least 2 months before the start of the run-in phase and during the study.

- Botulinum toxin (in the head and/or neck region) within 4 months before the start of the baseline phase and throughout the study

- Ergotamine derivatives, steroids, and triptans used for migraine **prophylaxis** within 2 months before the start of the baseline phase and throughout the study

- Procedures (e.g. nerve blocks) used for migraine prophylaxis within 2 months before the start of the baseline phase and throughout the study

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

- Contraindications to MRI 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)

- Pregnancy

- Lactation

- 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 receiving treatment in another drug study or an investigational device study, or less than 90 days prior to screening since ending treatment on another investigational device or drug study(-ies)

- Has received CGRP monoclonal antibody within 4 months of the start of the run-in phase

- Active chronic pain condition that in the investigator's opinion is unrelated to migraine (e.g. chronic pelvic pain)

- Acute pain condition that in the investigator's opinion is unrelated to migraine (e.g. post-surgical pain)

- Unable to provide informed consent

- Less than 80% compliance with providing headache diary data during the run-in phase (i.e. provides data on less than 80% of days)

<u>Run in Phase (4 weeks)</u>
At this initial visit , whether in person or via telephone, participants will be screened for inclusion/exclusion and data on their demographics, headache characteristics, current and past treatments, and medical history will be collected. Those meeting criteria for further participation will be trained on how to use the headache diary. Patients will be instructed to keep a prospective headache diary for the next 4 weeks. We assume that up to 25% of individuals participating in the run-in phase will not meet the migraine day frequency inclusion criteria and/or diary compliance minimum and thus will not continue in this study.

<u>Baseline (first treatment) Visit</u>
Patients will return for a baseline visit after 4 weeks (i.e. 28 days +/- 3 days since start of run-in phase) of prospective headache diary collection. Diary compliance and eligibility for study inclusion will be assessed. Patients who still meet eligibility criteria will have measurement of vital signs and urine pregnancy testing will be conducted for women of childbearing potential. Levels of depression and anxiety will be measured using the Beck Depression Inventory and State-Trait Anxiety Inventory, respectively. Functional disability will be assessed with the Migraine Disability Assessment (MIDAS) and the Migraine Functional Impairment Questionnaire (MFIQ). Symptoms of cutaneous allodynia will be assessed using the Allodynia Symptom Checklist 12. Symptoms of cognitive dysfunction associated with migraine will be assessed using the Mig-Scog Questionnaire. (24, 25) Patients will undergo

quantitative sensory testing (QST) for determination of heat pain thresholds and the temperature that results in moderate intensity heat pain. (13, 26, 27) To assess cognitive function, patients will complete two attention tasks; a computer version of the n-back task and Trails A and B.

Case Report Forms

Case report forms include:

1) Inclusion and Exclusion Criteria
2) Contact Information
3) Demographics: birthdate, gender, race, ethnicity, handedness
4) Vital Signs
5) Urine Pregnancy Test Results (for women of childbearing potential)
6) Headache Characteristics: headache frequency, duration, location, quality, intensity; associated symptoms; aura; number of years with migraine; current preventive and acute therapies
7) Personal Medical History
8) Current Medications and Non-Medication Treatments
9) Prior Migraine Medications
10) Migraine Functional Impact Questionnaire (MFIQ)
11) Beck Depression Inventory (BDI)
12) State-Trait Anxiety Inventory (STAI)
13) Migraine Disability Assessment (MIDAS)
14) Allodynia Symptom Checklist 12 (ASC-12): ictal and interictal
15) Migraine Scog
16) N-back task
17) Trails A and B
18) Quantitative Sensory Testing Results
19) Two Week Follow-up Headache Characteristics
20) Four Week Follow-up Headache Characteristics
21) Eight Week Follow-up Headache Characteristics
22) Twelve Week Follow-up Headache Characteristics
23) Patient Global Impression of Change
24) Adverse Events
25) Headache Diary
26) 26 Connor-Davidson Resilience Scale 25 (CD-RISC-25)

The case report forms are included within Appendix 1.

Questionnaires	First Visit (start of run-in phase)	First Tx Visit	Two-Week Visit	Four-Week Visit (second tx)	Eight-Week Visit	Twelve-Week Visit
Contact Information	X					
Inclusion/Exclusion Criteria	X	X				
Demographics	X					
Headache Characteristics	X	X				
Follow-up Headache Characteristics			X	X	X	X
Current Medications and Other Treatments	X	X	X	X	X	X
Prior Migraine Treatments	X					
Medical History	X					
ASC-12 (ictal/interictal)		X	X	X	X	X
MFIQ		X	X	X	X	X
MIDAS		X				X
BDI		X	X	X	X	X
STAI		X	X	X	X	X
Mig-Scog		X	X	X	X	X
PGIC			X	X	X	X
CD-RISC-25		X	X	X	X	X

Adverse Events		X	X	X	X	X

Tx = treatment; ASC-12 = allodynia symptom checklist – 12; MFIQ = migraine functional impact questionnaire; MIDAS = migraine disability assessment; BDI = Beck Depression Inventory; STAI = state-trait anxiety inventory; PGIC = patient global impression of change

Pain Threshold Testing

QST for determining cutaneous heat pain thresholds has been used extensively in our lab. (13, 26, 27) A Medoc Pathway platform with a 30 mm x 30 mm thermode is used for testing. Heat pain thresholds are determined for the right and the left forearm and for the right and left forehead. The thermode is applied to the skin and fastened with a Velcro strap. The method-of-limits is used: thermode starts at 32 degrees Celsius and increases in temperature at a rate of 1 degree Celsius per second until the subject presses a button on the response unit, indicating that the sensation changed from heat to pain. Testing will be performed three times at each body site and the average of the three measurements will be considered that individuals heat pain threshold.

The temperature required to cause moderately intense heat pain will be determined by using the ramp and hold method. Moderately intense heat pain is defined by an individual rating their pain intensity between 4 and 7 using an 11 point scale in which zero indicates no pain and 10 indicates the most severe pain. Initially, subjects are stimulated for 7.5 seconds with a temperature equal to their heat pain threshold plus 1 degree Celsius. Individuals then rate the pain intensity. If pain intensity is rated below 4, the temperature is increased in 0.5 degree Celsius increments until rated between 4 and 7. Conversely, if the pain intensity is rated greater than 7, the stimulation temperature is decreased in 0.5 degree Celsius increments.

Imaging Protocol

Brain MRI will be performed on a Siemens 3T scanner at the Mayo Clinic. The MRI paradigm will include: 1) high-resolution T1-weighted imaging allowing for advanced structural analyses such as determining regional volumes, cortical thickness and surface area; 2) T2-weighted imaging to rule out pre-existing structural brain abnormalities (e.g. incidental findings); 3) Diffusion Tensor Imaging (DTI) used for assessing white matter integrity; 4) ten minutes of resting-state Blood Oxygen Level Dependent (BOLD) signal collection for resting state functional connectivity analyses; 5) event-related paradigm during which patients are exposed to cutaneous thermal stimuli causing moderately intense heat pain so that brain responses to pain can be measured; and 6) Arterial Spin Labeling (ASL) to assess cerebral blood flow.

N-Back Task

For purposes of test standardization and data interpretation, all subjects will complete the computer-based version of the n-back task on one of two MacBook laptops. The software for the n-back task will be downloaded on the laptops and subject task performance will be automatically calculated and summarized- thus eliminating testing bias.

Trails A and B

Subjects will complete the standardized worksheets of Trails A and B. On Trails A, subjects are asked to connect consecutive numbers from 1-25. On Trails B, subjects are asked to alternate between

connecting numbers and letters. (i.e., 1-A-2-B-3-C, and so forth) Both tests are measuring attention and processing speed. For both tests, number of errors are recorded as well as the number of seconds required to complete each task.

Treatment with Erenumab

Patients receive treatment with 140 mg of erenumab via subcutaneous injection during their baseline visit and then again 4 weeks later. Patients will either be taught how to self-inject by a qualified research team member and then will do so under research team observation or receive the injections administered by a qualified research team member. Injections will be administered in the abdomen (except for a two inch area right around the navel), thigh, or outer area of upper arm (if someone else is injecting the patient) according to patient preference and will consist of two consecutive 70 mg injections. The second injection will not be given in the same spot as 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.

Daily Headache Diary

A daily headache diary will be completed for the next 12 weeks to allow for assessment of changes in headache and migraine frequency. Headache diary data will be analyzed to classify patients as "responders" (50% or greater reduction in migraine day frequency between weeks 5-8 post first erenumab treatment compared to frequency during the run-in phase) or "non-responders" (less than 50% reduction in migraine day frequency during weeks 5-8 post first erenumab treatment compared to the frequency during the run-in phase). Since patient outcome will be measured at 8 weeks (opposed to 12 weeks like is done in the majority of clinical trials), depending upon patient outcomes other definitions of "response" and "non-response" could be used. Furthermore, correlations between changes in migraine frequency and imaging outcomes could also be assessed.

A migraine day will be defined as follows: any calendar day during which a person experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for at least 30 minutes, and meeting at least one of the following criteria (a and/or b):

a) At least 2 of the following pain features: unilateral, throbbing, moderate to severe, exacerbated with exercise/physical activity
b) At least 1 of the following associated symptoms: nausea and/or vomiting, photophobia and phonophobia

If the participant takes a migraine-specific medication (i.e. triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

Missing values may exist in headache dairy data due to various reasons such as subjects' missed recording, early withdrawal, or inadequate entries prohibiting evaluation of the end point (responder vs. non-responder). To impute the missing data and allow for evaluation of migraine frequency,

classic imputation methods commonly used in clinical trials will be adopted.(6) Specifically, for months with 20-27 days of dairy data, the values for missing entries will be imputed by prorating scores of 28-day post-treatment periods. That is, monthly migraine frequency can be calculated as the ratio of number of observed migraine days to number of observed days multiplied by 28. For months with less than 10 days of dairy data, monthly migraine frequency will be estimated by the substitution of the patient's previous 28-day period score, multiplied by the ratio of the mean for all patients in the same period to the mean for all patients in the previous period. For post-treatment periods with 10–19 days of diary data, scores will be estimated using a mean of both methods.

Follow up visits One through Four (see table 1): Four follow-up visits will be scheduled: at weeks 2, 4, 8 and 12 post-initial treatment with erenumab (week 2 = 14 days +/- 2 days since first visit; week 4 = 28 days +3 days since first visit; week 8 = 56 days +/- 3 days since first visit; week 12 = 84 days +/- 5 days since first visit). The early follow-up at 2 weeks will be utilized for repeat QST, brain imaging and cognitive testing so that data are available for investigating early markers/predictors of treatment response. A second treatment with erenumab will occur during the 4-week visit. Imaging, QST and neurocognitive testing will be repeated during the 8-week visit, allowing for determination of biomarkers for treatment response that might not have been found at the early time-point of 2 weeks and that can be correlated with clinical measures of treatment response (i.e. changes in migraine day frequency). The 12-week visit will allow for further assessment of safety and efficacy.

Acute Migraine Therapy: Patients will be allowed to use acute headache treatments including migraine-specific medication (e.g. triptans, ergotamine derivatives) and NSAIDs during the study.

Other Migraine Preventive Therapy: Patients will be allowed to use two or fewer migraine preventive therapies in addition to erenumab as long as the dose has been stable for at least 2 months before the start of the run-in phase. Changes to the dose of such treatments will not be allowed during this study unless necessary due to safety issues or lack of tolerability.

Imaging Data Plans

All imaging will be collected at Mayo Hospital on a 3-Tesla Siemens (Siemens MAGNETOM Skyra, Erlangen, Germany) scanner using a 20-channel head/neck coil. Structural analyses will utilize *FreeSurfer* 5.3 (http://surfer.nmr.mgh.harvard.edu) a commonly used brain segmentation software for measurements of 68 regional volumes, 68 measurements of cortical thickness, and 68 measurements of cortical surface area. The methodology for FreeSurfer is well-documented and established and includes skull stripping, automated Talairach transformation, segmentation of gray and white matter regions, intensity normalization, brain boundary tessellation, topology correction and deformation of surface structures.(28-32) Resting state (rs)-fMRI data will be analyzed using SPM 8

MRI Sequences

Siemens Skyra 3T MRI	Technical Details	Acquisition Time
T1 3D MPRAGE	FOV: 256x256 mm^2; Thickness: 1.25 mm; TR:2400 ms; TE:3.03 ms; Voxel size: 1.x1.x1.3 mm^3	5.35 min
T2 Turbo Spin Echo	FOV: 256x256 mm^2; Thickness: 4 mm; TR:6800 ms; TE:84 ms; Voxel size: 1.x1.x4 mm^3	3.08 min
DTI	FOV: 220x220 mm^2; Thickness: 4 mm; TR:5100 ms; TE:71 ms; Voxel size: 1.7x1.7x4 mm^3; 60 directions	5.33 min
Arterial Spin Labeling (ASL)	FOV: 64x62mm^2; Thickness: 5mm; TR:4600 ms; TE: 22 ms; Voxel Size: 1.7x1.7x5 mm^3	5.09 min
BOLD Resting-State	FOV: 256x256 mm^2; Thickness: 4 mm; TR:2500 ms; TE:27 ms; Voxel size: 4.x4.x4 mm^3	10.00 min
Event-Related fMRI	FOV: 256x256 mm^2; Thickness: 4 mm; TR:2500 ms; TE:27 ms; Voxel size: 4.x4.x4 mm^3	26.60 min
		Total: 55.45 min

(Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) and the toolbox DPARSF interfaced with MATLAB version 11.0 (MathWorks, Natick, Ma, USA).(33) Rs-fMRI data will be pre-processed using standard procedures including the following steps: slice-time correction, motion correction, re-alignment, skull and non-brain tissue removal, spatial smoothing, and alignment to an average Montreal Neurological Institute (MNI-305) template.(34, 35) Further post-processing steps will include band-pass filtering, as well as removal of variance related to head motion, white matter signal and cerebrospinal fluid signal. Functional measurements will be imported into SPSS 21.0 (SPSS Inc, Chicago, IL) for further calculations. A region-of-interest approach will be utilized for functional connectivity analyses. The functional connectivity of 33 regions which commonly participate in pain-processing will be analyzed. Event-related BOLD data will be analyzed using a whole-brain analysis, comparing BOLD amplitude during painful stimuli vs. no stimuli. All preprocessing and general linear model (GLM) estimation of brain activation patterns for the event-related portion of the fMRI will also be performed using SPM8, interfaced with Matlab. Functional images will be realigned to the mean volume in the series, motion-corrected, realigned to each individual's structural images, normalized to standard stereotaxic space (Montreal Neurological Institute template) and smoothed using a 5 mm full width half maximum Gaussian kernel. Brain regions activated in response to painful stimuli will be identified by generating contrast maps representing brain activations associated with painful stimuli preceded by auditory cue vs. auditory cue with no painful stimuli. The BOLD signal will be modeled for each of eight successive MR frames (20 seconds) following stimulus presentation, with no assumption made about the shape of the hemodynamic response function. These contrast maps are entered into a mixed effects analysis. A main effects analysis will identify brain regions activated in subjects and a two-sample analysis will identify regions differentially activated when comparing subject cohorts. Cluster threshold correction and multiple comparisons correction will be utilized. 18 major fiber tracts will be reconstructed from DTI data using an automated technique based upon global probabilistic tractography (TRACULA).(36) This software toolbox is available online (http://surfer.nmr.mgh.harvard.edu/) and uses anatomical priors (T1-weighted data) as input. The robustness of the TRACULA software algorithm has been validated in prior papers.(36, 37) For each of the 18 fibertracts, tract volume, path length, axial diffusivity, radial diffusivity, mean diffusivity, and fractional anisotropy will be calculated. Arterial Spin Labeling data will be analyzed using SPM 8 and the toolbox ASLtbx.(38) SPM 8 and ASLbtx are freely downloadable online and will be interfaced with MATLAB version 11.0. ASL data will be preprocessed using standard SPM preprocessing steps including orientation resetting, image reorienting, motion correction, and co-registration (of each subjects' T1-weighted image with the ASL images) and data smoothing. Subsequent data post-processing steps will be conducted using the ASLtbx toolbox. Statistical analyses will be conducted using a GLM design.

Quality control of structural and functional imaging data: Radiology technicians at Mayo Clinic are already expert with the scanning paradigm and are trained to quality-check images during the MRI. Immediately after imaging is completed, all scans will be checked for motion artifacts. If necessary, patients will be re-scanned on the sequence where excessive motion was detected to ensure proper image quality in each individual. All image post-processing will be conducted on a single Mac workstation running OSX Lion 10.7.5 software to avoid post-processing irregularities related to the use of multiple workstations. All structural brain segmentations and parcellations will be reviewed by a trained technician for data quality. DTI and rs-fMRI data are very sensitive to movement artifacts. Therefore, we will exclude patients that exceed 2 degrees rotational, and/or 2mm translational movement, which are well-recognized cut-off points for movement.(39, 40)

Sample Size

The total sample size of 50 patients accounts for the likely scenario in which up to 15% of patients will not have full datasets due to loss-to-follow-up or unusable MRI data (e.g. patient motion, abnormal brain MRIs). Based upon the results of the phase 2 and 3 trials of erenumab and the fact that this is an open-label study, we anticipate that approximately 50% of patients will be "responders" at 8 weeks. (6-8) Thus, we would have at least 21 responders and 21 non-responders for this analysis, a sample size that is adequate for the imaging and multivariate modeling aims of this study. Sample size was determined by calculating the number of subjects needed per group to detect a difference in pain induced BOLD signal of 0.1% pre-erenumab to post-erenumab, assuming a standard deviation of 0.1. Based on a type I error of .05, a sample size of 21 patients per group will give 88% power to detect pre-treatment to post-treatment differences for responders and non-responders. The use of % signal change as the measure for calculating effect size is the standard recommendation when determining sample size for fMRI studies.(41)

Desmond and Glover, in their paper entitled "Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses", used data from fMRI studies of cognitive function and somatosensory stimulation to estimate sample sizes needed for fMRI studies. [Desmond 2002] They concluded that for a threshold of 0.05, about 12 subjects are required to achieve 80% power at the single voxel level for typical activations. However, they state that at more realistic thresholds that approach those used after correcting for multiple comparisons, the number of subjects doubles (n=24) to maintain this level of power.

As Mumford and colleagues point out, the number of stimulations/events that are included in the fMRI paradigm must also be considered when calculating power – the more stimulations/events, the greater the power to detect a difference.(41)

Russo et. al. used a similar study design as the one we have proposed to investigate pain-induced activations in migraine pre- and post-external trigeminal neurostimulation. [Russo 2017] In the Russo study there was a pre- to post-treatment change in pain-induced activation of the anterior cingulate of approximately 0.2% with a standard deviation of approximately 0.1%. Given this effect size, a sample size of 16 individuals (81% of whom were responders) was adequate to demonstrate significant pre- to post-treatment changes in pain-induced activation of the anterior cingulate cortex.

With limited available data to ensure that our effect size will be as large as 0.2%, we are more comfortable powering the analysis for an effect size half of that found in Russo et. al. (i.e. 0.1%).(11) The resultant sample size is consistent with that recommended by Desmond and Glover and considers the impact of the number of painful stimulations as recommended by Mumford.(41, 42)

Subject Recruitment and Screening

Subjects will be recruited from the Mayo Clinic Arizona Headache and Neurology clinics, from the clinical practices of colleagues practicing in the Phoenix region, and via posting of IRB-approved recruitment materials.

Subject Compensation

Subjects will be compensated $70 per research visit and $30 per month during which they are at least 80% compliant with the headache diary (i.e. provide data on at least 80% of days in a 4 week period).

Informed Consent

Informed consent procedures will be performed according to the requirements and recommendations of the Mayo Clinic Institutional Review Board. Written informed consent will be obtained from all subjects prior to their participation in this research. The informed consent process will be based upon principles discussed in the Declaration of Helsinki 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 prior and following consent. All consent forms will require IRB approval prior to their use. Patients will always have the right and will be informed of their right to withdraw from the study at any time. De-identified data collected until the time of withdrawal will be included in further analyses. 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. Any member of the research team who obtains informed consent from a subject will need to be approved by the Institutional Review Board. The informed consent process will occur in a location that is approved by the Institutional Review Board. Consent documents will be stored for a minimum of 3 years after conclusion of the study. The study participant will retain a copy of their signed consent document.

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 (e.g., 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 (8 weeks after the last dose of investigational product) are reported using the Adverse Event case report form. The Adverse Event case report form is included within the Appendix of this protocol.

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)
- intensity
- outcome
- action taken
- assessment of relatedness to investigational product

Assessment of whether the adverse event is possibly related to the investigational product 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 Adverse Event case report form will be completed by the member of the research team that receives the information from the participant about the adverse event. The Principal Investigator will always be responsible for initially and dating the form, indicating that the Principal Investigator has reviewed the adverse event with the research team member, determining the relationship of the adverse event to the study, and determining if the adverse event meets criteria for a serious adverse event.

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 (8 weeks after the last dose of investigational product) are recorded in the subject's record and to the local Institutional Review Board according to that Board's policy.

Reporting of adverse events to Amgen will occur in accordance with the "Safety Data Exchange Requirements" as provided by Amgen. These requirements dictate the need for and timing of reporting adverse events to Amgen. A copy of the "Safety Data Exchange Requirements" has been included within the Appendix of this protocol.

Subject Risks and Benefits

Possible Benefits:
As this is an open-label study, all participants will receive treatment with erenumab. It is likely that many patients will have improvements in their migraine patterns following treatment with erenumab, as has been demonstrated in the phase II and III clinical trials and by the US Food and Drug Administration approval.

Possible Risks:

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. 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 AIMOVIG 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 the 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.

Hypersensitivity reactions including rash and swelling/edema have been reported with erenumab in postmarketing experience.

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.

Protection Against Risks:

Individuals who are known to be pregnant or lactating will be excluded from study participation. Women of childbearing potential who are not known to be pregnant will have urine pregnancy testing before the 4 week run-in phase and prior to each of the two erenumab treatments. Women found to be pregnant will not receive any additional treatments with erenumab. Women of childbearing potential will be required to use a reliable form of contraception from the start of the run-in phase through 16 weeks after the last dose of erenumab (details provided in 'eligibility criteria' section of this protocol).

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. Data will be entered into REDCap. (43) REDCap is a secure web-based application used for designing and managing clinical research databases. REDCap's design addresses the National Center for Research Resources statement that the future of biomedical research will involve collaborations amongst many scientists in different locations linked by high-speed computer networks thus enabling data submission, data sharing and data analyses. (43, 44) REDCap is accessible to study investigators via any computer with a Web browser. Once data are entered into data collection forms, data automatically upload to the registry data file. The registry complies with all HIPAA regulations, requires a log-in ID and password, and users only have access to specific functions (e.g. view data, add data, change data, etc.) once granted rights for those specific functions. Data can be exported into numerous formats utilized by several frequently used statistical packages including SPSS, SAS, R, Excel, Stata and others.

<u>Subject Retention</u>

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. All research visits will be scheduled at the time of enrollment. Subjects will be contacted with reminders prior to each research appointment.

Diary compliance will be monitored on a daily basis. Subjects will be contacted immediately if non-compliance is observed. Individuals who have diary compliance less than 80% during the run-in phase will be withdrawn from the study.

<u>Analysis Plans</u>

Specific Aim #1 (i.e. identify changes in brain structure and function that correlate with response to erenumab): Pre-treatment and post-treatment MRI data will be used for within and between subject

comparisons. Within subject analyses will compare baseline brain activation and perfusion patterns and functional connectivity patterns pre-treatment to post-treatment. Between subject group analyses will compare post-treatment MRI data in erenumab responders to non-responders.

Similar comparisons will be made for pre- and post-treatment pain thresholds (i.e. results of quantitative sensory testing) and cognitive testing.

So as to help with the interpretation of differences between responders and non-responders, MRI data from erenumab-treated patients will be compared to healthy non-migraine control data that we have already collected during the conduction of previous studies, when available (although we have plenty of data for the majority of analyses, we have limited ASL data and no n-back data from healthy controls). Differences in brain structure and function of migraine patients prior to erenumab treatment compared to healthy controls will be identified. Results of this analysis will determine alterations of brain structure and functions in migraine patients compared to healthy controls. Areas where migraine patients show altered structure and function will be used as regions of interest (ROIs) to assess the longitudinal, within-group changes of erenumab responders and non-responders.

Although multiple analyses are planned using functional, structural, and perfusion data, the primary analysis for specific aim #1 will be the comparison of pre-treatment pain-induced regional activation strength vs. post-treatment pain-induced regional activation strength in erenumab responders and separately in erenumab non-responders.

Post-treatment changes in other measures of brain function as well as measures of brain perfusion, brain structure, cutaneous pain thresholds and cognitive function in those responding to erenumab and in those not responding will be explored.

Two–tailed T-Tests or Mann-Whitney U tests will be used to perform group comparisons on demographic and cognitive measures and on pain threshold data. Neuroimaging data will be analyzed using general linear model designs. Within-group changes on cognitive measures, sensory testing and neuroimaging data will be assessed by applying a general linear mixed model design.

Specific Aim #2 (i.e. Develop models to predict which patients will respond to erenumab): Pre-treatment scans will be used to identify MRI predictors of erenumab response. Multivariate machine-learning modeling of brain structural and functional data will be utilized for developing the predictive model. Because there are many imaging features available, but only a limited set of patients for this analysis, principal components analysis (PCA) will be performed on features collected from each imaging type to reduce the dimensionality of the data. The principal components (PCs) that result from PCA are linear combinations of the original imaging features, and can consolidate the information from the original features in such a way that only a few PCs are needed to explain most of the data variance. PCA will be performed separately on features from each imaging type to enhance clinical interpretability of PCs chosen for the predictive model.

To maximize the prediction accuracy, we will employ an ensemble learning approach by including a number of contemporary and complementary machine learning algorithms for building the predictive model, including Linear Discriminant Analysis (LDA), Quadratic Discriminant Analysis (QDA), Support Vector Machines (SVM), and Decision Tree (DT). Integrating these algorithms with Particle Swarm

Optimization (PSO)-based feature selection, we will identify the subset of features (PCs) that maximizes cross-validated accuracy of predicting responders and non-responders. Feature selection is a key step to avoid overfitting when building a predictive model with limited samples. PSO is a bio-inspired optimization algorithm that mimics the collective and collaborative behavior of social swarms in nature, e.g., colonies, honeybees, and bird flocks, in finding the optimal feature subset, and has been shown to outperform conventional feature selection algorithms in numerous recent publications.

Additionally, noting that this study will collect both widely accessible imaging data such as that derived from T1-weighted sequences as well as less accessible types such as pain-induced functional activations, we aim to determine how widely useable our predictive model is in clinical practice. To achieve this goal, we will first limit our PSO-based feature selection to select only PCs derived from structural measures of T1-weighted sequences. Then we will compare the accuracy to that of another analysis allowed to select resting state functional connectivity data, followed by selection of additional PCs from more advanced imaging data. This result will help determine how much value is added when using advanced imaging data in predicting treatment response; and if advanced imaging is not available in a clinic, how good the predictive accuracy can be.

Patient characteristics, cognitive function, and sensory thresholds can also be included in predictive models.

Safety Analysis: The proportion of subjects experiencing adverse events, the nature of the adverse events, as well as severity and relationship of the adverse events to the study will be reported using descriptive statistics. The proportion of subjects with adverse events that led to withdrawal from the study will also be reported. All subjects who received at least one dose of erenumab will be included in the safety analysis.

Protocol Maintenance

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

Study Registration

The study will be submitted to clinicaltrials.gov.

Appendix – Case Report Forms

Contact Information

Name: _____ _____
(First) (Last)

Home: (_____) _____-_____ Work: (_____) _____-_____

Mobile: (_____) _____-_____ Email: _____

Address:

_____ Unit/Apt#_____

(Street)

City_____ State_____ Zip_____

Eligibility Criteria

Inclusion Criteria (all must by "yes")

- 18-65 years of age Yes No
- Episodic or Chronic Migraine Yes No
- 6-25 migraine days per month Yes No
- Migraine started at least 12 months ago Yes No

Exclusion Criteria (all must be "no")

- Older than 50 years of age at migraine onset Yes No
- History of cluster headache or hemiplegic migraine Yes No
- Continuous headache Yes No
- Opioid or butalbital meds on 6 or more days per month Yes No
- History of major psychiatric disorder Yes No
- History of medical condition that contraindicates research participation Yes No
- No preventive therapeutic response to 4 or more medication classes Yes No
- Concomitant use of 3 or more meds for migraine prevention Yes No
- Botulinum toxin in head or neck within 4 months Yes No
- Ergotamines, steroids, or triptans for migraine prevention within 2 months Yes No
- Procedures for migraine prevention within 2 months Yes No

- Investigational meds or devices within 90 days Yes No
- History of MI, stroke, TIA, unstable angina, CABG or other revascularization Procedure within 12 months Yes No
- Contraindications to MRI Yes No

Exclusion Criteria (cont.)

- Factors that reduce MR image quality Yes No
- Sensory disorders that affect sensory testing Yes No
- Pregnancy Yes No
- Lactation Yes No
- Not using reliable contraception (if woman of childbearing potential) Yes No N/A
- Currently receiving treatment in another study Yes No
- Has received CGRP monoclonal antibody within prior 4 months Yes No
- Active chronic pain condition Yes No
- Acute pain condition Yes No
- Unable to provide informed consent Yes No
- Less than 80% compliant with headache diary Yes No

Demographics

DOB: ___ ___ / ___ ___ / ___ ___
Month Day Year

Current age (years): _____

Gender (circle one): 1 = Man 2 = Woman 3 = Other

Sex at Birth (circle one): 1 = Male 2 = Female

Race (circle all that apply):

1 = American Indian/Alaska Native 2 = Asian

3 = Black/African American 4 = Native Hawaiian/Other Pacific Islander

5 = White/Caucasian 6 = Other _____

Ethnicity: 1 = Hispanic 2 = Non-Hispanic

Handedness: 1 = Right Handed 2 = Left Handed

Vital Signs

Heart Rate: _____ beats per minute

Blood Pressure: _____ /_____ mmHg

Respiratory Rate: _____ breaths per minute

Temperature (oral): _____ °F

Urine Pregnancy Test

Result (circle one): Positive Negative N/A

Headache Characteristics (structured interview)

How many days per month (28 days) with headache of any kind/severity: _____/ 28 days

How many days per month (28 days) with complete headache freedom: _____/ 28 days

How long do headaches last if untreated/inadequately treated: hours

How long do headaches last if successfully treated: hours

Where are they usually located (circle all that apply):

Right Left Front Back Side

Unilateral location: Yes No

Quality (circle all that apply):

Pulsating/Throbbing Pressure/Aching Stabbing Burning

Intensity:

Mild Moderate Severe

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

Headaches worse with physical activity: Yes No

Headache worse with mental activity: Yes No

Nausea: Yes No

Vomiting: Yes No

Sensitivity to light: Yes No

Sensitivity to sound: Yes No

Conjunctival injection: Yes No

Tearing: Yes No

Nasal congestion/rhinorrhea: Yes No

Eyelid drooping: Yes No

Auras with headaches: Yes No

- Visual: Yes No
- Sensory: Yes No
- Motor: Yes No
- Dysphasia: Yes No
- Other: Yes No

Percentage of headaches you experience auras: _____

When was your first headache (month and year): _____

Family history of migraine: Yes No
If yes, who:

<u>Medications</u>

Currently taking medications to prevent headaches: Yes No

If yes, list medications:

_____	_____
_____	_____
_____	_____
_____	_____

Days per month (28 days) taking abortive medications: _____ days

Medication Name	Days/month taking
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Personal Medical History

Current Medical Conditions

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

11. _____

12. _____

13. _____

14. _____

Past Medical Conditions/ Surgeries

1. _____

2. _____

3. _____

4. _____

5. _____

6. _____

7. _____

8. _____

9. _____

10. _____

11. _____

12. _____

13. _____

14. _____

Current Medications and Other Treatments

	Medication/Treatment Name	Dose	Frequency	Start Date	Stop Date
1.	_____	_____	_____	_____	_____
2.	_____	_____	_____	_____	_____
3.	_____	_____	_____	_____	_____
4.	_____	_____	_____	_____	_____
5.	_____	_____	_____	_____	_____
6.	_____	_____	_____	_____	_____
7.	_____	_____	_____	_____	_____
8.	_____	_____	_____	_____	_____
9.	_____	_____	_____	_____	_____
10.	_____	_____	_____	_____	_____
11.	_____	_____	_____	_____	_____

12. _____ _____ _____ _____ _____

13. _____ _____ _____ _____ _____

14. _____ _____ _____ _____ _____

Prior Migraine Treatments

Medication/Treatment Name	Dose	Frequency	Months of Use
1. _____	_____	_____	_____
2. _____	_____	_____	_____
3. _____	_____	_____	_____
4. _____	_____	_____	_____
5. _____	_____	_____	_____
6. _____	_____	_____	_____
7. _____	_____	_____	_____
8. _____	_____	_____	_____
9. _____	_____	_____	_____
10. _____	_____	_____	_____

11. _____ _____ _____ _____

12. _____ _____ _____ _____

13. _____ _____ _____ _____

14. _____ _____ _____ _____

Allodynia Symptom Checklist 12 – Ictal

How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage in each of the following?

	Does not apply to me	Never	Rarely	Less than half the time	Half the time or more
Combing your hair					
Pulling your hair back (e.g., ponytail)					
Shaving your face					
Wearing eyeglasses					
Wearing contact lenses					
Wearing a necklace					
Wearing earrings					
Wearing tight clothing					
Taking a shower (when shower water hits your face)					
Resting your face or head on a pillow					
Exposure to heat					

(e.g., cooking, washing your face with hot water)					
Exposure to cold (e.g., using an ice pack, washing your face with cold water)					

Allodynia Symptom Checklist 12 – Interictal

How often do you experience increased pain or an unpleasant sensation on your skin <u>when you do not have a severe headache</u> when you engage in each of the following?

	Does not apply to me	**Never**	**Rarely**	**Less than half the time**	**Half the time or more**
Combing your hair					
Pulling your hair back (e.g., ponytail)					
Shaving your face					
Wearing eyeglasses					
Wearing contact lenses					
Wearing a necklace					
Wearing earrings					
Wearing tight clothing					
Taking a shower (when shower water hits your face)					
Resting your face or head on a pillow					
Exposure to heat					

(e.g., cooking, washing your face with hot water)					
Exposure to cold (e.g., using an ice pack, washing your face with cold water)					

Beck Depression Inventory

Instructions: Choose one statement from among the group of four statements in each question that best describes how you have been feeling during the past few days. Circle the number beside your choice.

1) 0 = I do not feel sad.
1 = I feel sad.
2 = I am sad all the time and I can't snap out of it.
3 = I am so sad or unhappy that I can't stand it.

2) 0 = I am not particularly discouraged about the future.
1 = I feel discouraged about the future.
2 = I feel I have nothing to look forward to.
3 = I feel that the future is hopeless and that things cannot improve.

3) 0 = I do not feel like a failure.
1 = I feel I have failed more than the average person.
2 = As I look back on my life, all I can see is a lot of failure.
3 = I feel I am a complete failure as a person.

4) 0 = I get as much satisfaction out of things as I used to.
1 = I don't enjoy things the way I used to.
2 = I don't get any real satisfaction out of anything anymore.
3 = I am dissatisfied or bored by everything.

5) 0 = I don't feel particularly guilty.
1 = I feel guilty a good part of the time.
2 = I feel quite guilty most of the time.
3 = I feel guilty all of the time.

6) 0 = I don't feel I am being punished.
1 = I feel I may be punished.
2 = I expect to be punished.

3 = I feel I am being punished.

7) 0 = I don't feel disappointed in myself.
1 = I am disappointed in myself.
2 = I am disgusted with myself.
3 = I hate myself.

8) 0 = I don't feel I am any worse than anybody else.
1 = I am critical of myself for my weaknesses or mistakes.
2 = I blame myself all the time for my faults.
3 = I blame myself for everything bad that happens.

9) 0 = I don't have any thoughts of killing myself.
1 = I have thoughts of killing myself, but would not carry them out.
2 = I would like to kill myself.
3 = I would kill myself if I had the chance.

10) 0 = I don't cry any more than usual.
1 = I cry more now than I used to.
2 = I cry all the time now.
3 = I used to be able to cry, but now I can't cry even though I want to.

11) 0 = I am no more irritated by things than I ever am.
1 = I am slightly more irritated now than usual.
2 = I am quite annoyed or irritated a good deal of the time.
3 = I feel irritated all the time now.

12) 0 = I have not lost interest in other people.
1 = I am less interested in people than I used to be.
2 = I have lost most of my interest in other people.
3 = I have lost all of my interest in other people.

13) 0 = I make decisions about as well as I ever could.
1 = I put off making decisions more than I used to.
2 = I have greater difficulty in making decisions than before.
3 = I can't make decisions at all anymore.

14) 0 = I don't feel that I look any worse than I used to.
1 = I am worried that I am looking old or unattractive.
2 = I feel that there are permanent changes in my appearance that make me look unattractive.
3 = I believe that I look ugly.

15) 0 = I can work about as well as before.
1 = It takes an extra effort to get started at doing something.
2 = I have to push myself very hard to do anything.

3 = I can't do any work at all.

16) 0 = I can sleep as well as usual.
1 = I don't sleep as well as I used to.
2 = I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 = I wake up several hours earlier than I used to and cannot get back to sleep.

17) 0 = I don't get more tired than usual.
1 = I get tired more easily than I used to.
2 = I get tired from doing almost anything.
3 = I am too tired to do anything.

18) 0 = My appetite is no worse than usual.
1 = My appetite is not as good as it used to be.
2 = My appetite is much worse now.
3 = I have no appetite at all anymore.

19) 0 = I haven't lost much weight, if any, lately.
1 = I have lost more than five pounds.
2 = I have lost more than ten pounds.
3 = I have lost more than fifteen pounds.
(Score 0 if you have been purposely trying to lose weight.)

20) 0 = I am no more worried about my health than usual.
1 = I am worried about physical problems such as aches and pains, or upset stomach, or constipation.
2 = I am very worried about physical problems, and it's hard to think of much else.
3 = I am so worried about my physical problems that I cannot think about anything else.

21) 0 = I have not noticed any recent change in my interest in sex.
1 = I am less interested in sex than I used to be.
2 = I am much less interested in sex now.
3 = I have lost interest in sex completely.

State Anxiety

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now that is, ***at this moment***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4

18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Trait Anxiety

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you ***generally*** feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Not at all	Somewhat	Moderately so	Very much so
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4

37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Migraine Disability Assessment (MIDAS)

*Instructions: Please answer the following questions about all your headaches over the last **3 months**. Write your answer in the box next to each question. Write zero if you did not do the activity in the last **3 months**.*

1) On how many days in the last 3 months did you miss work or school because of your headaches? (If you do not attend work or school enter zero in the box.)	___ ___ Days
2) How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school. If you do not attend school or work enter zero in the box.)	___ ___ Days
3) On how many days in the last 3 months did you not do household work because of your headaches?	___ ___ Days
4) How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days counted in question 3, where you did not do household work.)	___ ___ Days
5) On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?	___ ___ Days
(Questions 1-5) Total	___ ___
A) On how many days in the last 3 months did you have a headache? (If headache lasted more than 1 day, count each day.)	___ ___ Days
B) On a scale of 0-10, on average, how painful were these headaches? (Where 0=no pain at all, and 10=pain which is as bad as it can be.)	___ ___ 0-10

Migraine Functional Impact Questionnaire (MFIQ)

- The following questions are about your ability to function in the **past 7 days**.
- We would like to understand how a **migraine** affects your **day-to-day activities**.
- Symptoms of migraine can include headache pain, nausea, vomiting, or sensitivity to light or noise.
- We want you to think about the symptoms that **you** experience and how they impact **your** day-to-day activities.
- Please answer all questions by selecting the one option that best describes your experience.

1. In the past 7 days, how often did a migraine limit your ability to **move your head**?

   Never
   Rarely
   Sometimes
   Often
   Always

2. In the past 7 days, how often did a migraine limit your ability to **move your body**? (For example, standing up, walking, bending)

   Never
   Rarely
   Sometimes
   Often
   Always

3. In the past 7 days, how often did a migraine **limit your usual activities that required physical effort**?

   Does not apply; do not usually do activities that require physical effort
   Never
   Rarely

Sometimes
Often
Always

4. In the past 7 days, how often did you **feel that you needed to rest or lie down** during the day because of your migraine?

   Never
   Rarely
   Sometimes
   Often
   Always

5. In the past 7 days, how often did you **feel too tired to do things** because of your migraine?

   Never
   Rarely
   Sometimes
   Often
   Always

6. In the past 7 days, how difficult was it **to get yourself ready for the day**?

   Not difficult
   A little difficult
   Moderately difficult
   Very difficult
   Extremely difficult

7. In the past 7 days, how often did you have difficulty completing **specific personal grooming activities**? (For example, brushing hair, shaving, applying make-up)

   Never
   Rarely
   Sometimes
   Often
   Always

8. In the past 7 days, how often did a migraine **affect your daily routine or schedule**?

   Never
   Rarely
   Sometimes
   Often
   Always

9. In the past 7 days, how often did you have **to change your plans** because of a migraine?

   Never
   Rarely
   Sometimes
   Often
   Always

10. In the past 7 days, how difficult was it **to do your usual chores at home**?

    Not difficult
    A little difficult
    Moderately difficult
    Very difficult
    Extremely difficult

11. In the past 7 days, how much did a migraine limit your ability **to do your usual chores outside the home**? (For example, shopping or running errands)

    Not at all
    Slightly
    Moderately
    Very Much
    Extremely

12. In the past 7 days, how much did a migraine affect your **ability to do your usual work or study-related activities**?

    Does not apply; I have not worked* or studied at all during the past week for reasons unrelated to the disorder. *Work includes paid or unpaid work.
    Not at all
    Slightly
    Moderately

Very Much
Extremely

13. In the past 7 days, how much did a migraine affect your **ability to take care of your family**?

    Does not apply; I do not live with family.
    Not at all
    Slightly
    Moderately
    Very Much
    Extremely

14. In the past 7 days, how difficult was it for you **to do activities that required you to concentrate**?

    Not difficult
    A little difficult
    Moderately difficult
    Very difficult
    Extremely difficult

15. In the past 7 days, how difficult was it **to do activities in the presence of loud noises, strong smells, or bright lights**?

    Does not apply; I do not need to do activities in the presence of loud noises, strong smells, or bright lights.
    Not difficult
    A little difficult
    Moderately difficult
    Very difficult
    Extremely difficult

16. In the past 7 days, how much did a migraine **affect your usual activities**?

    Not at all
    Slightly
    Moderately
    Very Much
    Extremely

17. In the past 7 days, how much did a migraine affect your **usual social interactions**? (For example, with family, friends, or coworkers)

    Not at all
    Slightly

Moderately
Very Much
Extremely

18. In the past 7 days, how often did you **avoid being around other people** because of a migraine?

    Never
    Rarely
    Sometimes
    Often
    Always

19. In the past 7 days, how much did you have **to limit your social activities** because of a migraine?

    Not at all
    Slightly
    Moderately
    Very Much
    Extremely

20. In the past 7 days, how often did a migraine **interfere with your relationship** with your partner or spouse?

    Does not apply; do not have a partner or spouse
    Never
    Rarely
    Sometimes
    Often
    Always

21. In the past 7 days, how often did a migraine **limit your usual leisure activities**?

    Never
    Rarely
    Sometimes

Often
Always

22. In the past 7 days, how **frustrated** did you feel about being **unable to do what you needed** to do because of a migraine?

    Not at all
    Slightly
    Moderately
    Very Much
    Extremely

23. In the past 7 days, how often did you **worry about your migraines**?

    Never
    Rarely
    Sometimes
    Often
    Always

24. In the past 7 days, how often did you **feel like a burden on others** because of a migraine?

    Never
    Rarely
    Sometimes
    Often
    Always

25. In the past 7 days, how often did you feel you **lacked control of your life** because of a migraine?

    Never
    Rarely
    Sometimes
    Often
    Always

26. In the past 7 days, how **disappointed** did you feel about having a migraine?

    Not at all
    Slightly
    Moderately
    Very Much
    Extremely

Migraine Scog

In this section we want to understand whether your headaches affect your cognitive abilities while you experience a headache. We will provide you with a number of statements describing difficulties that you may face during a headache. We will ask you to indicate to what extent you experience these difficulties. The information you provide us with will inform how we approach your care and how well can deliver care to you.

During your Headaches…

Do you feel confused?
2: Often
1: Sometimes
0: No

Do you have trouble performing tasks at your normal speed?
2: Often
1: Sometimes
0: No

Is it difficult to follow a route or path (driving or walking)?
2: Often
1: Sometimes
0: No

Do you have trouble thinking?
2: Often
1: Sometimes
0: No

Do you have trouble maintaining a line of thought?
2: Often
1: Sometimes
0: No

Is it difficult to understand words spoken to you?
2: Often
1: Sometimes
0: No

Is it difficult to organize a sentence or a conversation?
2: Often
1: Sometimes
0: No

Do you have trouble speaking out other people's names?
2: Often
1: Sometimes
0: No

Is it difficult to remember the correct name of objects?
2: Often
1: Sometimes
0: No

N-Back Task

	Trial 1	Trial2	Trial 3
Sum of Hits:	_____	_____	_____
Sum of False Alarms:	_____	_____	_____
Sum of Misses:	_____	_____	_____
Sum of Correct Rejections:	_____	_____	_____

Sum of total Hits across all Trials: _____

Sum of total False Alarms across all Trials: _____

Proportion of (total Hits – total FA) /number of Trials: _____

Trails A and B

Trails A: _____seconds Trails A: _____number of errors

Trails B: _____seconds Trails B: _____number of errors

Quantitative Sensory Testing

Pain or headache medications in the last 48 hours: Yes No

Do you currently have a headache/migraine: Yes No

If yes, Current Pain Level: _____/ 10

If no, on what day did your last headache/migraine end (month/day/year): _____/_____/_____

At what time: _____ AM/PM (if went to sleep with it, list time woke up without)

Instructions:

As part of the research in which you are involved, we are going to test how sensitive your skin is to heat. The testing will use a piece of plastic, called a thermode. We will place the thermode at 4 different locations – each forearm and at 2 locations on the forehead. The thermode will start at about skin temperature, and then get warmer or hot. There are safety limits on the temperature so that you are not injured or burned. Please concentrate on the intensity of the heat that you feel with each test. We will give you a computer mouse which you will use to stop the heating process. With each test, the thermode will get warm and then hot. We want you to press the mouse button the moment that you begin to feel pain. The thermode will then cool off. We will do this three times at each body location. Remember, press the button the moment you begin to feel pain.

LIMITS				
Location	**Limit 1**	**Limit 2**	**Limit 3**	**Average**
Left Forehead				
Right Forehead				

Right Forearm				
Left Forearm				

THERMAL STIMULATION

Painful Stimulus

For the next test we will leave the thermode on your left forearm. The thermode will start at about skin temperature and then the temperature will gradually increase. Once it reaches a pre-programmed temperature it will hold at that temperature for 7.5 seconds and then you will hear a bell. At that time we will ask you to rate your pain on a scale of 0 to 10 (0 means no pain and 10 is the worst pain imaginable).

Begin with the average of the left forearm limits test +1°.

- ***If subject rates their pain level between 4-7 continue with the non-painful stimulus.***
- ***If subject rates their pain level as 8 or higher decrease temperature by 0.5° and repeat Ramp & Hold (continue to decrease temperature by 0.5° until subject rates their pain level between 4-7).***
- ***If subject rates their pain level as 3 or lower increase temperature by 0.5° and repeat Ramp & Hold (continue to increase temperature by 0.5° until subject rates their pain level between 4-7).***

RAMP & HOLD	
Temp.	**Rating (0-10)**

Non-painful Stimulus

For the next test we will continue with the thermode on your left forearm. The thermode will start at about skin temperature and then the temperature will gradually increase. Once it reaches a pre-programmed temperature it will hold at that temperature for 7.5 seconds and then you will hear a bell. At that time we will ask if that temperature caused you any pain.

Begin with the average of the left forearm limits test -2°.

- ***If subject answers no continue with MRI instructions..***

- ***If subject answers yes (that it caused pain) decrease temperature by 0.5° and repeat Ramp & Hold (continue to decrease temperature by 0.5° until subject answers no (it did not cause pain)).***

RAMP & HOLD	
Temp.	*Pain (yes/no)*

MRI Stimulations

During the MRI the thermode will be placed on your left forearm. For part of the MRI we will be running 3 different tests during which the thermode will heat up. Each test will last approximately 9 minutes. During each of these tests you will hear a bell and then the thermode temperature may change to a pre-programmed temperature. If so, it will hold at that temperature for 7.5 seconds and then return to baseline. This will be repeated 9 times during each test. You do not need to respond in any way during the tests.

MRI – RAMP & HOLD – temps programmed		
Painful	**Non-painful**	**No stimulus**

BOLD STIMULATION #1									
Sequence									
Temp.									
Secs before test									
MRI Frame									

BOLD STIMULATION #2									
Sequence									
Temp.									
Secs before test									
MRI Frame									

BOLD STIMULATION #3									
Sequence									
Temp.									

Secs before test									
MRI Frame									

Two Week Follow-up Headache Characteristics

How many days since baseline visit with headache of any kind/severity:

How many days since baseline visit with complete headache freedom:

How long do headaches last if untreated/inadequately treated: hours

How long do headaches last if successfully treated: hours

Intensity:

Mild Moderate Severe

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

Four Week Follow-up Headache Characteristics

How many days during last month (28 days) with headache of any kind/severity:

How many days during last month (28 days) with complete headache freedom:

How long do headaches last if untreated/inadequately treated: hours

How long do headaches last if successfully treated: hours

Intensity:

Mild Moderate Severe

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

Eight Week Follow-up Headache Characteristics

How many days during last month (28 days) with headache of any kind/severity:

How many days during last month (28 days) with complete headache freedom:

How long do headaches last if untreated/inadequately treated: hours

How long do headaches last if successfully treated: hours

Intensity:

Mild Moderate Severe

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

Twelve Week Follow-up Headache Characteristics

How many days during last month (28 days) with headache of any kind/severity:

How many days during last month (28 days) with complete headache freedom:

How long do headaches last if untreated/inadequately treated: hours

How long do headaches last if successfully treated: hours

Intensity:

Mild Moderate Severe

Average on 0 (no pain) to 10 (most severe pain) scale: /10

Maximum on 0 (no pain) to 10 (most severe pain) scale: /10

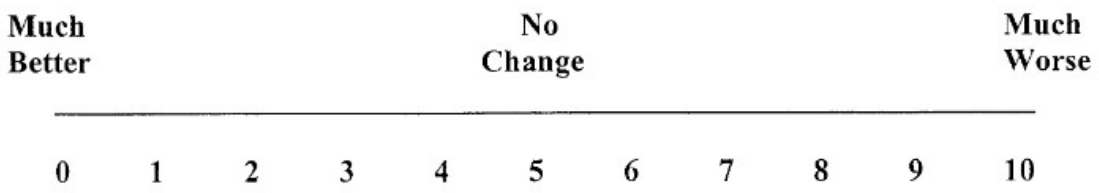
Patient Global Impression of Change

Since your first treatment, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE related to your painful condition?

Select One:

1. No change (or condition has got worse)
2. Almost the same, hardly any change at all
3. A little better, but no noticeable change
4. Somewhat better, but the change has not made any real difference
5. Moderately better, and a slight but noticeable change
6. Better, and a definite improvement that has made a real and worthwhile difference
7. A great deal better, and a considerable improvement that has made all the difference

In a similar way, please circle the number below that matches your degree of change since your first treatment:



Adverse Events

Adverse Event Flowsheet

Subject ID:
Protocol:
IRB #:

Adverse Event	**Date of Onset**	**Date of Resolution**	**Intensity** 1. Mild 2. Moderate 3. Severe 4. N/A	**Outcome** 1. Resolved 2. Resolved with sequalae 3. Unresolved 4. Death	**Action Taken** 1. None 2. Dose held 3. Dose reduced 4. Dose Increased 5. Dose incomplete 6. Dose delayed 7. Drug or dose discontinued permanently 8. Con Meds Given 9. Con Procedure 10. Hospitalized 11. Discontinued from study	**Investigator Initial and Date**	**Relationship to Study** 1. Unrelated 2. Unlikely 3. Possibly 4. Probably 5. Definitely	**Caused Study Withdrawal** Yes No	**SAE** Yes No

Investigator Signature and Date:_____

Page # _____

Headache Diary

For what day are you recording information (month/day/year)? ____ / ____ / ____

What time is it right now: _____ AM PM

Did you have a headache today (circle one)? Yes No

If yes:

What day and time did the headache begin:

Date (month/day/year): ____ / ____ / ____

Time: _____ AM / PM (circle one)

Do you still have the headache? Yes No

If no, what time did the headache end? _____ AM / PM (circle one)

What was the peak headache severity (circle one): Mild Moderate Severe

If pain reached moderate or severe intensity, how long did it remain at that intensity?

_____ minutes or hours (circle one)

Headache Location (circle one): One side of head only Both sides of head

During the headache:

Was the headache "throbbing" in quality? Yes No

Did lights bother you more than usual? Yes No

Did sounds bother you more than usual? Yes No

Were you nauseated? Yes No

Did you vomit? Yes No

Did routine physical activity (e.g. walking, climbing stairs) make your headache worse?

Yes No

How disabling was the headache/migraine (choose one):

Able to function normally Function somewhat reduced

Function severely reduced Not able to function at all (e.g. bedbound)

Did you take a medication(s) to abort this headache? Yes No

If yes, which medication(s)?

Medication Name	Number of Times Taken Today
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

In the past 24 hours, overall, how difficult was it to do your usual activities?

□ Not difficult
□ A little difficult
□ Moderately difficult
□ Very difficult
□ Extremely difficult

In the past 24 hours how much of the time did you have difficulty moving your head?

□ None of the time
□ A little of the time
□ Some of the time
□ Most of the time
□ All of the time

In the past 24 hours how much of the time did you have difficulty moving your body?
□ None of the time
□ A little of the time
□ Some of the time
□ Most of the time
□ All of the time

In the past 24 hours were you able to get out of bed?
□ Without any difficulty
□ With a little difficulty
□ With some difficulty
□ With much difficulty
□ Unable to do

In the past 24 hours were you able to bend over?
□ Without any difficulty
□ With a little difficulty
□ With some difficulty
□ With much difficulty
□ Unable to do

In the past 24 hours were you able to do your usual activities that required physical effort?
□ Without any difficulty
□ With a little difficulty
□ With some difficulty
□ With much difficulty
□ Unable to do

Connor-Davidson Resilience Scale 25 (CD-RISC-25)

*For each item, please mark an "**x**" in the box below that best indicates how much you agree with the following statements as they apply to you over the last **month**. If a particular situation has not occurred recently, answer according to how you think you would have felt.*

		Not true at all (0)	rarely true (1)	sometimes true (2)	often true (3)	true nearly all the time (4)
1.	I am able to adapt when changes occur.	☐	☐	☐	☐	☐
2.	I have at least one close and secure relationship that helps me when I am stressed.	☐	☐	☐	☐	☐
3.	When there are no clear solutions to my problems, sometimes fate or God can help.	☐	☐	☐	☐	☐
4.	I can deal with whatever comes my way.	☐	☐	☐	☐	☐
5.	Past successes give me confidence in dealing with new challenges and difficulties.	☐	☐	☐	☐	☐
6.	I try to see the humorous side of things when I am faced with problems.	☐	☐	☐	☐	☐
7.	Having to cope with stress can make me stronger.	☐	☐	☐	☐	☐
8.	I tend to bounce back after illness, injury , or other hardships.	☐	☐	☐	☐	☐
9.	Good or bad, I believe that most things happen for a reason.	☐	☐	☐	☐	☐
10.	I give my best effort no matter what the outcome may be.	☐	☐	☐	☐	☐
11.	I believe I can achieve my goals, even if there are obstacles.	☐	☐	☐	☐	☐
12.	Even when things look hopeless, I don't give up.	☐	☐	☐	☐	☐
13.	During times of stress/crisis I know where to turn for help.	☐	☐	☐	☐	☐
14.	Under pressure, I stay focused and think clearly.	☐	☐	☐	☐	☐
15.	I prefer to take the lead in solving problems rather than letting others make all the decisions.	☐	☐	☐	☐	☐
16.	I am not easily discouraged by failure.	☐	☐	☐	☐	☐
17.	I think of myself as a strong person when dealing with life's challenges and difficulties.	☐	☐	☐	☐	☐

18.	I can make unpopular or difficult decisions that affect other people, if it is necessary.	☐	☐	☐	☐	☐
19.	I am able to handle unpleasant or painful feelings like sadness, fear and anger.	☐	☐	☐	☐	☐
20.	I dealing with life's problems, sometimes you have to act on a hunch without knowing why.	☐	☐	☐	☐	☐
21.	I have a strong sense of purpose in life.	☐	☐	☐	☐	☐
22.	I feel in control of my life.	☐	☐	☐	☐	☐
23.	I like challenges.	☐	☐	☐	☐	☐
24.	I work to attain my goals no matter what roadblocks I encounter along the way.	☐	☐	☐	☐	☐
25.	I take pride in my achievements.	☐	☐	☐	☐	☐

Add up your score for each column 0 + ____ + ____ + ____ + ____

Add each of the column totals to obtain CD-RISC score = _____

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

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