Erenumab as a therapeutic approach for the management of Trigeminal Neuropathic Pain (TNP)

Protocol Number: HP-00097072 (UMB)

Grant Number: Amgen ISS 20207273

Principal Investigator: Marcela Romero Reyes DDS, PhD

IND/IDE Sponsor: IND EXEMPT

Draft or Version Number: <1.2>

REDACTED VERSION: 01/16/2024

Erenumab as a therapeutic approach for the management of Trigeminal Neuropathic Pain (TNP)

Protocol Number: HP-00097072 (UMB)

Grant Number: Amgen ISS 20207273

Principal Investigator: Marcela Romero Reyes DDS, PhD

IND/IDE Sponsor: IND EXEMPT

Draft or Version Number: <1.2>

March, 30th, 2022

STATEMENT OF COMPLIANCE

{Begin required text}

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

{End required text}

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 04/24/2022

Name: Marcela Romero Reyes DDS,PhD

Title: Clinical Associate Professor, Director, Brotman Facial Pain Clinic

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

{Please add all disease or study-specific abbreviations/acronyms in this section. Modify this list as needed for your particular study and remove abbreviations that are not used in the document.}

AE	Adverse Event/Adverse Experience
AMGEN	AMGEN (AMGEN, biopharmaceutical company)
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CGRP	Calcitonin Gene Related Peptide
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMFS	Decayed, missing, and filled tooth surfaces
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GCPS	Graded Chronic Pain Scale
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDA	New Drug Application
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
PAF	Peak Alpha Frequency
PGIC	Patient Global Impact of Change
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QST	Quantitative Sensory Testing
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
[redacted]	[redacted]
TNP	Trigeminal Neuropathic Pain
UP	Unanticipated Problem
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:

Erenumab as a therapeutic approach for the management of Trigeminal Neuropathic Pain (TNP)

Précis:

A total of 40 patients (20 each arm) aged 18-65 years old of either sex, and any race or ethnicity, presenting trigeminal neuropathic pain will be randomly assigned in a 1:1 parallel, double-blind clinical trial, to receive either Erenumab or placebo. Participants will attend 6 clinic visits (Visit 0-Visit 5) over a period of 21 weeks.

Potential participants will be pre-screened at the Brotman Facial Pain clinic, at the Oral and Maxillofacial Surgery Clinic both at the University of Maryland, School of Dentistry, at the Pain Medicine Clinic at the University of Maryland, School of Medicine or by telephone; those willing to participate will be scheduled for a screening and baseline visit (Visit 0). During this visit, potential participants will be evaluated for eligibility and written informed consent will be obtained. The screening and baseline procedures include medical history review, clinical examinations, tests and administration of questionnaires. Instructions will be given for the completion of a Daily Symptom Diary (DSD) and other questionnaires at home or online. Participants who show compliance with 80 % completion of the DSD and who meet the pain score (inclusion criteria) for 4 weeks/28 days during the baseline period from Visit 0, will be randomly assigned to one of two groups either the investigational drug or placebo and will be scheduled for Visit 1.

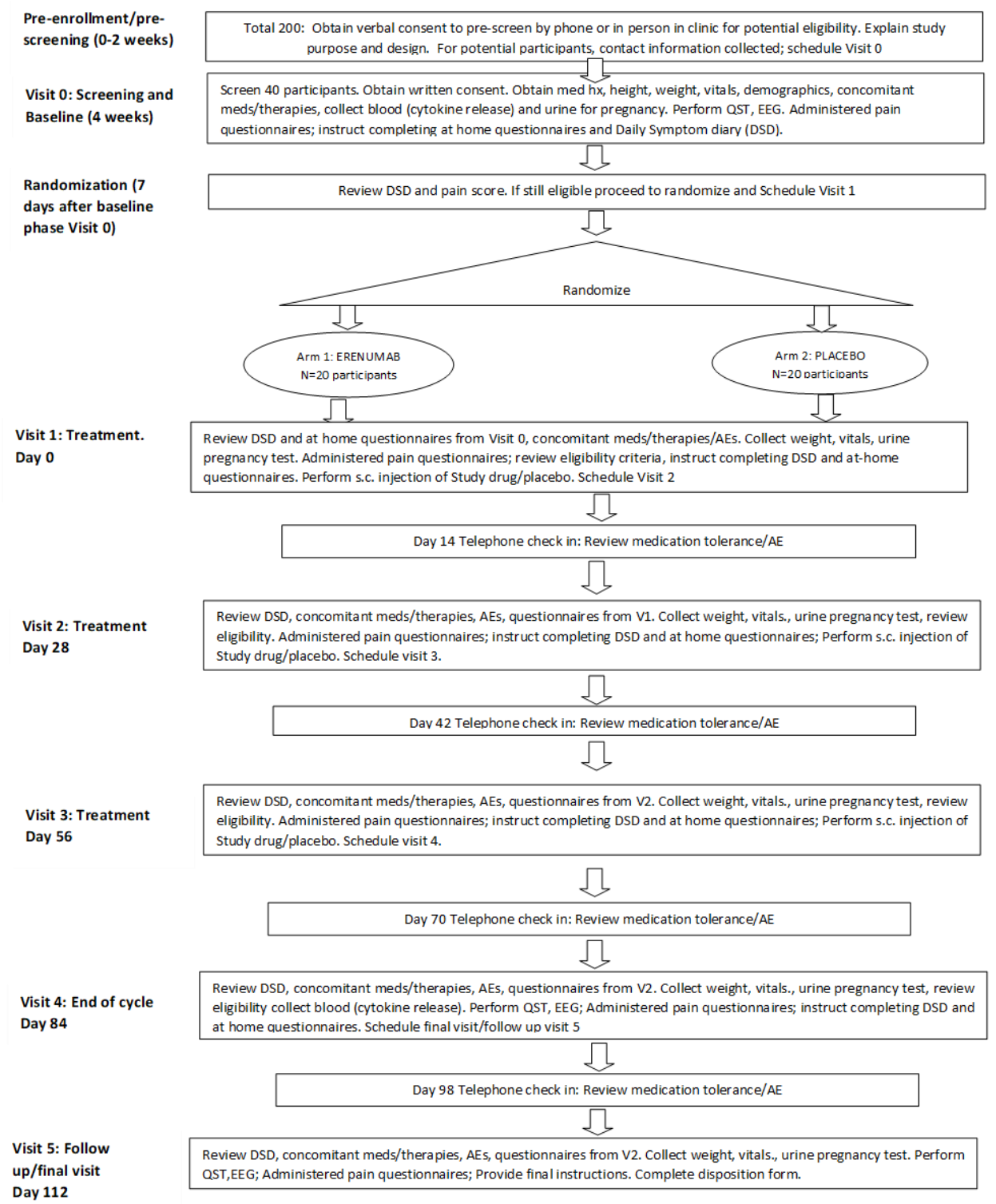
The study drug is Erenumab 140 mg, SC injection. After randomization and on Visit 1, the participant will receive the drug or placebo. This same treatment will be administered once a month for 3 months (3 cycles/12 weeks). The primary end point will be a change in average monthly (28 days) pain score (>=30% reduction) from baseline to Visit 4 (the last monthly pain cycle), compared to placebo. Each monthly pain score represents the mean of daily pain intensity score values (0-10) derived from Daily Symptom Diaries within the month between visits.

Secondary end points will be comparison with placebo of reduction of pain score from baseline to the end of 12 weeks, and between specific visits compared to the baseline, and

	participant ratings of other pain related outcomes, impact of quality of life and emotional functioning. Exploratory end points are change of pro-inflammatory and anti-inflammatory cytokine profiles (Th1/Th2); change in nociceptive processing (thermal thresholds, pressure pain thresholds, allodynia), an EEG biomarker of pain sensitivity called peak alpha frequency (PAF).
Objectives:	Primary: To investigate the efficacy of Erenumab compared to placebo on the proportion of subjects who achieved at least 30% reduction in monthly average daily pain score from baseline to the end of treatment period. Secondary: To investigate the efficacy of Erenumab compared to placebo on the reduction in monthly average daily pain score from baseline to the end of treatment period. To investigate the efficacy of Erenumab compared to placebo on the proportion of subjects who achieved a least 30% reduction in monthly average daily pain score from baseline to Visit 5 (follow-up/final visit). To determine the efficacy of Erenumab using functional measures related to TNP impact in daily activities, disability and emotional functioning measured by questionnaires (GCPAs, HADS, PGIC and PENN Facial Pain Scale). Exploratory: To explore changes in pro-inflammatory and anti-inflammatory cytokines from plasma/serum induced by Erenumab. To determine the influence of Erenumab in nociceptive processing and sensitization using QST. To determine the influence of Erenumab in EEG-based peak alpha frequency.
Population:	40 adults of either sex and any ethnicity between the ages of 18 and 65 years meeting the diagnostic criteria for Trigeminal neuropathic pain (idiopathic trigeminal neuralgia with concomitant continuous pain, painful post-traumatic trigeminal neuropathy or idiopathic painful trigeminal neuropathy), according to the diagnosis criteria based on the International classification of headache disorders ICHD-3 and International

	classification of Orofacial Pains ICOP) and with no contraindications for the use of Erenumab, will be enrolled from the Brotman Facial Pain Clinic, the Oral and Maxillofacial Surgery clinic from the University of Maryland, School of Dentistry and the Pain Clinic at the Department of Anesthesiology, School of Medicine.
Phase:	II
Number of Sites:	University of Maryland, School of Dentistry
Description of Intervention:	Study drug is Erenumab 140 mg or an inert placebo will be administered by subcutaneous injection once a month (3 cycles) over a 12-week period.
Study Duration:	30 months
Subject Participation Duration:	21 weeks
Estimated Time to Complete Enrollment:	Approximately 24 months.

Schematic of Study Design:



1 KEY ROLES [redacted]

Principal Investigator:	Marcela Romero Reyes DDS, PhD [redacted]
Medical Monitor:	DSMB
Clinical Site Investigators:	David A. Seminowicz, PhD [redacted]
Institutions:	University of Maryland, School of Dentistry

Other Key Personnel:

Jane L Phillips RDH MS

[redacted]

Gary Warburton MD, DDS

[redacted]

Thelma Wright MD, JD

[redacted]

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Pain is a major global health problem and it is unfortunate that the burden of chronic orofacial pain conditions still underestimated [1]. Some of the most prevalent and debilitating pain conditions arise from the structures innervated by the trigeminal system (head, face, intraoral structures, masticatory musculature, temporomandibular joint and associated structures).

Chronic pain in the orofacial region can arise from different regions and etiologies. Pain attributed to a disorder of the trigeminal nerve such as trigeminal neuropathic pain conditions can cause severe psychosocial burden [2-4]. These conditions can arise idiopathically such as in some cases of trigeminal neuralgia but also from injury secondary to dental procedures, infection, neoplasia, disease or dysfunction of the peripheral and/or central nervous system [5-8]. For trigeminal neuropathic pain (TNP), pharmacological therapy is the first line of treatment with medication categories including anticonvulsants and antidepressants [9]. However, their effectiveness varies from patient to patient and undesired side effects can be present causing withdrawal from treatment or a decrease in dosage to an unsatisfactory level in many patients.

Unfortunately, it is estimated that an effective drug for chronic pain is one that provides only partial relief for one out of five patients, while the remaining four patients experience no relief from pain [10, 11]. Data for TNP management is based on the evidence associated with neuropathic pain management in other parts of the body and of different etiologies [12, 13] and currently we do not have any pharmacological approach exclusively for the management of trigeminal neuropathic pains based on evidence and approved by the FDA. Therefore, novel safer and targeted-directed therapies are urgently needed to address this unmet medical need with significant social and psychological implications.

The calcitonin gene-related peptide (CGRP) is a pro-inflammatory vasodilating neuropeptide involved in migraine pathophysiology in where CGRP levels increase during a migraine attack [14]. Targeting the CGRP pathway has proven to be effective and safe for migraine therapeutics. Erenumab is the first antibody therapeutic targeting the CGRP receptor and is the first in its class to be FDA approved for the management of chronic migraine [15] and also approved for the prevention of episodic migraine, demonstrating its efficacy in randomized controlled clinical trials; in addition, to also show promising for the management post-traumatic headache attributed to brain injury [16, 17].

Moreover, CGRP has been shown to have a significant role in other types of pains in the trigeminal system. We and others have shown that CGRP is also involved in other orofacial pains such as in temporomandibular disorders (TMD) [18] and we demonstrated that blocking CGRP with a CGRP receptor antagonist in a pre-clinical model of TMD, significantly decreased nociception [19] as well as we demonstrated its role in the comorbidity between migraine and TMD [20].

In regards orofacial pain of neuropathic origin, preclinical studies have shown that CGRP plays a role in trigeminal afferent sensitization [21] and blocking the CGRP receptor results in antinociceptive effects in models of trigeminal neuropathic pain [22]. In addition, there are reports indicating elevated CGRP levels in blood, cerebrospinal fluid, and plasma in trigeminal neuralgia patients [23-25].

The management of trigeminal neuropathic pains by inhibiting CGRP with an FDA approved medication that has been proved safe for another indication such as migraine which shares CGRP as a potential target, would be very promising. Therefore, the purpose of this study is to evaluate the efficacy of Erenumab for the management of trigeminal neuropathic pain. We have hypothesized that Erenumab - a monoclonal antibody that inhibits CGRP-receptor decreases pain symptomatology in patients suffering of trigeminal neuropathic pain.

The study will be a randomized, double blind, placebo-controlled pilot trial comparing Erenumab vs Placebo. Participants will be evaluated for trigeminal neuropathic pain and have other related assessments. Blood samples will be collected, and participants will need to answer some questionnaires. We are going to assess changes in pain intensity and other pain outcomes related to trigeminal neuropathic pain.

The ultimate goal of this pilot study is to provide the foundation for the treatment of trigeminal neuropathic pain based upon CGRP targeted approaches.

2.2 Rationale

TNP are a considerable burden and affects significantly the quality of life of the sufferer [4]. There are medications for their management but while they may work for some patients, may not work for the others; in addition, side effects may be present for some patients with the need to decrease dosage to not optimal levels. Furthermore, the indications of these drugs are for other neuropathic pain disorders and currently there is no medication specifically indicated for the management of TNP based on its molecular pathophysiology.

The calcitonin gene-related peptide (CGRP) is a key neuropeptide involved in migraine pathophysiology [14].There is evidence showing that CGRP has a role in other disorders mediated by the trigeminal system in addition to migraine; CGRP has shown to have a role in orofacial pain such as in TMD [18-20] and in trigeminal neuropathic pain [21-25].

Erenumab is the first antibody therapeutic targeting the CGRP receptor with FDA approval for migraine prevention [15] that is well tolerated and with a good safety profile [26-28]. Therefore, the scientific premise for this study is that inhibiting the CGRP pathway in trigeminal neuropathic pain will decrease pain and pain related outcomes in a safe and well tolerated manner for this patient population.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Use of Erenumab: Erenumab is a fully human monoclonal antibody that inhibits CGRP receptor and is FDA approved for the preventive treatment of migraine. As of 16 May 2020, approximately 6,550 people have received erenumab in research studies. Since it was first approved for sale on 17 May 2018, approximately 423,800 people have been prescribed erenumab (Aimovig®) for treatment as of 16 May 2020.

The safety profile of erenumab has been favorable in clinical trials and in the post-marketing setting. A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritus) have been identified at low frequencies (< 5%) in clinical trials. In the long-term use of erenumab, the safety profile remained consistent through 5 years of open-label treatment. In post-marketing settings, hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions) and constipation with serious complications have been reported. In addition, oral sores (eg, stomatitis, mouth ulceration, oral mucosal blistering), alopecia and rash (eg, rash papular, exfoliative rash, rash erythematous, urticaria, blister) have been observed in post-marketing surveillance.

Serious constipation has been reported in patients prescribed erenumab. In some cases, hospitalization or surgery was required. Constipation and the use of medications that decrease gastric motility are in our exclusion criteria, however if a new onset of constipation occurs, the participant will be withdrawn of the study and will be referred to an appropriate practitioner for continued care (see section 9.2).

High blood pressure: High blood pressure or worsening of high blood pressure.

After taking erenumab, antibodies against erenumab may be produced; this has been observed in clinical studies. No side effects associated with these antibodies were observed.

Side effects of the use of erenumab in combination with other drugs are unknown at this time.

There are no adequate data on the developmental risk associated with the use of erenumab in pregnant women or breastfed babies. There are no data on the presence of erenumab in human milk, or on milk production. Pregnant women, breastfeeding women and women planning to become pregnant will be excluded from this study. If a participant

gets pregnant, decides to breastfeed her baby or father a child while taking erenumab will be withdrawn from the study and will be monitored and referred to an appropriate practitioner for continued care (see section 9.2 and 9.4.1).

Participants will be closely monitored for any AEs, during the clinic visit and between visits by telephone. Potential risks and discomforts will be clearly stated in the ICF.

Quantitative Sensory Testing (QST): A QST examination will assess sensory impairment by applying different stimuli in different body parts, and extraorally such as pressure or heat to the skin.

Extraoral sensory testing: The quantitative sensory testing (QST) will include stroking and/or applying gentle pressure with a brush, in the face. The examination will also include applying pressure with a probe on fingers, head and shoulders, and applying a heat sensor on the forearm. The test will be performed extraorally ipsilateral and contralateral to the area of pain. The potential, risks is a slight risk of tissue trauma or burning but this is avoided because the procedure is under the control of the examiner and the subject can stop it at any time. Study personnel will be trained and calibrated to perform these procedures.

General sensory testing:

Thermal (heat) stimulation: The potential risk involves burning of the skin (ventral forearm) This will be avoided with the thermal probe temperature not exceeding 50 degrees Celsius. The research staff will take the following precautions against potential burn risk: 1 1) provisions for immediate stimulus removal by the subject, and 2) provisions for skin temperature and duration of thermal stimulus by the researcher to include a built-in minimum and maximum temperature limitation system in the thermal stimulator. Discomfort of the subject will be minimized by delivering stimuli that are below the subject's self-reported thermal pain tolerance level.

Mechanical cutaneous sensitivity: The potential risk involves transient discomfort. This is performed with weighted probes (2mm diameter; 8–512 mN forces) applied to the dorsum of digits 2, 3, and 4 of the left hand. Participants will be instructed to signal (verbally or by raising the right hand) when the sensation first becomes painful at which time the researcher will remove the probe. Because the probe is completely under the control of the examiner, there is little opportunity for bruising from this procedure.

These assessments will be performed on 2 clinic visits. It is expected that these assessments will evoke brief pain or discomfort within a range that is acceptable for the participant. Transient redness or tenderness of the skin may appear after these assessments but none of them is expected to result in lasting discomfort or tissue damage. In addition, the participants may request to stop the examination/test at any time. These assessments will end upon the completion of the modality or upon the participant’s request, whichever comes first.

EEG assessment. Peak alpha frequency (PAF): There is no potential risk or harm in the EEG assessment. PAF is based on a 5-minute, eyes-closed resting state EEG. The EEG device will be placed on the Scalp of the participants and EEG data will be collected using a CGX quick8r dry electrode system. Participants will be asked to make facial muscle contractions such as clenching their teeth, blinking, and saccades, while EEG is recorded. Participants may find uncomfortable the EEG device as well as the facial contractions, but these may only induce transitory discomfort. The facial contractions are necessary because will be used to aid in automated artefact removal. Participants will then be told to relax their muscles and resting state eyes closed EEG will be recorded for 5 minutes and used for PAF calculation.

Questionnaires: It is possible that some participants may experience discomfort associated with answering several questionnaires as well as with being asked personal questions about his/her emotional state and feelings, health history or symptomatology. The participants will be informed that they can choose not to answer any question for any reason.

Blood collection: Participants may find the blood draw unpleasant and there is a possibility of mild pain and bruising associated with it. Trained personnel will perform the blood draw using standard procedures. If for any reason the blood draw is being difficult (i.e. finding a vein) and the subject/patient is uncomfortable, the blood draw will be stopped immediately. The participants will be informed that they can choose to stop the blood collection for any reason.

2.3.2 Potential Benefits

Participants may or may not receive benefit from the use of Erenumab in pain reduction. If Erenumab proves to be effective, this will be the first pharmacological approach specifically indicated for Trigeminal Neuropathic Pain (TNP) with a clear mechanism of action and will provide a novel therapeutic approach to fulfill this highly unmet medical need, changing current management paradigms for the patients suffering of TNP.

3 OBJECTIVES

3.1 Study Objectives

Primary Objective

To investigate the efficacy of Erenumab compared to placebo on the proportion of subjects who achieved at least 30% reduction in monthly average daily pain score from baseline to the end of treatment period.

Secondary Objectives

To investigate the efficacy of Erenumab compared to placebo on the reduction in monthly average daily pain score from baseline to the end of treatment period.

To investigate the efficacy of Erenumab compared to placebo on the proportion of subjects who achieved a least 30% reduction in the monthly average daily pain score from baseline to Visit 5 (follow-up/final visit).

To determine the efficacy of Erenumab using functional measures related to TNP impact in daily activities, disability and emotional functioning measured by questionnaires (GCPAs, HADS, PGIC and PENN Facial Pain Scale).

Exploratory Objectives

To explore changes in pro-inflammatory and anti-inflammatory cytokines from plasma/serum.

To determine the influence of Erenumab in nociceptive processing and sensitization using QST.

To determine the influence of Erenumab on PAF.

3.2 Study Outcome Measures

3.2.1 Primary

The primary end point will be to achieve >=30% reduction (Yes/no) in monthly (28 days) average pain score from baseline to Visit 4 (the last monthly treatment cycle), compared to placebo. The daily pain intensity score will be measured on a 11-point (0-10) numeric rating scale (NPRS) and reported in the Daily Symptom Diary (DSD). The monthly mean pain intensity score will be determined from baseline (4 weeks/28 days), for each month during the 12 weeks of treatment.

The monthly mean pain intensity score will be calculated if a participant has at least 80% compliance with the DSD.

A relevant decrease in chronic pain showing a beneficial effect will be a reduction of >=30% from baseline in the average pain intensity score [29, 30].

3.2.2 Secondary

Efficacy will be investigated further using secondary outcomes:

Secondary outcome measures will be a comparison with placebo of reduction of pain score from baseline continuously through to the end of 12 weeks (Visit 4).

Assess the efficacy of Erenumab compared to placebo on the proportion of subjects who achieved a least 30% reduction in the monthly average daily pain score from baseline to Visit 5 (follow-up/final visit).

A change in participant ratings compared to placebo from baseline of other pain related outcomes using functional measures related to TNP impact in daily activities, disability and emotional functioning measured by questionnaires (GCPAs, HADS, PGIC and PENN Facial Pain Scale), assessed over the length of the study.

Functional measures related to TNP impact in daily activities, disability and emotional functioning:

Penn Facial Pain Scale-Revised: Change/improvement in burden/disability of daily activities related to trigeminal neuropathic pain (e.g. chewing, eating, talking, touching) [31].

Graded Chronic Pain Scale (GCPS): Changes in pain intensity and pain related disability [32]

Patient Global Impression of Change (PGIC): Assesses patient perspective of pain improvement [33].

Hospital Anxiety and Depression Scale: Change in Anxiety and depression [34].

Exploratory Endpoint

To investigate whether Erenumab decreases pro-inflammatory cytokine release and increase anti-inflammatory cytokine release [redacted].

To investigate whether eremumab induces changes in nociceptive processing and sensitization determined with QST measurements. In patients with persistent trigeminal

neuropathic pain altered pain modulation is present. We will investigate if erenumab influences sensitization [35-38].

To investigate whether erenumab decreases pain sensitivity determined by PAF measurements during EEG assessment. In chronic pain patients, alpha rhythms are slower in frequency and elevated in power relative to matched, healthy controls [39, 40]. We have shown that PAF predicts future pain sensitivity in multiple experimental pain models [41-43]. We will examine whether erenumab can modulate PAF and therefore, influence pain sensitivity.

4 STUDY DESIGN

This study is a single center, placebo-controlled, double blind, randomized, phase II pilot to evaluate the efficacy of Erenumab in the management of trigeminal neuropathic pain. 40 patients (20 per each arm) aged 18-65 years old of either sex, and any race or ethnicity presenting trigeminal neuropathic pain (subjects with diagnosis based on the International classification of headache disorders ICHD-3 [44] and International classification of Orofacial Pains ICOP [8] of idiopathic trigeminal neuralgia with concomitant continuous pain, painful posttraumatic trigeminal neuropathy or idiopathic painful trigeminal neuropathy) will be randomly assigned in a 1:1 parallel, double-blind, phase 2 single center clinical trial, to receive either Erenumab, or placebo. Participants will attend 6 clinic visits (Visit 0-Visit 5) over a period of 21 weeks. The study should be completed over a period of 2.5 years, with an estimated duration of recruitment of 2 years.

Participants will be pre-screened in person at the Brotman Facial Pain clinic, the Oral and Maxillofacial Surgery Clinic both at the University of Maryland, School of Dentistry, Pain Medicine Clinic at the University of Maryland, School of Medicine or by telephone. Potentially eligible and interested participants will be scheduled for a screening and Baseline Visit (Visit 0). During Visit 0, participants will provide informed consent and be evaluated for eligibility; information including demographics, medical history, concomitant medications, and therapies will be collected. In addition, participants will be assessed for pain level, pain symptoms, disability, health status, among other measures and a blood sample will be collected. Procedures will include clinical examinations and tests and the dispensation of various questionnaires, all of which are listed in the Schedule of Events (Appendix A).

Participants who show compliance with the Daily Symptom Diary of at least 80% and who meet the pain score (inclusion criteria) for 28 days/4 weeks (baseline period) after Visit 0, will be randomly assigned to one of two groups (Erenumab or placebo) and will be scheduled for Visit 1 within a week of randomization.

At Visit 1, randomized participants will receive the 1st cycle of management and begin a 12-week drug treatment/placebo phase that will be divided into once a month injection/cycle for a total of 3 cycles. During that period, Visits 2-4 will take place, and many of the baseline assessments will be repeated. Between visits, communication will be conducted by telephone. The final study visit, visit 5, will occur 4 weeks after the last assessment (visit 4) and 8 weeks after the last dosage of drug treatment (Visit 3).

The primary end point will be a change in average monthly (28 days) pain score (>=30% reduction) from baseline to Visit 4 (the last monthly treatment cycle), compared to placebo. The daily pain intensity score will be measured on a 11-point (0-10) numeric rating scale (NPRS) and reported in the Daily Symptom Diary (DSD). The monthly mean pain intensity score will be determined from baseline (4 weeks/28 days), for each month during the 12 weeks of treatment.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study is planning to enroll a total of 40 subjects that will be randomly assigned to one of the two study groups. It is anticipated that a total of 200 subjects will be screened in order to meet recruitment goals.

Participants will be pre-screened in person at the Brotman Facial Pain clinic, the Oral and Maxillofacial Surgery Clinic both at the University of Maryland, School of Dentistry, Pain Medicine Clinic at the University of Maryland, School of Medicine or by telephone.

Vulnerable subjects: No specific vulnerable populations are being targeted for recruitment for this study.

5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provide signed and dated informed consent form
2. Is between 18 and 65 years of age (inclusive; male or female and any race or ethnicity)
3. Trigeminal neuropathic pain symptoms for a minimum of 3 months prior to randomization visit, localized in any trigeminal distribution (intraoral or extraoral).
4. Meets diagnostic criteria for Trigeminal neuropathic pain with diagnosis based on the International classification of headache disorders ICHD-3 [44] and International classification of Orofacial Pains ICOP [8].

- Diagnosed with idiopathic trigeminal neuralgia with concomitant continuous pain per ICDH-3.

- Diagnosed with Painful posttraumatic trigeminal neuropathy or idiopathic painful trigeminal neuropathy per ICOP. May include:
    - Subjects with a history of persistent pain of idiopathic origin or after dental extractions, mandibular fracture, surgical procedure, implant procedure and root canal therapy.

5. Participants must have a minimum mean of average daily pain intensity score of 4/10 in where 0= no pain and 10= maximum pain imaginable on a numerical rating scale (0-10), during the 4 weeks/28 days baseline period prior randomization.

6. If taking a prescription medication daily for the management of pain (taken for at least 30 days before baseline), agrees to continue the daily use of the medication throughout the study at the same dosage.
7. If taking prescription medication, opioid medication or OTC medications as needed or episodically for the management of pain agrees to discontinue its use prior to the Screening and Baseline Visit.
8. If taking OTC pain medications daily agrees to continue its daily use at the same dosage throughout the study.
    - If a participant is taking an over-the-counter medication daily for management of other type of pain or for prophylaxis of myocardial infarction or stroke, the participant will be encouraged to continue the same usage of that medication throughout the study.
9. If subjects diagnosed with migraine, are allowed only if episodic.
10. Agrees to not start any new prescription medication for the management of trigeminal neuropathic pain or other type of pain throughout the study.
11. Agrees to not modify their prescription regimen for current trigeminal neuropathic pain or other types of pain throughout the study
12. Agrees not to receive any injection therapy for the management of neuropathic pain or migraine (e.g. nerve blocks, SPG blocks, steroid injections, Botox) during the course of the study
13. Agrees not to use any neuromodulatory device for the management of neuropathic pain or migraine during the course of the study
14. Agrees not to undergo any surgical procedure for the management of neuropathic pain during the course of the study
15. Agrees to not use CBT, biofeedback or acupuncture for the management of pain during the course of the study.
16. Females of childbearing potential agree to use one of the following methods of contraception throughout the study: licensed hormonal method, intrauterine device, female or male condoms with contraceptive foam, abstinence, bilateral tubal ligation/occlusion, or vasectomy in partner (if postmenopausal, must not have menstruated for at least 12 consecutive months)
17. Willing and able to understand and comply with all study procedures and be available for the duration of the study.

5.2 Subject Exclusion Criteria

1. Participants with a history of congestive heart failure or uncontrolled diabetes.

2. Participants with serious hepatic, respiratory, hematologic or immunologic illnesses, an unstable cardiovascular disease, or any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or Erenumab or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the participant inappropriate for entry into this trial.

3. Participants with high blood pressure, uncontrolled high blood pressure, malignant disease, chronic constipation, any malabsorption disorders such as IBSc or any other severe acute or chronic medical or psychiatric condition (major depression, schizophrenia, dementia) or laboratory finding that may increase the risk associated with trial participation with Erenumab, that in the judgement of the investigators would interfere with study assessments and/or would make the participant inappropriate for entry into this trial.

4. Participants with active malignancy of any type or a history a malignancy (with exception of participants with malignancy surgically removed with no evidence of recurrence within 5 years before enrollment.

5. Participants with evidence or a history of drug or alcohol abuse within the past 12 months or has been diagnosed with a substance abuse disorder.

6. Participants with dental pain (determined pain of odontogenic/periodontal origin).

7. Participants with significant neurological disorders.

8. Patients with chronic migraine with and w/o aura following the ICHD-3 criteria treated or not treated with medication

- Without excluding headache attributed to TMD

9. Participants currently taking or have previously taken Erenumab or other CGRP monoclonal antibody (mAmb) or currently taking a CGRP-Receptor antagonist (gepants) for migraine prevention.

10. Patients with hypersensitivity to Erenumab

11. Participants with trigeminal neuropathic pain taken medications for the management of trigeminal neuropathic pain in where daily dosage has been modified within three weeks before baseline.

12. Neuroimaging showing the presence of neurovascular compression or AV malformation.13. Neuroimaging showing the presence of intracranial pathology (i.e. multiple sclerosis, tumor).

14. Presence of extracranial pathology in the area of pain (tumor, lesion).

15. Has been treated with another investigational drug or treatment within 30 days prior to the Screening and Baseline Visit

16. Has commenced a new daily prescription medication for the management of pain within 30 days prior to the Screening and Baseline Visit

17. Currently taking opioid medication whether episodically or daily, within 30 days prior to the Screening and Baseline Visit.

18. Patients sensitive to Latex

19. If planning to become pregnant, pregnant or breastfeeding.

20. Anything that, in the opinion of the investigator, would place the participant at increased risk or impede the participant's full compliance with or completion of the study.

5.3 Strategies for Recruitment and Retention

Participants will be recruited from direct contact with patients who have relevant diagnoses recorded in electronic health records or patient registries at the Brotman Facial Pain Clinic, the Clinic of Oral and Maxillofacial Surgery at the University of Maryland, School of Dentistry and from the Pain Clinic at the University of Maryland, School of Medicine, Department of Anesthesiology. Providers at these clinics will be made aware of the study and asked to inform their patients about the study and to provide them with study contact information. Previous study participants who gave prior permission may be contacted. Participants may be also recruited through advertisements, websites, print, and electronic media. All recruitment materials will be submitted to the IRB for review and approval prior to their use.

Participants will be contacted to be reminded of each upcoming visit by telephone, text message, email, or letter. Participants will be informed about the importance of keeping each scheduled appointment, and they will be instructed to contact the study staff as soon as possible in case they are unable to attend a scheduled appointment. Participants who miss a scheduled visit without notifying the study staff will be contacted by telephone, text message, email, or letter to encourage their continued participation in the study and to ask them to contact the study team concerning their next appointment. Unscheduled visits may occur at the investigator's discretion (Section 7.6).

Participants will be compensated for their participation in the study in an amount stated in the informed consent form. In some cases, the participant may be eligible for reimbursement of travel expenses.

5.4 Treatment Assignment Procedures

This study will be a conventional factorial design, randomized, double-blinded clinical trial with two parallel arms to evaluate efficacy of Erenumab:

- Erenumab, a monoclonal antibody medication that inhibits CGRP pathway, which is FDA-approved for the prevention of migraine. The comparison will be to placebo.

5.4.1 Randomization Procedures (if applicable)

Extensive screening procedures of potential participants to determine their eligibility based on the inclusion and exclusion criteria will be carried out prior randomization. Participants who do not meet these criteria will not be enrolled in the study.

Randomization visit will be within 7 days after Baseline Phase period has finished (4 weeks/28 days), eligibility will be further confirmed based on completion of Daily Symptom Diaries and pain intensity score. Qualified participants will be randomly assigned to one of the two arms of the study in a 1:1 ratio:

1) Investigational arm: Erenumab: N= 20 participants
2) Placebo: N=20 participants

Randomization
Subjects will be randomized to the investigational treatment group (Erenumab) or the placebo group using a blocked randomization scheme. The examiners and patients will be blind to the group assignment. Randomization will be done by Investigational Drug Services (IDS/Research pharmacy). There will be a 1:1 ratio of treatment to placebo participants.

Blinding
Blinding will be done by Investigational Drug Services (IDS). The PI and study staff will be blind to what the participant is receiving.

Treatment/randomization codes
IDS will be responsible for randomization of participant assignment to either the study medication or placebo groups. IDS will use a random number generation program to determine assignment.

5.4.2 Masking Procedures (if applicable)

All study staff, including investigators, study care providers, study clinician, study coordinators, and research assistants, will remain blinded to the participants' medication assignments throughout the study. Erenumab and Placebo will be packaged in identical vials and stored. Only IDS, the research pharmacy will be unblinded. If the IRB and/or Data and Safety Monitoring Board (DSMB) request an unblinded data report during the data collection period, an unblinded biostatistician will generate the report.

Unmasking/unblinding prior to study completion will occur only if there is evidence that a participant's health or safety is threatened and therefore, knowledge of treatment assignment is necessary to protect the participant.

Except in extreme medical emergencies, before a participant's treatment assignment is revealed, the investigator must confer the request for unmasking with the IDS. For a medical emergency that occurs during business hours, the site investigator will contact the IDS to determine the participant's treatment assignment; for a medical emergency that occurs outside of business hours, medical personnel will contact the IDS pharmacy to determine the treatment assignment.

An event is considered an extreme medical emergency when medical management of a participant requires the knowledge of the treatment assignment. Study participants will be provided with instructions and contact information for emergency situations. Emergency unmasking will be recorded and reported to the PI, and the medical monitor as soon as possible, with a full accounting of the event, date and time of occurrence, the reason for unmasking, and names of all individuals who were notified of the emergency. Unblinding will be reported to the Data Safety Monitoring Board (DSMB) and IRB according to the University of Maryland policies and guidelines.

5.5 Subject Withdrawal

Subjects may withdraw voluntarily from the study or the investigator may terminate a subject's participation at any time.

5.5.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time, for any reason, with no explanation upon request. This decision will not interfere or alter in any way their following treatments and pain management if they are patients of the dental school, the Brotman Facial Pain Clinic, the Oral and Maxillofacial Surgery Clinic or the Pain Clinic at the medical school.

If a participant does not return for a scheduled visit, every effort will be made to contact the participant and to document the outcome. If a participant withdraws consent and

refuses to come to an Early Termination Visit, no further evaluations will be performed, and no attempts will be made to collect additional data.

Investigators may withdraw a participant for any of the following reasons:

- Withdrawal of consent
- The participant does not meet eligibility criteria for randomization.
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Pregnancy
- At Investigator discretion

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

Participants withdrawn after randomization will not be replaced. Participants who are withdrawn voluntarily or by the investigator will be discontinued from the study.

Study staff will complete a study disposition form in the eCRF, indicating the reason for discontinuation.

If the patient is a patient from the school and/or is interested in following orofacial pain care at the Brotman Facial Pain clinic, will be referred to the faculty practice clinic front desk for information and to schedule an appointment if wants to.

Unblinding, if required, will be carried out according to the procedures described in Section 5.4.2. A participant who has an AE at the time of discontinuation will be followed until the event returns to baseline, resolves, or is stabilized. If the AE does not meet one of these outcomes within 30 days after discontinuation or the end of the study, the participant will be referred to an appropriate provider for continued medical care (See section 9.2).

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause as determined by sponsor the PI, medical monitor, DSMB, or IRB. Written

notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY INTERVENTION

6.1 Study Product Description

The investigational drug is Erenumab-aooe (Aimovig), an FDA approved medication for the prevention of migraine. Erenumab-aooe is a fully human monoclonal antibody IgG2 that binds in a competitive and reversible manner to the Calcitonin Gene Related Peptide (CGRP) receptor. It is available as a subcutaneous injection only and it is used once a month.

Erenumab injection is a sterile, preservative-free, clear to opalescent, colorless to light yellow solution for subcutaneous administration. The needle shield of the prefilled syringes contain dry natural rubber (a derivative of latex). The syringe is a prefilled glass syringe with a stainless-steel needle and delivers 1 mL of 140 mg/mL. Each 1 mL 140 mg single-dose prefilled glass syringe contains 140 mg erenumab-aooe, acetate (2.0 mg), polysorbate 80 (0.10 mg), and sucrose (65 mg).

The placebo injection is a sterile solution. The syringe is a 1 mL prefilled glass syringe of [redacted] Sodium Acetate, [redacted] Sucrose, [redacted] polysorbate 20, pH 5.2

6.1.1 Acquisition

Our study will use Erenumab at the dosage of 140 mg/mL once monthly. The drug will be acquired from AMGEN, the manufacturer, and shipped to the research pharmacy at the University of Maryland. The research pharmacy will release the drug to study personnel, who will dispense it to the participants at study visits. The placebo will be also acquired from AMGEN and will be packaged, labeled, dispensed, and administered in the same manner as described above for the active drug. Placebo ingredients are [redacted] Sodium Acetate, [redacted] Sucrose, [redacted] polysorbate 20, at pH 5.2. Storage requirements for the placebo are the same as for the active drug.

6.1.2 Formulation, Packaging, and Labeling

Erenumab 140 mg, in 1 mL prefilled glass syringe will be used. The syringe is a prefilled glass syringe with a stainless-steel needle and delivers 1 mL of 140 mg/mL. Each 1 mL 140 mg single-dose prefilled glass syringe contains 140 mg erenumab-aooe, acetate (2.0 mg), polysorbate 80 (0.10 mg), and sucrose (65 mg) at pH 5.2. The placebo will be Placebo 1 mL in a prefilled glass syringe consisting of [redacted] Sodium Acetate, [redacted] Sucrose, [redacted] polysorbate 20, pH 5.2. Neither study personnel nor study participants will be able to differentiate the study drug from placebo by appearance alone.

The research pharmacy will label and dispense the autoinjectors in individual cartons. The cartons will be labeled with the following information:

- Name and address of the dispensing pharmacy

- Protocol number
- Name of the drug labeled as “Erenumab or placebo” to protect the blinding
- Strength of the drug or placebo (140 mg/ml). Dispense 1
- Name of the prescribing clinician
- Instructions for use
- Participant name and clinic record number
- Date dispensed
- The following statement: “Limited by Federal Law to Investigational Use Only”

6.1.3 Product Storage and Stability

Erenumab will be stored following the instructions of the manufacturer. Erenumab needs to be stored refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use.

• If removed from the refrigerator, Erenumab should be kept at room temperature (up to 25°C [77°F]) in the original carton and must be used within 7 days. It will be thrown away if it has been left at room temperature for more than 7 days. It should not be freeze or shaken.

Study personnel will pick up the study product from the research pharmacy the day prior or the same day that will be administered to participants. If picked up a day before to be administered, the study product will be stored in an allocated refrigerator specifically for its storage at the Brotman Facial Pain Clinic.

6.2 Dosage, Preparation and Administration of Study Product

Erenumab 140 mg/mL or placebo prefilled glass syringe will be administered subcutaneously once monthly.

Erenumab or placebo will be administered by the study personnel who will be trained in how to administer it using the single-dose prefilled syringe, including aseptic technique and according to the instructions of the manufacturer.

- Prior to subcutaneous administration, allow Erenumab to sit at room temperature for at least 30 minutes protected from direct sunlight.

- Do not warm by using a heat source such as hot water or a microwave.
- Do not shake the product.
- Inspect visually for particulate matter and discoloration prior to administration [see Dosage]
- Do not use if the solution is cloudy or discolored or contains flakes or particles.
- Erenumab or placebo will be administered in the abdomen, thigh, or upper arm subcutaneously.
- It will not be injected into areas where the skin is tender, bruised, red, or hard.
- Both prefilled autoinjector and prefilled syringe are single-dose and deliver the entire contents.
- Erenumab or placebo administration to participants will be once a month for 3 months on Visits 1-3. The study personnel will explain the participant how it will be injected. Participants will receive the first dose on Visit 1. The second dose a month after on Visit 2 and the third and last dose a month after the second dose on Visit 3 for a total of 3 cycles. After administration, the patient will wait 20 minutes in our clinic to make sure there is not any reaction. After the 20 minutes, study personnel will assess, schedule next visit and the patient will be free to leave.
- Erenumab or placebo is for subcutaneous use only. The needle shields of erenumab and placebo prefilled syringe contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex. Sensitivity to latex is included in the exclusion criteria (See 5.2)

6.3 Modification of Study Product Administration for a Subject

If a dose of Erenumab is missed, will be administered as soon as possible. Thereafter, Erenumab will be scheduled monthly from the date of the last dose.

The safety profile of erenumab has been favorable in clinical trials and in the post-marketing setting. A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritus) have been identified at low frequencies (< 5%) in clinical trials. In the long-term use of erenumab, the safety profile remained consistent through 5 years of open-label treatment. In post-marketing settings, hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions) and constipation with serious complications have been reported. In addition, oral sores (eg, stomatitis, mouth

ulceration, oral mucosal blistering), alopecia and rash (eg, rash papular, exfoliative rash, rash erythematous, urticaria, blister) have been observed in post-marketing surveillance.

Adverse reactions with the use of Erenumab have been hypersensitivity reactions, constipation with serious complications and hypertension. Exclusion criteria includes medical history of constipation or taking medications associated with decrease of G.I motility as well as pre-existent hypertension (See 5.2). If the participant reports a hypersensitivity reaction (rash, angioedema, anaphylaxis), new onset constipation or new onset of hypertension or if the participant decides against using Erenumab, he/she will be discontinued from the study (See 2.3.1 and 5.5.2).

6.4 Accountability Procedures for the Study Product

The research pharmacy will be responsible for maintaining logs (paper or electronic) to document the acquisition and dispensing of Erenumab and placebo. The pharmacy will also be responsible for maintaining and monitoring storage conditions. The logs and records of storage conditions will be reviewed by the study clinical monitor during periodic monitoring visits.

6.5 Assessment of Subject Compliance with Study Product Administration

Participants will receive the medication or placebo injection by a trained study staff member once a month on Visits 1, 2 and 3.

Between visits, study personnel will contact participants by telephone to assess study drug tolerance (AEs), and to remind them when they are scheduled for another dosage.

6.6 Concomitant Medications/Treatments

At the Screening and Baseline Visit (Visit 0), information concerning prior and concomitant medications for the previous 30 days will be collected, including name(s) of medication(s), total daily dose, start date, stop date (if applicable), and primary reason for use. Similarly, information about prior and concomitant therapies, including injection therapy (nerve blocks, botox), will also be collected for all participants for the 30 days prior to the Screening and Baseline Visit. The concomitant medication/therapy information will also be updated at subsequent study visits (Visits 1-5).

6.6.1 ***Allowable Pain Medication***

6.6.1.1 ***Prescription medications***

Participants who enter the study already on a daily regimen of a prescription medication for the management for trigeminal neuropathic pain or for other type of pain in other region of the body will be encouraged to continue that regimen throughout the study and it should not be modified. The usage of all prescription medications for pain during the study will be recorded and quantified at each visit.

Rescue medications will be defined as over-the-counter topical anesthetics and over-the-counter analgesics and anti-inflammatories. In case a patient presents pain, the medications described below may be used.

6.6.1.2 ***Over-the-counter medications***

Topical anesthetics can be used as a rescue strategy for pain exacerbations. Benzocaine 20% to use intraorally (orabase) or lidocaine 4% (aspercreme with lidocaine) to use extraorally could be used. Participants using these topical non-prescription anesthetics during the study, will be recorded and their use will be quantified at each visit; the usage will be classified as either episodic or daily.

Episodic use of non-prescription analgesics and anti-inflammatories (acetaminophen, NSAIDs) will be defined as use for no more than 2 consecutive days and for no more than 18 days from baseline to visit 4. This type of analgesics should not be used for more than 2 days a week prior to Baseline and a week prior to V4, when the exploratory outcome is assessed.

If a participant is taking an over-the-counter medication daily for management of any type of pain or for prophylaxis of myocardial infarction or stroke, the participant will be encouraged to continue the same usage of that medication throughout the study.

6.6.4 **Not allowed medications**

Participants cannot take as rescue medication or start therapy with any oral anti-epileptics, SSRIs, SSNRIs, MAOIs, tricyclics antidepressants, tizanidine, baclofen, prednisone during the study (Please see Appendix B). In addition, they cannot receive any nerve blocks, onabotulinum toxin A injections, or use prescription compound topicals (except the ones that can be used as rescue mentioned above) or drug infusions for the management of TNP.

Participants who are currently taking pain medication for TNP and the rescue medication was not helpful and are in need of other strategy due to TNP, they will need to be withdrawn from the study to follow up with TNP management (this being dosage adjustment of the medication they are currently taking for the management of TNP or other).

Participants who are not currently taking pain medication for TNP, and the rescue medication was not helpful and are in need of other strategy. They will need to be withdrawn from the study to follow up with TNP management.

6.6.5 ***Nonpharmacologic Therapy***

During the course of the study, participants will not be restricted in the use of non-pharmacological therapies, excluding Cognitive Behavioral Therapy (CBT) and acupuncture. If a participant starts these for the complementary management of pain during the study, the use of these therapies will be recorded in the eCRF and the patient will need to be withdrawn of the study.

7 STUDY SCHEDULE

7.1 Pre-Screening

Pre-screening (0-2 weeks, Day -15 to -1)

Potential participants may be contacted by telephone or in person for pre-screening; in some instances, it may also be conducted simultaneous with the Screening and Baseline Visit (Visit 0) or during a scheduled visit to the Brotman Facial Pain Clinic, Oral Surgery Clinic or Pain Medicine Clinic (School of Medicine).

After contacting potentially eligible participants and after obtaining their verbal consent we will proceed to conduct a pre-screening interview with questions designed to identify participants with a high probability of meeting inclusion criteria. This interview will be conducted by trained study staff using a standard script. For the potential participants who express interest in the study, documentation of verbal consent, the pre-screening date, and screening ID will be recorded. In addition, an in-clinic Screening and Baseline Visit (Visit 0), will be scheduled within 2 weeks from the date of the pre-screening interview.

7.2 Screening and Baseline Visit (Visit 0, 4 weeks period)

This visit will happen with 2 weeks after pre-screening. Participants will start the baseline period that will consist of 4 weeks.

- Obtain and document consent from subject participation in the study.
- Obtain signed Health Insurance Portability and Accountability Act (HIPAA)

Authorization

- Review medical/dental history to determine eligibility based on inclusion/exclusion criteria.
- Take blood pressure and collect weight and height.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
    - Record concomitant medications and therapies
- Perform QST examination
- Perform EEG
- Collect blood for Cytokine release assay

- Perform urine pregnancy test (in women with childbearing potential)
- Provide instruction to complete 4 outcome measure questionnaires in paper or electronically for review next visit
- Provide instruction to complete Daily Symptom Diaries electronically or in paper dispense forms.

7.2.1 Randomization

The participant to be eligible requires to present symptoms of trigeminal neuropathic pain for a minimum of 3 months (12 weeks). In addition, the participant to be eligible is required to have 80% compliance with the Daily Symptom Diary for the baseline period after visit 0 and reported an average pain intensity score of 4/10 in where 0= no pain and 10= maximum pain imaginable on a numerical rating scale (0-10), during the 4 weeks/28 days baseline period prior randomization as specified in the inclusion criteria. Participants then will be randomly assigned to one of two groups (Erenumab or placebo) and will be scheduled for Visit 1. Visit 1 should be scheduled within a week after randomization.

7.3 Treatment Visits

Visits 1-4

Participants will be receiving 3 cycles of either erenumab or placebo in visits 1-3. On visit 4, treatment will not be delivered but assessments will be performed.

7.3.1 First treatment cycle (Visit 1, Day 0)

- Review Daily Symptom Diaries in eCRF or collect and review it in paper forms
- Review medical/dental history to determine eligibility based on inclusion/exclusion criteria.
- Record concomitant medications and therapies
- Take blood pressure and collect weight
- Assess and record adverse events (AEs)
- Perform urine pregnancy test (in women of childbearing potential)
- Review 4 questionnaires from Visit 0 in eCRF or collect and review the paper forms

- Provide instruction to complete 4 new outcome measure questionnaires in paper or electronically for review at Visit 2.
- Provide instruction to complete Daily Symptom Diaries electronically or provide them in paper forms
- Deliver the injection of the study drug or placebo
- Schedule next visit

7.3.2 Visit 2, 2nd treatment/cycle (Day 28+/-3 days/ 4 weeks after Visit 1)

- Review Daily Symptom Diaries in eCRF or collect and review it in paper forms
- Assess compliance with Daily Symptom Diaries
- Review medical history
- Record concomitant medications and therapies
- Take blood pressure and collect weight
- Assess and record adverse events (AEs)
- Perform urine pregnancy test (in women of childbearing potential)
- Review 4 questionnaires from Visit 1 in eCRF or collect and review the paper forms
- Provide instruction to complete 4 new outcome measure questionnaires in paper or electronically for review at Visit 3.
- Provide instruction to complete Daily Symptom Diaries electronically or provide them in paper forms
- Deliver the injection of the study drug or placebo
- Schedule next visit

7.3.3 Visit 3, 3rd and final treatment cycle (Day 56+/- 3 days after 4 weeks from Visit 2)

- Review Daily Symptom Diaries in eCRF or collect and review it in paper forms

- Assess compliance with Daily Symptom Diaries
- Review medical history
- Record concomitant medications and therapies
- Take blood pressure and collect weight
- Assess and record adverse events (AEs)
- Perform urine pregnancy test (in women of childbearing potential)
- Review 4 questionnaires from Visit 2 in eCRF or collect and review the paper forms
- Provide instruction to complete 4 new outcome measure questionnaires in paper or electronically for review at Visit 4.
- Provide instruction to complete Daily Symptom Diaries electronically or provide them in paper forms
- Deliver the injection of the study drug or placebo
- Schedule next visit

7.3.4 Visit 4, assessment of last treatment cycle (Day 84+/- 3 days,4 weeks after Visit 3)

- Review Daily Symptom Diaries in eCRF or collect and review it in paper forms
- Assess compliance with Daily Symptom Diaries
- Review medical history
- Record concomitant medications and therapies
- Take blood pressure and collect weight
- Assess and record adverse events (AEs)
- Perform QST

- Perform EEG
- Collect blood for Cytokine release assay
- Perform urine pregnancy test (in women of childbearing potential)
- Review 4 questionnaires from Visit 3 in eCRF or collect and review the paper forms
- Provide instruction to complete 4 new outcome measure questionnaires in paper or electronically for review at Visit 5.
- Provide instruction to complete Daily Symptom Diaries electronically or provide them in paper forms
- Schedule next visit

7.4 Follow up and final Study Visit, Visit 5 (Day 112 +/- 3 days, 4 weeks after Visit 4)

- Review Daily Symptom Diaries in eCRF or collect and review it in paper forms
- Assess compliance with Daily Symptom Diaries
- Review 4 questionnaires from Visit 4 in eCRF or collect and review the paper forms
- Review medical history
- Record concomitant medications and therapies
- Take blood pressure and collect weight
- Assess and record adverse events (AEs)
- Perform urine pregnancy test (in women of childbearing potential)
- Provide final instructions to subject (in case of AE showing later)
- Complete a disposition form

7.5 Withdrawal Visit

An early termination visit will be performed if a participant is suspended before the completion of the study, prior to withdrawal of consent and with the participant's permission. This could happen during a scheduled or unscheduled visit. The investigator, study coordinator or research staff will discuss with the participant to contact the research team in case AE arise after the withdrawal visit. The assessment and procedures of Visit 4 will be conducted at this visit.

7.6 Unscheduled Visit

These visits may occur at the discretion of the investigator. Reasons may include but not limited: The need for withdrawal of the study; the participant is not able to attend a scheduled visit on a specific date; inability to collect the blood sample at the scheduled visit and in case of an Adverse Effect.

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

- **Medical History**

The medical history will be taking by trained personnel during the interview and will be entered into the eCRF and will be updated each visit. As a part of the medical history, the study staff will administered a symptom inventory to assess/screen for possible AEs anticipated with the use of Erenumab throughout the study (V1-V5). Staff will record and evaluate new or worsened symptoms as possible AEs.

- **Medications and other therapies**

Pharmacological therapies such as prescription and OTC medications and non-pharmacological therapies used in the last 30 days prior Visit 0 and during the course of the study will be recorded by trained personnel in the eCRF and will be updated in each visit.

- **Vital Signs and weight collection**

After the medical history is taken, trained personnel will take the blood pressure and collect height and weight. Weight collection and blood pressure reading will be performed in each visit.

- **Pregnancy Test**

Erenumab is not recommended to use during pregnancy, therefore female participants of childbearing potential will be screened for pregnancy with a urine test (instant type) that will be performed at every study visit. The results will be read by the study staff. The urine will be discarded after the test.

- **Blood Collection**

A blood sample will be collected at Visits 0 and 4 by staff trained in phlebotomy. Blood samples will be evaluated then for the presence [redacted] cytokines by Luminex assay.

- **Sensory Testing/QST**

QST is a psychophysical procedure in which a test stimuli is applied at a defined intensity to a participant. The participant will report his/her perceptions of the intensity and the quality of the stimulus. We will be performing an extraoral QST [35-38].

<u>General sensory testing:</u>

Mechanical cutaneous pain sensitivity: Will be performed with weighted probes (2mm diameter; 8–512 mN forces) applied to the dorsum of digits 2, 3, and 4 of the left hand.

Thermal (heat) stimulation: Contact heat stimuli will be applied to the ventral forearm using a thermal probe temperature not exceeding 50 degrees Celsius.

Extraoral chair side QST: The cotton swab test will test sensitivity to non-painful mechanical stimulation (low-sensitivity). With the use of a cotton swab, the skin will be gently stroked 3-4 times with strokes of 1-2 cm in length in the area of V1, V2 and V3 and we will compare responses between the non-painful side to the painful side to detect normosensitivity, hyposensitivity, hypersensitivity and allodynia.

The spatula test will test temperature sensitivity following the same procedure as in the other 2 tests and temperature will be applied for 2-3 seconds. It is performed with a spatula that will be cold not exceeding 5 degrees Celsius or heated in a water bath until is 40 degrees Celsius.

- **EEG Assessment**

EEG assessment will be performed in all participants. In chronic pain patients, alpha rhythms are slower in frequency and elevated in power relative to matched, healthy controls[39, 40]. Within the alpha band, the frequency at which maximum power is displayed, known as peak alpha frequency (PAF), varies considerably amongst individuals [45]. We have shown that PAF predicts future pain sensitivity in multiple experimental pain models [41-43]. We will examine whether erenumab can modulate PAF and therefore mediate clinical effects. PAF is based on a 5-minute, eyes-closed resting state EEG.

- **Daily Symptom Diary**

Participants will be asked to complete the Daily Symptom Diary at the end of each day starting at the baseline phase and through the entire study (visits 1-5). Participants should have at least 80% compliance with the DSD the entire month, the equivalent of 23 completed days.

The diary collects the participant's pain intensity (reported on a 0-10 numeric rating scale) and use of pain medication. Participants are required to complete a Daily Symptom Diary electronically or on paper and a new form will be used for each month of the study. These forms may be returned in person at study visits.

Outcome Measure Questionnaires

Listed in the Schedule of Events (Appendix A). Questionnaire forms on paper will be provided to the participants if an electronic form is not feasible.
Some questionnaires are self-administered, and others will be administered by trained study staff.

- Penn Facial Pain Scale-Revised: Brief 12 item questionnaire (the higher the score the more pain and disability) to assess burden and restrictions of daily activities in patients with trigeminal neuralgia (e.g. chewing, eating, talking, touching) and assess and monitor the impact of treatment interventions [31].

- Graded Chronic Pain Scale (GCPS). The GCPS includes 7 items and assesses 2 dimensions of pain: pain intensity and pain-related disability [32].

- Patient Global Impression of Change (PGIC). This instrument measures change in participant's overall status on a scale ranging from 1 (very much improved) to 7 (very much worse). The PGIC is based on the Clinical Global Impression of Change, which is a validated scale [33, 46].

- Hospital Anxiety and Depression Scale. Evaluates anxiety and depression with a 14-item instrument [34].

8.2 Laboratory Procedures/Evaluations

8.2.1 Clinical Laboratory Evaluations

- Pregnancy test: Female participants of childbearing potential will be screened for pregnancy with a urine test (instant type) that will be performed at every study visit. The results will be read by the study staff. The urine will be discarded after the test.

8.2.2 Special Assays or Procedures

Blood Collection to evaluate cytokine profile

• A blood sample will be collected at Visits 1 and 4 by staff trained in phlebotomy. Blood samples will be evaluated then for the presence of pro-inflammatory [redacted] and anti-inflammatory [redacted] cytokines by Luminex assay.

• Pre-collection preparation – participants do not require any special preparation for the sample collection.

• Mode of collection – A blood sample will be taken by a blood draw.

• Amount, frequency, and quality of specimen collection – The blood sample will consist of 10-15 ml this will be for each subject and will be taking on visits 1 and 4

• Specimen collection duration – We estimate that the collection procedure will have a duration of 15 minutes.

8.2.3 Specimen Preparation, Handling, and Storage

Collection of blood will be performed by trained staff in phlebotomy at the School of Dentistry and serum/plasma isolation and storage will be held at the same school. The samples will be labeled with the same unique identification number provided for the participant at the moment of enrollment in our study and randomization. Peripheral blood leukocytes (PBLs) and plasma will be isolated from 10-15 ml of the subjects' blood and stored at -80°C. The plasma fraction will be used for analysis of the presence of soluble cytokines, proinflammatory ([redacted] and anti-inflammatory ([redacted]) cytokines by Luminex assay. At the end of the sample analysis, any remaining sample will be discarded.

8.2.4 Specimen Shipment

The analysis of the specimens will be performed by the Center for Innovative Biomedical Resources (CIBR core).

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

This study involves the use of Erenumab, a fully human monoclonal antibody that is a CGRP antagonist FDA approved for the management of chronic migraine.

The participants of this study will be closely monitored and follow up in their clinic visits and between visits with telephone calls. As part of the study outcomes, the study staff will record information regarding AEs. Overall health parameters will be captured on case report forms. These will be completed at every visit and data will be compiled for review by the IRB and AMGEN.

The description of potential risks is described in 2.3 and 6.3. The most common side effects of the use of Erenumab are:

- Injection site reactions: which may include tenderness, pain, redness, itching,

bruising, firmness, or hypersensitivity

- Constipation
- Muscle spasms/Cramps
- Itching (pruritus)

Allergic reactions can happen within hours to days after using erenumab. Therefore, after the injection is administered, the participant will wait in the room for 20 minutes and the evening of the treatment visit, the participant will receive a follow up phone call and the information will be recorded.

9.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Severe allergic reactions due to Erenumab: Severe skin reactions, difficulty breathing or swallowing.
- Severe constipation that may need hospitalization.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI and staff personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation. At each study visit, the study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution, returns to baseline or stabilizes. If the AE does not meet these outcomes within 30 days after discontinuation of Erenumab or the end of the study, the participant will be referred to an appropriate practitioner for continued care.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

9.3.2 Expectedness of SAEs

AMGEN and the Study PI will be responsible for determining whether an AE/SAE is expected or unexpected.

The most common adverse reactions (incidence ≥ 3% and more often than placebo) in the migraine studies were injection site reactions and constipation. Common side effects that may affect between 1 and 10 people in every 100:

- Injection site reactions: which may include tenderness, pain, redness, itching, bruising, firmness, or hypersensitivity
- Constipation
- Muscle spasms/cramps

- Itching (pruritus)

Since erenumab was approved in May 2018, the following events have been reported in patient's exposed to erenumab in the post-marketing setting:

1)Severe allergic reactions such as rash, swelling and difficulty breathing, or swallowing.

2) Mouth/lip sores (e.g., stomatitis, mouth ulcerations, and oral mucosal blistering)

3) Skin and subcutaneous tissue disorders

o Alopecia (loss of hair)

o Rash (e.g., papular rash [small raised red rash], exfoliative rash [redness and/or peeling of skin], erythematous rash [red rash], urticaria [hives], and blisters)

4)Constipation and the use of medications that decrease gastric motility are in our exclusion criteria, however if a new onset of constipation occurs, the participant will be withdrawn of the study and will be referred to an appropriate practitioner for continued care (see section 9.2).

5) Hypertension or worsening of high blood pressure can happen after receiving Erenumab. Hypertension is in our exclusion criteria, however if a new onset of hypertension occurs, the participant will be withdrawn of the study and will be the participant will be referred to an appropriate practitioner for continued care (see section 9.2)

An adverse event (AE) will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention, protocol, investigator's brochure and/or informed consent document.

9.3.3 Severity of Event

Severity grades will be based on the Common Terminology Criteria for Adverse Events (CTCAE)

grade 1 = mild; grade 2 = moderate; grade 3 = severe or medically significant; grade 4 = life-threatening consequences; and grade 5 = death.

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting to IRB and AMGEN

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form within the Electronic Data Capture (EDC) system. Following OHRP recommendations the investigators will include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB and AMGEN Safety:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number.

- A detailed description of the adverse event, incident, experience, or outcome.

- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem.

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

[redacted]

- All unanticipated problems will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to AMGEN Safety via email by the investigator. These reports will be reviewed by the IRB.

[redacted]

[redacted]

9.4.2 Serious Adverse Event Reporting to AMGEN Safety and UMB IRB

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to the IRB and AMGEN Safety. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

o [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

The PI will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.

- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

9.4.3 Reporting of SAEs and AEs to FDA

FDA reporting is not applicable.

9.4.4 Events of Special Interest (if applicable)

Any clinically significant finding of worsening of a medical condition other than Trigeminal Neuropathic Pain (TNP) established at baseline/Visit 0 or the development of any new clinically significant medical condition throughout the study will be considered an AE and will be reported as described previously.

9.4.5 Reporting of Pregnancy

If a participant becomes pregnant at any time during the study, it will be recorded on a case report form within the EDC system. Pregnancy/lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital anomaly etc.) will be reported within 1 business day of sponsor/PI awareness, for reports meeting serious criteria and not to exceed 15 calendar days of sponsor awareness, for non-serious reports to IRB and AMGEN Safety (As mentioned on 9.4.2 Table 2).

Participants who become pregnant while participating in the study will be withdrawn from the study and referred for appropriate care. If a participant becomes pregnant while receiving the study drug, she will be followed for safety until a pregnancy outcome is reached. If the pregnancy results in an outcome other than a normal birth or elective abortion of a healthy fetus, it will be reported as an SAE.

9.5 Halting Rules

This is addressed in Section 5.6. Based on the findings of a (scheduled or ad-hoc) safety review, the study may be temporarily suspended to enrollment (or to an intervention), or it may be prematurely terminated.

Depending on the findings of a safety review, the medical monitor, UMB (sponsor) IRB, or the DSMB will determine whether the study: should continue per protocol; proceed with caution; be further investigated; be modified; or be terminated.

Some types of events that might trigger a safety review are: number of SAEs overall; prevalence of a specific SAE; number/type of severe AEs; or increased frequency of AEs.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in pain management and orofacial pain management at the sponsor site . The PI, and DSMB will meet on a predetermined schedule to assess safety and efficacy data, study progress, and data integrity for the study.

11 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the IRB UMB The monitor will evaluate study processes and documentation based on IRB UMB standards and the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The primary efficacy hypothesis is a higher proportion of participants in Erenumab group will achieve at least 30% reduction in monthly average pain score from baseline (monthly data prior to Visit 1) to end of treatment (monthly data prior to Visit 4) than those in placebo group.

The secondary efficacy hypothesis:

To investigate the efficacy of Erenumab compared to placebo on the reduction in monthly average daily pain score from baseline to the end of 12-week treatment period.

To investigate the efficacy of Erenumab compared to placebo on the proportion of subjects who achieved a least 30% reduction in the monthly average daily pain score from baseline to Visit 5 (follow-up/final visit).

To determine the efficacy of Erenumab using functional measures related to TNP impact in daily activities, disability and emotional functioning measured by questionnaires (GCPAs, HADS, PGIC and PENN Facial Pain Scale).

The exploratory hypothesis:

[redacted]

12.2 Sample Size Considerations

The sample size was calculated based on the primary objective to compare the percentage of participants who had at least 30% reduction in pain from baseline to end of the treatment between experimental groups. Gomez-Arguelles et al. reported a reduction in pain frequency in days from 12.26(SD, 3.86) at baseline to 5.16(SD, 2.16) after 12 weeks anticonvulsants therapy for a group of trigeminal neuropathic pain patients [47] The changes was estimated as a very large effect size Cohen's d=2.1. The effect size in the animal studies has also been shown to be extremely large, approximately of 7 SD [48]. We assume the proposed trial will have a large effect size with Cohen's d=.8 or OR=4.2. Based on this assumption and two-sided type I error of α=.05, a sample of n=36 will provide sufficient power (Power >80%) to detect a large effect size between two groups [49]. This effect size could be interpreted as that about 58% of the participants in intervention group will reach at least 30% reduction in pain scores at the end of treatment

while 25% occur in the placebo group. Considering a 15% overall dropout rate, we will recruit N=40 participants (20 in each experimental group).

12.3 Final Analysis

Descriptive statistics including measures of central tendency, dispersion and appropriate visualization approaches (e.g., box plots and spaghetti plots) will be performed on each outcome variable (pain scores, and outcomes in secondary and exploratory objectives) by time points and groups. This will be done to ascertain distributional characteristics and ensure that the assumptions (e.g., normality) associated with the planned statistical procedures are met. When necessary, transformations will be performed. All analyses will be done in SAS and will follow an intent-to-treat philosophy.

The main goal of the statistical analyses is to compare the changes in study primary and secondary endpoints between groups to evaluate efficacy of Erenumab. For the primary objective, the generalized Linear Mixed Models (GLMM) with binomial distribution will be used to assess the efficacy of Erenumab on the primary endpoint (i.e., at least 30% reduction in pain score; yes/no). The fixed effects included in the models will be treatment group (intervention versus placebo), time (dummy coded from baseline to visits 2-4), and the interaction terms of group by time. The random effects include the participants to account for correlations between repeated measures. The primary hypothesis will be tested by evaluating the interaction term of group and time from baseline to visit 4. In the meantime, the Erenumab efficacy from baseline to visits 2 and 3 will be evaluated through the interaction terms at the corresponding time points. The secondary objective of the difference in change (>30% reduction) from baseline to visit 5 will also be evaluated using the similar GLMM model with the corresponding time (baseline, V2-V5), group and interaction terms between time and group. The interaction of time (baseline to V5) and group will be evaluated to test the hypothesis. The difference from V4 to V5 will also be evaluated by contrast estimation from the model. We will use a significance level of two-sided $\alpha < 0.05$ as primary hypothesis test.

Separate linear mixed models will be applied to test other secondary objectives (e.g., monthly mean pain scores, measures of daily activities and functions, etc.) and exploratory objectives (e.g., QST measures) where the outcome variables are continuous. The model and testing will be the same as described in the above primary objective. The use of mixed models will provide flexibility with regard to assumptions related to the covariance structure of the residuals and the presence of missing data for the repeated measures.

Descriptive statistics for safety measures will also be calculated. We will collect the following data for descriptive purposes and, if necessary, to use as covariates: Demographic information (age and race/ethnicity), rescue medication history, psychological factors and perceived change in overall status (PGIC).

Missing Data

Participants may miss specific data points for a variety of reasons such as a missed visit, early withdrawal from the study, or inability to evaluate an endpoint at a time point. If participants miss entering data in the DSD, the missing data will be imputed by the mean of observed daily data if the missing days are less than 80% within a month. If the missing days are more than 80%, the monthly measurement from the previous month will be carried forward to replace the missing value for continuous endpoints.

If there is significant dropout, we will identify baseline characteristics that differ between those dropped out and retained. Maximum likelihood methods will be used for primary analyses, which address non-informative dropout [missing at random (MAR)]. If "informative" dropout is present, we will consider sensitivity analyses that add these relevant baseline covariates to make the MAR assumption more plausible [50]

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

All information collected considered to be source of that data such as original records of clinical findings, observations, participant self-reported information, hospital and pharmacy records, medical records, laboratory and diagnostic reports, notes to file, and all other information that is necessary to reconstruct and evaluate this clinical trial, will be kept. Clinical examination, daily symptom diary, and questionnaire data will be recorded directly from the participant onto eCRFs, with the eCRFs being the source document. Study staff will have access to the records in accordance with their assigned responsibilities outlined in the Delegation of Responsibility Log.

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of UMB, clinical monitors, and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety progress and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control is the ongoing, concurrent review of data collection forms for completion and logic/consistency. Quality assurance is the comprehensive, retrospective review of all components of research records to assess adherence to the protocol, standard operation procedures, and regulatory requirements, and to evaluate the accuracy of the records. Quality management is the overall process of assessing the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control and quality assurance.

The quality management program will include but will not be limited to, the following:

- Training of staff on the protocol, study procedures, data collection forms, and data entry methods
- Documentation and tracking of training for each staff member
- A Quality Management Plan that describes processes and activities to be used to ensure compliance with the study protocol and accuracy in relation to source documents and data entry
- A Data Management Plan that describes procedures for collecting and entering data, storing data securely, and integrating data quality control and validation
- A Clinical Monitoring Plan that describes the periodic site visits to be made by study monitors to insure that human subjects are protected, that the study has been implemented in accordance with the protocol and that study data are current, complete, and are securely stored.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval from AMGEN and the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Potential participants may be contacted by telephone or in person for pre-screening; in some instances, it may also be conducted simultaneous with the Screening and Baseline Visit (Visit 0) or during a scheduled visit to the Brotman Facial Pain Clinic, Oral Surgery Clinic or Pain Medicine Clinic. Written informed consent will be obtained at Visit 0 in where will be evaluated eligibility, obtain demographics, medical history, medication information, and perform evaluations and provide the daily symptoms diaries and questionnaires and then schedule visit 1.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be approved by the sponsor (UMB) IRB, and the subject is required to read and review the document or have the document read to him or her.

The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

There are no exclusions based on gender or racial/ethnic groups. The age range for participation is 18-65 years old.
Children will not be included in the study since Erenumab has not been validated in children and because TNP rarely occurs in children.

15.5 Subject Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to the participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study safety monitor, or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site (UMB School of Dentistry) will permit access to such records.

Research data from participants will be collected on either paper or electronic forms. Only a unique study identification number will appear on such forms; therefore, no information that could be used to individually identify a participant will be displayed.

Only study staff will be given access to the key that links name and identification number. All paper records and study-related information will be kept under lock and key in a private, locked research office. Electronic records will be stored according to UMB requirements for research data security.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Blood samples will be stored until analysis. At the end of the sample analysis, any remaining sample will be discarded.

The urinary sample taken for the pregnancy test will discarded after the test is performed.

16 DATA HANDLING AND RECORD KEEPING

Participant's research data will be collected on either paper or electronic forms. Only a unique study identification number will appear on such forms; therefore, no information that could be used to individually identify a participant will be displayed.

Only a minimum number of study staff will be given access to the key that links name and identification number and will be strictly controlled. Individual identifiers will never appear on data forms. All paper records and study-related information will be kept under lock and key in a private, locked research office. Electronic records will be stored according to UMB requirements for research data security.

Participants can complete the questionnaires and diaries at home or at the research study site. A private (locking) room will be provided for data collected at the study site. All data entry, transfer, and storage will be accomplished in strict accordance with all regulations and UMB requirements for data security.

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making corrections, the original entry will be crossed out with a single line and the correction will be entered and dated. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

16.2 Data Capture Methods

Study staff will complete case report forms online via a password-protected, web-based EDC system that has been validated and is compliant with Title 21 CFR Part 11. Data quality will be continuously monitored, with real-time detection and correction of errors. This system will incorporate an audit trail, such that all elements of data entry (date, time, name of person performing data entry, verbatim alpha/numeric responses) can be retrained and reviewed as needed, in accordance with federal regulations.

16.3 Types of Data

Demographic and medical history data, concomitant medication information, clinical examination information, psychosocial and clinical questionnaire information, pressure

pain threshold testing information, laboratory test results and serum/plasma cytokines will be collected in the study.

16.4 Schedule and Content of Reports

The study coordinator will continuously monitor data collection. It will post study progress reports (numbers screened, screen failures, enrolled, and randomized) to the study website monthly throughout the study period, as directed by the IRB and the PI. It will also post data management reports that contain measures of data quality (i.e., number of outstanding data queries and data completion rates). Study reports will be provided to the DSMB according to an established schedule, and the DSMB report will be submitted to the UMB IRB as part of the study's annual renewal.

16.5 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB according to their requirements.

17 PUBLICATION/DATA SHARING POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

The study will comply with AMGEN requirements and will provide AMGEN the pre-publication / presentation, abstract for review in their specific timelines. Amgen may request sponsors to withhold any publication or presentation an additional period upon request. The sponsor is expected to keep study results confidential until publication and must acknowledge Amgen's support in all publications. Sponsor to grant Amgen, subject to publisher's rights, a license to distribute copies of any publication / presentation within Amgen and to licensees, licensors, affiliates, and authorized representatives and to prepare derivative works of any publication.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

18 LITERATURE REFERENCES

1. Mignogna, M.D. and S. Fedele, *The Neglected Global Burden of Chronic Oral Diseases.* Journal of Dental Research, 2006. **85**(5): p. 390-391.
2. Baad-Hansen, L., et al., *Comparison of clinical findings and psychosocial factors in patients with atypical odontalgia and temporomandibular disorders.* J Orofac Pain, 2008. **22**(1): p. 7-14.
3. Peñarrocha, M.A., et al., *Post-traumatic trigeminal neuropathy. A study of 63 cases.* Med Oral Patol Oral Cir Bucal, 2012. **17**(2): p. e297-300.
4. Smith, J.G., et al., *The psychosocial and affective burden of posttraumatic neuropathy following injuries to the trigeminal nerve.* J Orofac Pain, 2013. **27**(4): p. 293-303.
5. Eliav E, M.M., *Management of neuropathic pain*, in *Orofacial pain. From basic science to clinical management.* , L.G. Sessle B, Lund J, Dubner R, editors., Editor. 2008, Quintessence: Chicago. p. 195-202.
6. Baad-Hansen, L. and R. Benoliel, *Neuropathic orofacial pain: Facts and fiction.* Cephalalgia, 2017. **37**(7): p. 670-679.
7. Romero-Reyes, M. and J.M. Uyanik, *Orofacial pain management: current perspectives.* J Pain Res, 2014. **7**: p. 99-115.
8. *International Classification of Orofacial Pain, 1st edition (ICOP).* Cephalalgia, 2020. **40**(2): p. 129-221.
9. Lewis, M.A.O., et al., *Management of neuropathic orofacial pain.* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. **103**: p. S32.e1-S32.e24.
10. McQuay, H.J., et al., *A systematic review of antidepressants in neuropathic pain.* Pain, 1996. **68**(2-3): p. 217-27.
11. McQuay, H., et al., *Anticonvulsant drugs for management of pain: a systematic review.* Bmj, 1995. **311**(7012): p. 1047-52.
12. Dworkin, R.H., et al., *Recommendations for the pharmacological management of neuropathic pain: an overview and literature update.* Mayo Clin Proc, 2010. **85**(3 Suppl): p. S3-14.
13. Zakrzewska, J.M., *Medical management of trigeminal neuropathic pains.* Expert Opin Pharmacother, 2010. **11**(8): p. 1239-54.
14. Lars, E., *The CGRP Pathway in Migraine as a Viable Target for Therapies.* Headache: The Journal of Head and Face Pain, 2018. **58**(S1): p. 33-47.
15. King, C.T., et al., *Discovery of the Migraine Prevention Therapeutic Aimovig (Erenumab), the First FDA-Approved Antibody against a G-Protein-Coupled Receptor.* ACS Pharmacol Transl Sci, 2019. **2**(6): p. 485-490.
16. Reuter, U., et al., *Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study.* Lancet, 2018. **392**(10161): p. 2280-2287.

17. Ashina, H., et al., *Efficacy, tolerability, and safety of erenumab for the preventive treatment of persistent post-traumatic headache attributed to mild traumatic brain injury: an open-label study.* J Headache Pain, 2020. **21**(1): p. 62.
18. Cady, R., et al., *Calcitonin gene-related peptide promotes cellular changes in trigeminal neurons and glia implicated in peripheral and central sensitization.* Molecular Pain, 2011. **7**(1): p. 94.
19. Romero-Reyes, M., V. Pardi, and S. Akerman, *A potent and selective calcitonin gene-related peptide (CGRP) receptor antagonist, MK-8825, inhibits responses to nociceptive trigeminal activation: Role of CGRP in orofacial pain.* Experimental Neurology, 2015. **271**: p. 95-103.
20. Akerman, S. and M. Romero-Reyes, *Preclinical studies to dissect the neural mechanism for the comorbidity of migraine and temporomandibular disorders (TMD): the role of CGRP.* Br J Pharmacol, 2020.
21. Sugawara, S., et al., *Interaction between calcitonin gene-related peptide-immunoreactive neurons and satellite cells via P2Y(12) R in the trigeminal ganglion is involved in neuropathic tongue pain in rats.* Eur J Oral Sci, 2017. **125**(6): p. 444-452.
22. Michot, B., et al., *CGRP receptor blockade by MK-8825 alleviates allodynia in infraorbital nerve-ligated rats.* Eur J Pain, 2015. **19**(2): p. 281-90.
23. Qin, Z.L., et al., *Clinical study of cerebrospinal fluid neuropeptides in patients with primary trigeminal neuralgia.* Clin Neurol Neurosurg, 2016. **143**: p. 111-5.
24. Farajzadeh, A., et al., *Different Pain States of Trigeminal Neuralgia Make Significant Changes in the Plasma Proteome and Some Biochemical Parameters: a Preliminary Cohort Study.* J Mol Neurosci, 2018. **66**(4): p. 524-534.
25. Zhang, Y., et al., *CGRP Plasma Levels Decrease in Classical Trigeminal Neuralgia Patients Treated with Botulinum Toxin Type A: A Pilot Study.* Pain Medicine, 2020. **21**(8): p. 1611-1615.
26. Tepper, S., et al., *Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial.* Lancet Neurol, 2017. **16**(6): p. 425-434.
27. Ashina, M., et al., *Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study.* Cephalalgia, 2018. **38**(10): p. 1611-1621.
28. Lattanzi, S., et al., *Erenumab for Preventive Treatment of Migraine: A Systematic Review and Meta-Analysis of Efficacy and Safety.* Drugs, 2019. **79**(4): p. 417-431.
29. Dworkin, R.H., et al., *Core outcome measures for chronic pain clinical trials: IMMPACT recommendations.* Pain, 2005. **113**(1-2): p. 9-19.
30. Farrar, J.T., et al., *Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale.* Pain, 2001. **94**(2): p. 149-58.

31. Symonds, T., et al., *Measuring the impact of trigeminal neuralgia pain: the Penn Facial Pain Scale-Revised.* J Pain Res, 2018. **11**: p. 1067-1073.
32. Von Korff, M., et al., *Grading the severity of chronic pain.* Pain, 1992. **50**(2): p. 133-49.
33. Perrot, S. and M. Lantéri-Minet, *Patients' Global Impression of Change in the management of peripheral neuropathic pain: Clinical relevance and correlations in daily practice.* Eur J Pain, 2019. **23**(6): p. 1117-1128.
34. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
35. Svensson, P., et al., *Neurosensory testing of orofacial pain in the dental clinic.* J Am Dent Assoc, 2012. **143**(8): p. e37-9.
36. Kim, H.J., et al., *Racial/ethnic differences in experimental pain sensitivity and associated factors - Cardiovascular responsiveness and psychological status.* PLoS One, 2019. **14**(4): p. e0215534.
37. Rolke, R., et al., *Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values.* PAIN, 2006. **123**(3): p. 231-243.
38. Nasri-Heir, C., et al., *Altered pain modulation in patients with persistent postendodontic pain.* Pain, 2015. **156**(10): p. 2032-41.
39. Sarnthein, J., et al., *Increased EEG power and slowed dominant frequency in patients with neurogenic pain.* Brain, 2006. **129**(Pt 1): p. 55-64.
40. de Vries, M., et al., *Altered resting state EEG in chronic pancreatitis patients: toward a marker for chronic pain.* J Pain Res, 2013. **6**: p. 815-24.
41. Seminowicz, D.A., et al., *A novel cortical biomarker signature for predicting pain sensitivity: protocol for the PREDICT longitudinal analytical validation study.* Pain reports, 2020. **5**(4): p. e833-e833.
42. Seminowicz, D., et al., *Slow peak alpha frequency and corticomotor depression linked to high pain susceptibility in transition to sustained pain.* bioRxiv, 2018: p. 278598.
43. Furman, A.J., et al., *Cerebral peak alpha frequency reflects average pain severity in a human model of sustained, musculoskeletal pain.* J Neurophysiol, 2019. **122**(4): p. 1784-1793.
44. *Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition.* Cephalalgia, 2018. **38**(1): p. 1-211.
45. Bazanova, O.M. and D. Vernon, *Interpreting EEG alpha activity.* Neurosci Biobehav Rev, 2014. **44**: p. 94-110.
46. Hurst, H. and J. Bolton, *Assessing the clinical significance of change scores recorded on subjective outcome measures.* J Manipulative Physiol Ther, 2004. **27**(1): p. 26-35.
47. Gomez-Arguelles, J.M., et al., *Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia.* J Clin Neurosci, 2008. **15**(5): p. 516-9.

48. Doyle, T., et al., *Targeting the Overproduction of Peroxynitrite for the Prevention and Reversal of Paclitaxel-Induced Neuropathic Pain.* The Journal of Neuroscience, 2012. **32**(18): p. 6149-6160.
49. Faul, F., et al., *G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences.* Behav Res Methods, 2007. **39**(2): p. 175-91.
50. Son, H., E. Friedmann, and S.A. Thomas, *Application of pattern mixture models to address missing data in longitudinal data analysis using SPSS.* Nurs Res, 2012. **61**(3): p. 195-203.

[redacted]

APPENDICES

- *Appendix A: Schedule of Events*
- Appendix B: List of medications used for the management of neuropathic pain

[redacted]

APPENDIX A: SCHEDULE OF EVENTS

Study Phase	Pre-screening[A]	Screening and Baseline	Randomization[B] and Treatment (12 weeks of treatment/3 cycles of Erenumab)				Follow Up	Early termination
Clinic Visit		V0	V1[C]	V2	V3	V4	V5	ET
Study Day/	0-2 weeks prior to V0	4 weeks prior V1	Day 0	Day 28	Day 56	Day 84	Day 112	
Procedures								
Contact Information	X							
Pre-screening interview Script	X							
Informed consent[D]		X						
Eligibility Review	X	X						
Demographic information		X						
Medical history and Review	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X
Concomitant therapies		X	X	X	X	X	X	X
Adverse Event Review			X	X	X	X	X	X
Dispense Daily Symptom Diaries [E]		X	X	X	X	X		
Collect Daily Symptom Diaries [E]		X	X	X	X	X	X	
Assess compliance with Daily Symptom Diaries		X	X	X	X	X		
Provide study drug injection[F]			X	X	X			

Study Phase	Pre-screening[A]	Screening and Baseline	Randomization[B] and Treatment (12 weeks of treatment/3 cycles of Erenumab)				Follow Up	Early termination
Clinic Visit		V0	V1[c]	V2	V3	V4	V5	ET
Study Day	0-4 weeks prior to V0	1-3 weeks prior V1	Day 0	Day 30	Day 60	Day 90	Day 120	
Clinical Examination and Tests								
Weight		X	X	X	X	X	X	X
Height		X						
Vital signs		X	X	X	X	X	X	X
Urine pregnancy test		X	X	X	X	X	X	X
QST		X				X		
EEG		X				X		
Schedule next visit	X	X	X	X	X	X		
Laboratory								
Blood draw for Cytokine release assay		X				X		
Questionnaires								
Symptom Inventory		X	X	X	X	X	X	X
Graded Chronic Pain Scale[G]		X	X	X	X	X	X	X
Penn Facial Pain Scale-Revised [G]		X	X	X	X	X	X	X
Patient Global Impression of Change[G]		X	X	X	X	X	X	X
Hospital Anxiety and Depression Index[G]		X	X	X	X	X	X	X

APPENDIX B: List of medications used for the management of neuropathic pain

- Anticonvulsants and channel blockers: Including but not limited to:

- Carbamazepine, gabapentin, pregabalin, oxcarbazepine, verapamil, divalproex sodium, topiramate

- Tricyclics Antidepressants: Including but not limited to:
  - Amitriptyline, nortriptyline, imipramine, desipramine, doxepin
- Serotonin and Norepinephrine Reuptake Inhibitors: Including but not limited to:
  - Duloxetine (Hcl), venlafaxine
- Muscle relaxants: Including but not limited to
  - Baclofen
  - Tizanadine