Erenumab For Treatment of Hemicrania Continua

NCT04303845

10/6/2021

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Study Product: erenumab

Funding sponsor: Amgen

Protocol Number: (IRBe): 19-007088

Protocol Version: 3.0 – October 6, 2021

Background:

Hemicrania Continua (HC) is a primary headache disorder manifested by severe, continuous, unilateral head pain with associated ipsilateral cranial autonomic symptoms such as lacrimation, rhinorrhea, nasal congestion, or even a sense or restlessness or agitation[1]. The ICHD-3 classifies it as a Trigeminal Autonomic Cephalalgia (TAC), as it shares features with cluster headache and other TACs. Functional imaging studies using positron emission tomography (PET) have demonstrated activation of the contralateral posterior hypothalamus with HC, which is an area of activation also seen in cluster headache, and hypothesized as potentially responsible for the autonomic symptoms associated with these headache disorders by disinhibiting the trigeminal autonomic reflex[2]. Furthermore, these PET studies have also shown activation of other brainstem areas with HC, including the ipsilateral dorsal rostral pons and periaqueductal gray, an area also implicated in migraine pathophysiology and may help explain the overlap in associated symptoms between these two primary headache disorders[3].

By definition, HC responds to treatment with indomethacin, a nonsteroidal anti-inflammatory drug (NSAID) that has a structural similarity to serotonin and also inhibits nitric oxide-induced vasodilation[4,5]. As with other indomethacin-responsive headache disorders, the mechanism by which it treats HC is not clear but there is some speculation that indomethacin may inhibit trigeminal nociceptive transmission and trigeminoautonomic activation[6,7]. While patients with HC tend to respond within a matter of days to indomethacin, the literature reveals that most patients will relapse when it is discontinued and therefore will need to remain on it as a chronic treatment[8]. This can be problematic, as tolerability and risks of adverse effects with continued use remains a significant concern[9]. As an NSAID, the most common issue with indomethacin involves gastrointestinal complications, from indigestion and worsening acid reflux to gastric ulceration and hemorrhage. Patients may also experience renal insufficiency, and the drug can have an impact on blood pressure and platelet functioning among other things[4]. These risks are likely greater in patients with other co-morbid medical problems or on other

medications, or in the elderly who may have baseline renal and cardiac issues. There is a real need to find new treatment options for HC.

As there is significant overlap between HC and migraine, we anticipate that patients with HC will respond to treatment with erenumab.

Specific Aims:

1. Evaluate the response of hemicrania continua to treatment with erenumab
2. Evaluate the safety and tolerability of erenumab in patients with hemicrania continua

Methods:

Study Design: This is a prospective, open-label, study of patients with hemicrania continua treated with a single dose of erenumab 140 mg SQ.

Participants: Up to 25 adult patients who are at least 18 years of age with hemicrania continua will be enrolled into the screening phase of this study at Mayo Clinic Arizona. Enrollment will stop once 25 subjects provide headache diary during the screening phase that meets eligibility criteria (i.e. meet diagnostic criteria for hemicrania continua). Exclusion and inclusion criteria will be modeled after those used in the phase 2 and 3 trials of erenumab for the prevention of migraine and adapted for the diagnosis of hemicrania continua.[10,11] Potential participants will be excluded if they have active chronic pain conditions other than hemicrania continua (e.g. chronic pelvic pain) or acute pain conditions (e.g. recent surgery).

Subject Eligibility

Inclusion Criteria

- Adults ages 18 and over
- At least a 12 month history of hemicrania continua according to International Classification of Headache Disorders, 3rd Edition (ICHD-3)[1]
- Previous or current complete response to indomethacin
- Stable preventive treatment for at least 2 months and no anticipated need to adjust/add current headache prevention treatment

Exclusion Criteria

- Nonresponse to a therapeutic dose of indomethacin for hemicrania continua when used for at least 1 week
- Pregnant or lactating subjects
- Use of barbiturate or opioid >6 days per month; history of chronic migraine
- History of previous trigeminal-autonomic cephalalgia

- History within previous 2 months of interventional procedure for headache (occipital or other extracranial nerve block, sphenopalatine ganglion block, cervical facet block, facet rhizotomy)
- History of cranial nerve/rhizolysis
- Botulinumtoxin injection within previous 4 months
- Parenteral infusion of an oral corticosteroid use for more than 3 days within 4 weeks prior to screening phase

Screening Phase (1 week) (Day -7)

At this initial visit, 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 have measurement of vital signs and urine pregnancy testing (for women of childbearing potential), and will be trained on how to use the headache diary. Patients will be instructed to keep a prospective headache diary for the next week. We assume that up to 20% of individuals participating in the screening phase will not meet the inclusion criteria and/or diary compliance minimum and thus will not continue in this study. It is anticipated that 25 patients will be enrolled in the screening phase of the study to obtain 20 evaluable patients. If a subject is on indomethacin for the prevention of hemicrania continua, indomethacin will be stopped at this visit.

Baseline (treatment) Visit (Day 0)

Patients will return for a baseline visit after 1 week (i.e. 7 days since start of screening 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).

Treatment with Erenumab (Day 0)

Patients will receive treatment with 140 mg of erenumab via subcutaneous injection during their baseline visit. 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 4 weeks to allow for assessment of changes in headache frequency and intensity. Headache diary data will be analyzed to classify patients as "responders" (50% or greater reduction in headache frequency at week 4 post erenumab treatment compared to frequency during the screening phase) or "non-responders" (less than 50% reduction in headache frequency at week 4 post erenumab treatment compared to the frequency during the screening phase). Since patient outcomes will be measured at 4 weeks (opposed to 12 weeks like it is done in the majority of clinical trials), depending upon patient outcomes other definitions of "response" and "non-response" could be used.

Acute Headache Therapy: Patients will be allowed to use acute headache treatments including NSAIDs during the study if needed. The use of these treatments will be recorded.

Table: Schedule of Events

	Screening Phase (7 days) **(Day -7)**	Baseline Visit **(Day 0)**	Weekly, weeks 1-4 **(Day 0 to Day 28)**	Follow-up Visit, week 4 **(Day 28)**	Safety follow-up visit, week 8 **(Day 56)**
Visit Window (days)	-2	+/- 0	n/a	+/- 3	+/- 3
Eligibility: I/E criteria	X				
Vital signs	X	X		X	X
Demographics, PMH	X				
Urine pregnancy test	X	X			
Headache characteristics	X			X	X
Concomitant medications / treatments	X			X	X
BDI		X		X	
STAI		X		X	
MIDAS		X		X	
PGIC				X	
Adverse events			X	X	X
Headache diary, daily	X		X		
Treatment: Erenumab injection		X			

Sample Size

A sample size of 20 will have 80% power to detect a decrease of frequency of headache days (in 28-day period) of 2 or more from baseline, assuming a standard deviation of 3, using a paired t-test with a 0.05

two-sided significance level. It is anticipated that up to 25 patients will be enrolled in the study in order to obtain 20 evaluable patients for the primary outcome.

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 $50 per research visit and $50 at study completion provided they are at least 80% compliant with the headache diary (i.e. provide data on at least 80% of days in the 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 member of the research team who receives the information from the participant about the adverse event will complete the Adverse Event case report form. 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. Please see Appendix 1.

Annual reporting requirements:

Adverse events, any protocol non-compliance and UPIRTSOs will be reported to the reviewing Institution Review Board (Mayo Clinic IRB) at the time of annual IRB continuing review, in accordance with Mayo Clinic research policies.

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 headache 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:

According to the FDA label for erenumab, it is contraindicated in patients with serious hypersensitivity to erenumab-aooe or to any of the excipients. Reactions have included anaphylaxis and angioedema.

Erenumab has been shown to be well tolerated and associated with few side effects. The most common side effects are injection site pain, erythema, and edema. Less than 5% of patients in the phase II and III clinical trials reported these side effects. In addition, constipation was reported by approximately 3% of individuals receiving erenumab.

Hypersensitivity Reactions: If a serious hypersensitivity reaction occurs, discontinue administration of AIMOVIG and initiate appropriate therapy. Hypersensitivity reactions can occur within hours to more than one week after administration.

Hypertension: 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. Hypertension may occur at any time during treatment but was most frequently reported within seven days of dose administration.

Constipation with Serious Complications: Serious complications of constipation may occur.

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[12]. 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[12,13]. 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.

Subject Retention

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

At the time of considering an individual for participation in this study, it will be ensured that the individual will be available for the duration of the study. The responsibilities of the subject will be clearly defined. 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 screening phase will be withdrawn from the study.

Statistical Methods & Analysis

This is a prospective, open-label, study of patients with hemicrania continua treated with a single dose of erenumab 140 mg SQ. Estimates of efficacy (decrease in frequency of headache) will be assessed. For the primary endpoint, patients will be classified as a responder (50% or greater reduction by week 4 post erenumab treatment) or a non-responder (less than 50% reduction in headache frequency). SAS version 9.4 (SAS Institute, Cary, NC) will be used for analysis. The analysis will be kept descriptive and efficacy will be evaluated based on clinical meaningfulness threshold.

Analysis Plans

Primary endpoint & analyses: All eligible patients that successfully complete the screening phase and have initiated treatment with erenumab will be considered evaluable for assessing the primary endpoint. The primary endpoint of this trial will consist of the proportion of patients who are considered to have a response as defined above at the end of week 4 divided by the total number of evaluable patients on the study. Patients will not be considered evaluable if they did not complete the screening phase requirements or discontinued the study due to withdrawal before receiving erenumab. A point estimate and two-sided 95% confidence interval will be computed for this endpoint based on properties of the binomial distribution.

The analysis plan for additional (secondary) endpoints are listed below.

Headache days (>4 hours moderate/severe pain) weeks 4 compared to baseline: Change in headache days at the end of weeks 4 will be compared to baseline. Headache frequency will be described at each time point using the mean, 95% confidence interval, median, and range. Changes from baseline in headache frequency will also be described using the mean, 95% confidence interval, median and range, and assessed using paired t-tests or non-parametric Wilcoxon signed-rank tests as appropriate. Graphical procedures will include plots of average headache frequency over time. The proportion of responders will be computed at week 4. Response at the end of week 4 is the primary endpoint.

Headache hours (moderate/severe pain intensity: Change in the amount of total headache hours (with moderate or severe pain) at the end of week 4 will be compared as separate time points to baseline. Headache hours will be analyzed similar to specific aim #1 as above.

Acute medication use (# days over weeks 4): Acute medication use at the end of week 4 will be compared as separate time points to baseline. Medication usage will be analyzed similar to specific aim #1 as above.

Remission rate (proportion of patients free of headache weeks 4): The proportion of patients who do not have any occurrence of headache at the end of week 4 will be divided by the total number of evaluable patients in the study. A point estimate and confidence interval will be computed for these endpoints, headache freedom at week 4.

Patient-reported Outcomes: Patients will complete the BDI, STAI, MIDAS, 4-week Follow-up Headache Characteristics and the PGIC. Patient reported outcomes (BDI, STAI, MIDAS) will be scored using published scoring algorithms and described at each time point using the mean, 95% confidence interval, median, and range. Changes from baseline will also be described using the mean, 95% confidence interval, median and range, and assessed using paired t-tests or Wilcoxon signed-rank tests as appropriate. Graphical procedures will include plots of average values over time. The PGIC will be described to assess patient perception of improvement.

Adverse Events 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. The maximum grade for each type of adverse event will be summarized as the number of patients experiencing the event divided by the total number of evaluable patients. Frequency tables will be constructed. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

Protocol Approval and Maintenance by IRB

Initial IRB application will be submitted for review by Mayo Clinic's IRB, full board review committee. Mayo's IRB has several meetings each week and there are no submission deadlines. After review takes place by the full board review committee a meeting minute will be generated typically within 3 to 5 business days on the approval decision.

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.

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 Headache Medications

10) Beck Depression Inventory (BDI)

11) State-Trait Anxiety Inventory (STAI)

12) Migraine Disability Assessment (MIDAS)

13) Four Week Follow-up Headache Characteristics

14) Patient Global Impression of Change

15) Adverse Events

16) Headache Diary

References:

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Appendix 1

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