Erenumab as a therapeutic approach for the management of painful chronic temporomandibular disorders (TMD)

Protocol Number: HP-0093037 (UMB)

Grant Number: Amgen ISS 20207211

Principal Investigator: Marcela Romero Reyes DDS, PhD

IND/IDE Sponsor: IND EXEMPT

Draft or Version Number: <1.2>

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11 March 2022

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation 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.

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: 3/31/2022

Name: Marcela Romero Reyes DDS,PhD

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

{For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site. For a clinical trial involving an Investigational New Drug (IND), this is the individual who signs the Form FDA 1572 for a drug or the investigator agreement for a device.}0

TABLE OF CONTENTS

{This table uses the Table of Contents function in Microsoft Word that will automatically update headings and page numbers used in the body of the report. To update the Table of Contents and all cross-references in the document, press CTRL-A to select the entire document, then press F9.}

PAGE
STATEMENT OF COMPLIANCE I
SIGNATURE PAGE II
TABLE OF CONTENTS III
LIST OF ABBREVIATIONS VI
PROTOCOL SUMMARY VIII
1 KEY ROLES AND CONTACT INFORMATION 12
2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE 14
2.1 Background Information 14
2.2 Rationale 15
2.3 Potential Risks and Benefits 16
2.3.1 Potential Risks 16
2.3.2 Potential Benefits 17
3 OBJECTIVES 18
3.1 Study Objectives 18
3.2 Study Outcome Measures 18
3.2.1 Primary 18
3.2.2 Secondary 18
4 STUDY DESIGN 20
5 STUDY ENROLLMENT AND WITHDRAWAL 21
5.1 Subject Inclusion Criteria 21
5.2 Subject Exclusion Criteria 23
5.3 Strategies for Recruitment and Retention 24
5.4 Treatment Assignment Procedures 25
5.4.1 Randomization Procedures (if applicable) 25
5.4.2 Masking and Unbliniding Procedures (if applicable) 26
5.5 Subject Withdrawal 27
5.5.1 Reasons for Withdrawal 27
5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention 27
5.6 Premature Termination or Suspension of Study 28
6 STUDY INTERVENTION 29
6.1 Study Product Description 29
6.1.1 Acquisition 29
6.1.2 Formulation, Packaging, and Labeling 29
6.1.3 Product Storage and Stability 30
6.2 Dosage, Preparation and Administration of Study Product 30

6.3 Modification of Study Product Administration for a Subject 31
6.4 Accountability Procedures for the Study Product 32
6.5 Assessment of Subject Compliance with Study Product Administration 32
6.6 Concomitant Medications/Treatments 32
7 STUDY SCHEDULE 34
7.1 Pre-Screening 34
7.2 Screening and Baseline Visit (Visit 0, 1-3 weeks period) 34
7.3 Treatment Visits 35
7.4 Follow up and final Study Visit, Visit 5 (Day 120, 4 weeks after Visit 4) 38
7.5 Withdrawal Visit 39
7.6 Unscheduled Visit 39
8 STUDY PROCEDURES /EVALUATIONS 40
8.1 Study Procedures/Evaluations 40
8.2 Laboratory Procedures/Evaluations 42
8.2.1 Clinical Laboratory Evaluations 42
8.2.2 Special Assays or Procedures 42
8.2.3 Specimen Preparation, Handling, and Storage 42
8.2.4 Specimen Shipment 43
9 ASSESSMENT OF SAFETY 44
9.1 Specification of Safety Parameters 44
9.1.1 Unanticipated Problems 45
9.1.2 Adverse Events 45
9.1.3 Serious Adverse Events 45
9.2 Time Period and Frequency for Event Assessment and Follow-Up 46
9.3 Characteristics of an Adverse Event 46
9.3.1 Relationship to Study Intervention 46
9.3.2 Expectedness of SAEs 47
9.3.3 Severity of Event 47
9.4 Reporting Procedures 48
9.4.1 Unanticipated Problem Reporting to IRB and AMGEN 48
9.4.2 Serious Adverse Event Reporting to AMGEN Safety and UMB IRB 49
9.4.3 Reporting of SAEs and AEs to FDA 53
9.4.4 Events of Special Interest (if applicable) 53
9.4.5 Reporting of Pregnancy 53
9.5 Halting Rules 53
10 STUDY OVERSIGHT 55
11 CLINICAL SITE MONITORING 56
12 STATISTICAL CONSIDERATIONS 57
12.1 Study Hypotheses 57
12.2 Sample Size Considerations 58
12.3 Planned Interim Analyses (if applicable) 58
12.3.1 Safety Review 58
12.3.2 Efficacy Review 58

12.4 Final Analysis Plan 58
13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS 60
14 QUALITY CONTROL AND QUALITY ASSURANCE 61
15 ETHICS/PROTECTION OF HUMAN SUBJECTS....62
15.1 Ethical Standard 62
15.2 Institutional Review Board 62
15.3 Informed Consent Process 62
15.4 Exclusion of Women, Minorities, and Children (Special Populations)....63
15.5 Subject Confidentiality 63
15.6 Future Use of Stored Specimens and Other Identifiable Data 63
16 DATA HANDLING AND RECORD KEEPING....64
16.1 Data Management Responsibilities....64
16.2 Data Capture Methods....64
16.3 Types of Data 64
16.4 Schedule and Content of Reports 65
16.5 Study Records Retention 65
16.6 Protocol Deviations....65
17 PUBLICATION/DATA SHARING POLICY 66
18 LITERATURE REFERENCES....67
SUPPLEMENTAL MATERIALS 70
APPENDICES....71
APPENDIX A: SCHEDULE OF EVENTS 72

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)
CFR	Code of Federal Regulations
CGRP	Calcitonin Gene Related Peptide
CIOMS	Council for International Organizations of Medical Sciences
CIBR	Center for Innovative Biomedical Resources
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DC/TMD	Diagnostic Criteria/Temporomandibular Disorders
DHHS	Department of Health and Human Services
DMFS	Decayed, missing, and filled tooth surfaces
DSD	Daily Symptom Diary
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
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
ICTR	Institute for Clinical & Translational Research
IDE	Investigational Device Exemption
IDS	Investigational Drug Services

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
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
OFP	Orofacial Pain
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SC	Subcutaneous (as subcutaneous injection)
SOP	Standard Operating Procedure
TMD	Temporomandibular Disorders
UMB	University of Maryland
UMBSOD	University of Maryland, School of Dentistry
UP	Unanticipated Problem
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:

Erenumab as a therapeutic approach for the management of painful chronic temporomandibular disorders (TMD*)*.

Précis:

A total of 60 patients (30 per each arm) aged 18-65 years old of either sex, and any race or ethnicity presenting chronic temporomandibular disorders (TMD) 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 and the Oral and Maxillofacial Surgery Clinic both at the University of Maryland, School of Dentistry 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 80% compliance with the DSD and who meet the pain score (inclusion criteria) after Visit 0 (baseline period), 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 70mg, 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 the average pain index score from baseline, representing the mean of daily average pain intensity score values (0-100 scale) derived from Daily Symptom Diaries for 12 weeks (12 weeks treatment).

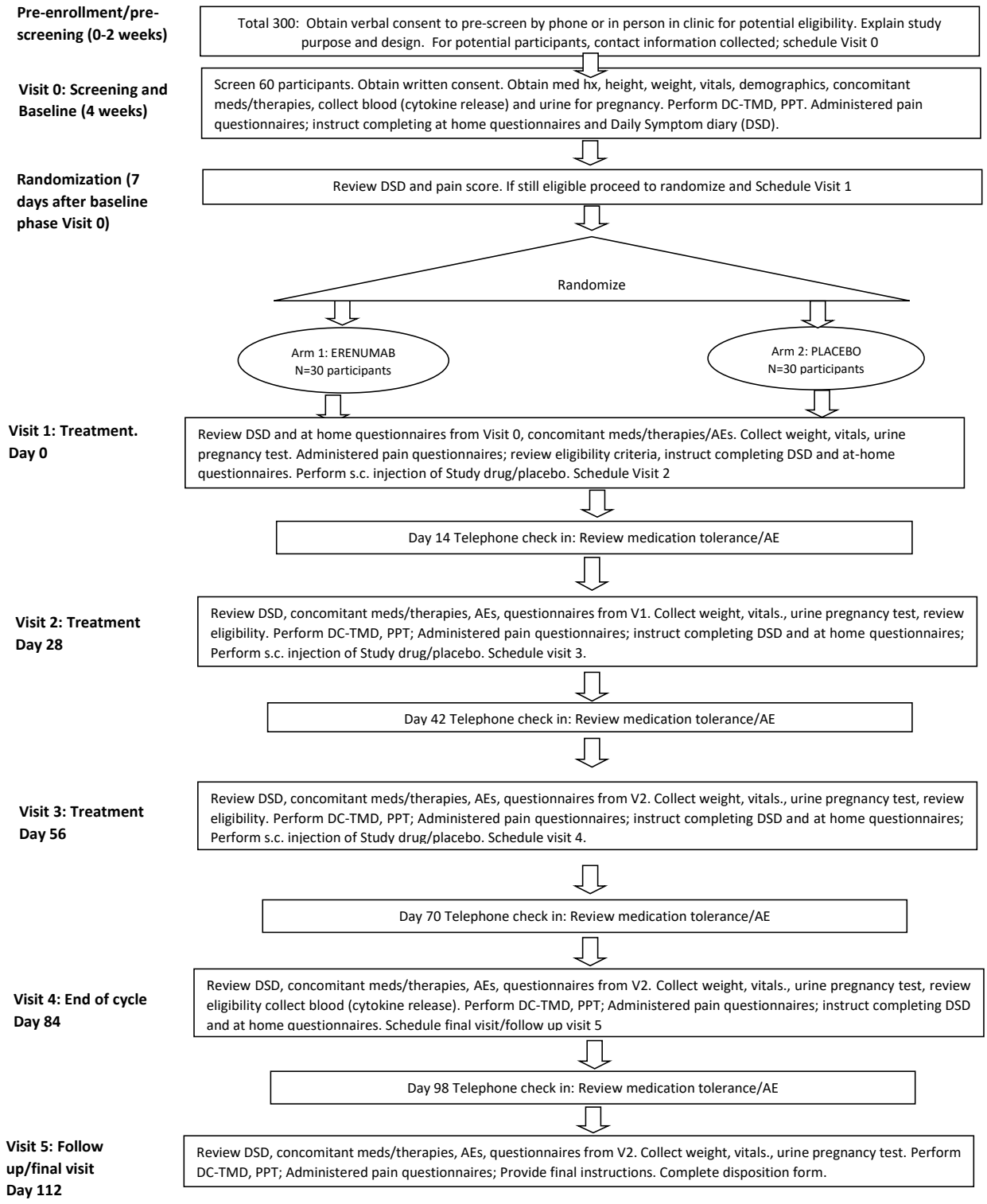
Secondary end points will be participant ratings of other pain related outcomes, examiner assessment of pain, occurrence of symptoms and adverse events.

Exploratory end points are change of [redacted] cytokine profiles [redacted]

Objectives:	Primary: To investigate the efficacy of Erenumab compared to placebo on the reduction of pain scores in patients with TMD during a 12-week treatment period. Secondary: To determine the efficacy of Erenumab on the proportion of subjects with at least 50% reduction from baseline in mean monthly TMD pain days and to determine the efficacy of Erenumab using functional measures namely, jaw functional limitation, pressure pain thresholds and oral behaviors disability, and emotional functioning. Exploratory: To investigate the efficacy of Erenumab in [redacted] cytokine release [redacted]
Population:	60 adults of either sex and any ethnicity between the ages of 18 and 65 years with a diagnosis (According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications) of chronic TMD (myalgia +/- arthralgia) and no contraindications for the use of Erenumab will be enrolled from the Brotman Facial Pain Clinic and the Oral and Maxillofacial Surgery clinic from the University of Maryland, School of Dentistry.
Phase:	II
Number of Sites:	University of Maryland, School of Dentistry
Description of Intervention:	Study drug is Erenumab 70mg or an inert placebo will be administered by subcutaneous injection once a month (3 cycles) over a 12-week period.
Study Duration:	36 months

Subject Participation Duration:	21 weeks
Estimated Time to Complete Enrollment:	Approximately 2.5 years (30 months)

Schematic of Study Design:



1 KEY ROLES AND CONTACT INFORMATION

Principal Investigator: Marcela Romero Reyes DDS, PhD

[redacted]

Medical Monitor: DSMB

Program Official:

Other Key Personnel: Jane L Phillips RDH MS

[redacted]

Gary Warburton MD, DDS

[redacted]

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Temporomandibular disorders (TMD) are a group of related heterogenous musculoskeletal disorders that affect the temporomandibular joint (TMJ), masticatory muscles, and associated structures [1]. TMD pain commonly can be localized in the muscles of mastication, along the mandible, the pre-auricular area, the ear, the temple area as well as associated with TMJ biomechanics, such as mandibular movements, including chewing, talking, yawing and mouth opening[2].

Pain associated with TMD is one of the most common complaints in the craniofacial and cervical area and the most common non-dental reason why patients seek treatment in the dental office [3, 4]. TMD have an overall prevalence estimated between 5% and 12% [5] and are more prevalent in women [5, 6]. TMD include myalgia, arthralgia, intra-articular disorders and degenerative joint diseases [7]. TMD exert a significant burden on the population affecting the productivity and quality of life [8] and it can also be present with other pain conditions such as lower back pain, fibromyalgia and headache[9, 10].

For some patients, TMD has a tendency to remit or improve pain symptomatology over time [11, 12] but for others, TMD have the potential to become chronic and to lead to persistent dysfunction [13-15]. TMD management should be conservative, reversible and based in evidence based therapeutics [16, 17] and includes a combination of home self-care, physical therapy, pharmacotherapy, oral appliance therapy, and behavioral interventions [2, 18]. Pharmacotherapy includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, muscle relaxants, benzodiazepines, and some anticonvulsants and antidepressants [18] but clear evidence establishing their efficacy is limited. Gabapentin, and anti-epileptic medication have shown to be superior than placebo in reducing myalgia [19] but dizziness and sedation, often present in this drug class with other important side effects, have been reported with its use [20]. Recently propanonol, a non-selective beta adrenergic receptor antagonist, was shown to reduce TMD myalgia when compared to placebo [21]. However, no medical treatment exists that is approved by the Food and Drug Administration (FDA) specifically for the management of TMD. Therefore, safer, and novel pharmacological therapy protocols 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 [22]. Targeting the CGRP receptor pathway has proven to be effective in migraine therapeutics. Erenumab is a fully human monoclonal antibody that inhibits CGRP pathway and is the first in its class to be FDA approved for the management of migraine as a migraine preventive[23].

TMD and migraine are often co-morbid. The presence of TMD significantly increases the likelihood of any form of headache, particularly migraine and can exacerbate its disability

impact [10, 24-26]. We and others have shown that CGRP is also involved in TMD pathophysiology [27] and we demonstrated that blocking CGRP with a CGRP receptor antagonist in a pre-clinical model of TMD, significantly decreased nociception[28]. The management of chronic TMD inhibiting CGRP pathway with an FDA approved medication that has been proved safe for another indication such as migraine which shares CGRP as a molecular link, would be very promising. Therefore, we have hypothesized that Erenumab - a monoclonal antibody that inhibits CGRP receptor- reduces pain and restores function in patients suffering of chronic TMD. This proposed clinical trial is the first study of this nature, looking at Erenumab as a new pharmacological therapy for patients suffering of chronic TMD.

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

2.2 Rationale

Chronic TMD is a considerable burden and affects significantly the quality of life of the sufferer [8]. Medications such as gabapentin and propranolol have indicated to be beneficial in clinical studies [19, 21], but tolerability and side effects may be present for some patients. Furthermore, the indications of these drugs are for other disorders, so it is unclear their mechanism of action in TMD pathophysiology. Currently there is no medication specifically indicated for the management of TMD based on its molecular pathophysiology. However, there is evidence showing that CGRP has a role in TMD pathophysiology [27] and we demonstrated that targeting CGRP in a preclinical model of TMD decreased nociception [28].

CGRP is a key molecule in migraine pathophysiology. Erenumab is the first antibody therapeutic targeting the CGRP receptor with FDA approval [23]. It has shown efficacy, to be well tolerated and with a safety profile similar to placebo for the prevention of chronic migraine in adults [29-31]. Erenumab is also approved in the prevention of episodic migraine in adults demonstrating its efficacy in randomized controlled clinical trials and has been shown promising for the management post-traumatic headache attributed to brain injury [32, 33]. Migraine and TMD share CGRP as a molecular link [26]. Therefore, the scientific premise for this study is that inhibiting CGRP in chronic TMD will decrease pain, pain related outcomes and improve TMJ biomechanics (function) 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 in adults. 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).

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)

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.

TMD examination and pressure pain threshold testing (PPT): A TMD examination will assess muscles of mastication and TMJ sensitivity to manual palpation. The PPT will assess pain applying pressure with the use of an algometer in muscles and the TMJs. Both assessments will be performed on 4 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.

Self-care: It is possible that some participants may feel frustrated if they are unable to incorporate and to understand some self-management approaches.

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 and improved function. Additionally, if Erenumab proves to be effective, this will be the first pharmacological approach specifically indicated for TMD 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 chronic TMD.

3 OBJECTIVES

3.1 Study Objectives

Primary Objective

To investigate the efficacy of Erenumab compared to placebo in the reduction of pain scores in participants with chronic TMD during a 12-week treatment period.

Secondary Objectives

To determine the efficacy of Erenumab on the proportion of subjects with at least 50% reduction from baseline in mean monthly TMD pain days.

To determine the efficacy of Erenumab using functional measures and pain related behaviors: Jaw function, Pressure Pain Thresholds, Oral Behaviors, changes in pain intensity and pain related disability, perspective of pain improvement, and anxiety and depression.

Exploratory Objectives

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

3.2 Study Outcome Measures

3.2.1 Primary

The primary endpoint will be a monthly mean pain intensity score change from baseline, representing the arithmetic mean of daily average pain intensity score values. The daily average pain intensity score will be measured on a 0-100 numeric rating scale (NRS) and reported in the Daily Symptom Diary (DSD). The monthly mean pain intensity score will be determined from baseline, for each month/cycle (4 weeks/28 days) during the 12 weeks (3 cycles) of treatment and the last month prior last visit (Follow up).

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

3.2.2 Secondary

Efficacy will be investigated further using secondary outcomes:

TMD pain days: Percentage of participants with at least a 50% reduction from baseline in monthly TMD pain days. Time Frame: Baseline phase, the 12 weeks of management and until Visit 4.

Definition of TMD pain day: A TMD pain day was any calendar day in which the participant experienced pain, stiffness, soreness, tenderness, in the jaw or temple area or either side being brief or continuous; and/or pain with TMJ biomechanics (chewing, mouth opening or any jaw movement; and/or pain with jaw activities (yawning, kissing, talking); and/or pain with jaw habits (chewing gum, clenching, grinding).

At least a 50% reduction from baseline in monthly TMD days will be determined if the change in monthly TMD days from baseline phase through the 12 weeks treatment phase (3 cycles) * 100 / baseline monthly TMD days less than or equal to -50%.

Functional measures related to TMJ biomechanics and pain related behaviors:

TMD examination and Jaw functional limitation Scale: Change related to TMJ biomechanics/Jaw function and symptomatology in response to TMD examination.

Oral Behaviors (OBC): Changes in parafunctional behaviors

Pressure Pain Thresholds: Changes in myalgia and arthralgia

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

Patient Global Impression of Change (PGIC): Assesses patient perspective of pain improvement

Hospital Anxiety and Depression Scale: Evaluation of Anxiety and depression

Exploratory Endpoint

To investigate the efficacy of Erenumab in decreasing pro-inflammatory cytokine release [redacted]

4 STUDY DESIGN

60 patients (30 per each arm) aged 18-65 years old of either sex, and any race or ethnicity presenting chronic painful temporomandibular disorders (TMD) 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 3 years, with an estimated duration of recruitment of 2.5 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 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, jaw function, 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 endpoint will be the change in a monthly mean pain intensity score derived from the Daily Symptom Diary. Efficacy will be evaluated as the difference between Erenumab arm and the placebo arm in the monthly pain intensity score (on a 0-100 scale) during the 12 week treatment period.

5 STUDY ENROLLMENT AND WITHDRAWAL

The study is planning to enroll a total of 60 subjects that will be randomly assigned to one of the two study groups. It is anticipated that a total of 300 subjects will be screened in order to meet recruitment goals.

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. Meets diagnostic criteria for TMD: Myalgia with or without arthralgia

    - The participant must meet 2 criteria relating: 1) reported pain, ache or tenderness in the face, jaw/mandible, pre-auricular area, inside the ear or temple that it is modified by TMJ biomechanics. 2) finding(s) of TMD myalgia according to the classification DC/TMD criteria.

4. Has experienced facial pain and/or pain with TMJ biomechanics for the last 3 months episodically or unremitting

5. Has experienced facial pain for at least 10 days of the last 30 days prior to Baseline Visit (Visit 0)

6. Prior to randomization, has been compliant 80% with the entries in the Daily Symptom Diary within the baseline period and reported an average pain level ≥30 on a numerical rating scale (0-100) in the DSD, or has experienced a pain level ≥30 on the same scale for at least 3 days in the week prior to Visit 1.

7. 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.

8. If taking prescription medication, opioid medication or OTC medications as needed or episodically for the management of TMD pain agrees to discontinue its use prior to the Screening and Baseline Visit.

    - Rescue medications will be defined as allowable over-the-counter analgesics used for treatment of TMD pain. In case a patient presents pain during the study, only it is allowed the use of OTC medications as a “rescue” and as described on section 6.6.3: Participants use of short-acting non-prescription analgesics such as NSAIDs, acetaminophen or aspirin during the study, will be recorded and quantified at each visit, and the usage will be classified as either episodic or daily. Episodic use of non-prescription analgesics 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 visit 4, when the exploratory outcome is assessed (cytokine release assay).

9. 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.

10. Agrees to not start any new prescription medication for the management of pain throughout the study

11. Agrees to not start any injection therapy for the management of TMD (trigger point injections, steroid injections, Botox) during the course of the study

12. Agrees to not use acupuncture for the management of pain during the course of the study

13. Agrees to not have Physical therapy for the management of TMD during the course of the study.

14. Agrees to not start intraoral appliance therapy during the course of the study. If the patient has used a nightguard for more than one month before the study, agrees to continue use it only at night.

15. 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)

16. 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, rheumatoid arthritis 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, history of abnormal electrocardiograms, history of heart conductance defects, malignant disease, chronic constipation, IBSc or any other severe acute or chronic medical or psychiatric condition or laboratory finding that may increase the risk associated with trial participation with Erenumab

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. History of facial trauma or orofacial or orthognathic surgery within the previous 6 months

6. Patients with dental pain

7. Patients with trigeminal neuralgia or other neuropathic pain in the craniofacial area

8. Patients with rheumatoid arthritis or any systemic arthritis

9. 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

10. 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. CGRP-Receptor antagonist (gepants) for acute use for migraine are allowed.

11. Patients with hypersensitivity to Erenumab

12. Patients who have received the Botox injection protocol in the masseters and/or Migraine protocol within 3 months prior screening and baseline visit.

13. Used injections for management of TMD (trigger point injections, steroid injections) within 2 weeks prior to the Screening and Baseline Visit

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

15. Has commenced intraoral appliance therapy for the management of facial pain within 30 days prior to the Screening and Baseline Visit

16. Patient currently undergoing active orthodontic treatment (passive retainers are permitted)

17. Treatment for drug or alcohol abuse within the last year

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

19. Patients sensitive to Latex

20.Patient is pregnant, planning to become pregnant or breastfeeding

21. 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 and from the Clinic of Oral and Maxillofacial Surgery at the University of Maryland, School of Dentistry. 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 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 the CGRP pathway, which is FDA-approved for the prevention of migraine in adults. 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 Visit 0, 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= 30 participants
2) Placebo: N=30 participants

<u>Randomization</u>
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 and Unbliniding 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/or the 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 or the Oral and Maxillofacial Surgery Clinic.

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 TMD 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 the 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 migraine in adults. 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 with greater selectivity. 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 70 mg/mL. Each 1 mL 70 mg single-dose prefilled glass syringe contains 70 mg erenumab-aooe, acetate (1.5 mg), polysorbate 80 (0.10 mg), and sucrose (73 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 70 mg 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, pH 5.2. Storage requirements for the placebo are the same as for the active drug.

6.1.2 Formulation, Packaging, and Labeling

An Erenumab 70 mg/mL, 1 mL prefilled glass syringe (15mM sodium acetate, 8.5% (w/v) sucrose, 0.010% (w/v) polysorbate 80, pH 5.2) will be used. 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 (70mg/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 storage in an allocated refrigerator specifically for its storage at the Brotman Facial Pain Clinic.

6.2 Dosage, Preparation and Administration of Study Product

Erenumab 70 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 or placebo 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.

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.

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).

Participants will be closely monitored for any of these AEs, during the clinic visit and between visits by telephone. Potential risks and discomforts will be clearly stated in the ICF. 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 any of the reactions described above, if there is worsening of TMD signs and symptoms during the 18 weeks of participation or if the participant decides against using Erenumab, he/she will be discontinued from the study (See 2.3.1 and 5.5.2).

The following expected events will not be considered reportable AEs:

- Temporary injection site reactions such as pain, erythema, pruritus after the injection of Erenumab

- Minor bleeding or bruising resulting from the blood draw

- Temporary pain or temporary increases in existing pain prompted during the TMD clinical examination or PPT.

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, acupuncture, physical therapy, and intraoral appliance therapy, 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 (Visits1-5).

6.6.1 ***Allowable Pain Medication***

6.6.2 ***Prescription medications***

Participants who enter the study already on a daily regimen of a prescription medication for pain management will be encouraged to continue that regimen throughout the study and 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 allowed over-the-counter analgesics used for treatment of TMD pain. In case a patient presents pain, the medications described below may be used:

6.6.3 ***Over-the-counter medications***

NSAIDs are very often used to manage pain in TMD patients and for other pain conditions. Participants use of short-acting non-prescription analgesics such as NSAIDs, acetaminophen or aspirin during the study, will be recorded and quantified at each visit, and the usage will be classified as either episodic or daily.
Episodic use of non-prescription analgesics 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 ***Nonpharmacologic Therapy***

During the course of the study, participants will not be restricted in the use of non-pharmacological therapies, with the exception of acupuncture, physical therapy and splint therapy. If a participant starts these therapies for the 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. The use of intraoral appliances at night only is allowed if was started at least 30 days prior to Screening and Baseline V0.

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 or Oral Surgery Clinic.

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 after 0-2 weeks from the date of the pre-screening interview.

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

- 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
- Administer Symptom Inventory
- Perform TMD examination (Including Panoramic X-Ray).
- Perform Pressure Pain examination

- Collect blood for Cytokine release assay
- Perform urine pregnancy test (in women with childbearing potential)
- Provide instruction to complete 6 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

Prior randomization, 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 level ≥30 on a numerical rating scale (0-100) or had experienced a pain level ≥30 on the same scale for at least 3 days the week before randomization. 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 history
- Record concomitant medications and therapies
- Take blood pressure and collect weight
- Administer the Symptom Inventory
- Assess and record adverse events (AEs)
- Perform TMD examination
- Perform Pressure Pain examination

- Perform urine pregnancy test (in women of childbearing potential)
- Review 5 questionnaires from Visit 0 in eCRF or collect and review the paper forms
- Provide instruction to complete 6 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/ 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
- Administer the Symptom Inventory
- Assess and record adverse events (AEs)
- Perform TMD examination
- Perform Pressure Pain examination
- Perform urine pregnancy test (in women of childbearing potential)
- Review 6 questionnaires from Visit 1 in eCRF or collect and review the paper forms
- Provide instruction to complete 6 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/ 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
- Administer the Symptom Inventory
- Assess and record adverse events (AEs)
- Perform TMD examination
- Perform Pressure Pain examination
- Perform urine pregnancy test (in women of childbearing potential)
- Review 5 questionnaires from Visit 2 in eCRF or collect and review the paper forms
- Provide instruction to complete 6 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 84/4 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
- Administer the Symptom Inventory
- Assess and record adverse events (AEs)
- Perform TMD examination
- Perform Pressure Pain examination
- Collect blood for Cytokine release assay
- Perform urine pregnancy test (in women of childbearing potential)
- Review 5 questionnaires from Visit 3 in eCRF or collect and review the paper forms
- Schedule next visit
- Administer the <intervention>.
- Record subject's compliance with <intervention>.
- Following administration of <intervention>
    - Assess vital signs
    - Administer Symptoms Questionnaire

7.4 Follow up and final Study Visit, Visit 5 (Day 112/ 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 medical history
- Record concomitant medications and therapies

- Take blood pressure and collect weight
- Administer the Symptom Inventory
- Assess and record adverse events (AEs)
- Perform TMD examination
- Perform Pressure Pain examination
- Perform urine pregnancy test (in women of childbearing potential)
- Review 5 questionnaires from Visit 4 in eCRF or collect and review the paper forms
- 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 administer 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 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 of [redacted] cytokines by Luminex assay.

- **TMD Examination**

The TMD examination will be performed according the Diagnostic Criteria for Temporomandibular Disorders (DC-TMD) [7] by trained and calibrated staff. The examination consists of bilateral digital palpation of masticatory muscles (masseter and temporalis) as well as the palpation of the temporomandibular joint (TMJ) and the manipulation of the jaw to assess if these elicit pain in these structures.
The participant must meet 2 of the criteria for TMD listed in the inclusion criteria: 1) reported pain or ache in the face, jaw/mandible, pre-auricular area, inside the ear or temple that it is modified by jaw function. 2) finding(s) of TMD myalgia according to the classification DC-TMD criteria.

- **Pressure Pain Thresholds**

The Pressure Pain Threshold (PPT) will be defined as the amount of pressure at which the participant first perceives pressure to be painful. The PPT measurements will be performed by trained staff using a pressure algometer (Wagner, Greenwich, CT). Calibrated pressured will applied bilaterally over the masseter, temporalis, upper trapezius, the TMJs, and the lateral epicondyles. One pre-trial assessment will be performed at each anatomic structure followed by additional assessments until 2 measures differing by less than 0.2 kg are obtained, or 5 assessments are administered. In either case, the mean of the 2 closest values will be
recorded as the threshold estimate. Pressure stimuli will be delivered at an approximate rate of 1 kg/s. The cutoff pressure for all sites will be 5 kg. The values from the right and left sides will be averaged to obtain a single PPT value per anatomical site [34, 35].

- **Daily Symptom Diary**

Participants will be asked to complete the Daily Symptom Diary at the end of each day during the baseline phase and during the study (visits 1-5).
Participants should have at least 80 % compliance with the DSD.

The diary collects the participant's pain intensity (reported on a 0-100 numeric rating scale) and duration (reported on a 0-100 percentage scale), pain days 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.

- Jaw Functional Limitation Scale. This is a 20-item instrument that measures limitations across 3 domains related to TMJ biomechanics: masticatory function (6 items), vertical jaw mobility/jaw opening (4 items), and verbal and emotional expression (8 items). Two items are not scored as part of these 3 subscales. A degree of limitation is rated on a 0-10 scale from 0 ("no limitation") to 10 ("severe limitation")[36, 37].

- Oral Behaviors Checklist (OBC). Evaluates parafunctional behaviors and generates a single scale representing the frequency of 21 activities such as clenching, chewing gum, and holding objects between teeth, yawn [38, 39].

- Graded Chronic Pain Scale (GCPS). The GCPS includes 7 items and assesses 2 dimensions of pain: pain intensity and pain-related disability [40].

- 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 [41, 42].

- Hospital Anxiety and Depression Scale. Evaluates anxiety and depression with a 14-item instrument [43].

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 0 and 4 by staff trained in phlebotomy. Blood samples will be evaluated then for the presence [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 at the school of Dentistry and serum/plasma isolation and storage will be held at the same facility. 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,

[redacted] 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 Cytokine Core Laboratory (CCL).

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 receptor antagonist FDA approved for the prevention of migraine in adults

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.

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.

If the participant reports a hypersensitivity reaction (rash, angioedema, anaphylaxis), new onset constipation or new onset of hypertension or any of the reactions described above, if there is worsening of TMD signs and symptoms during the 18 weeks of participation or if the participant decides against using Erenumab, he/she will be discontinued from the study (See 2.3.1 and 5.5.2).

The following expected events will not be considered reportable AEs:

- Temporary injection site reactions such as pain, erythema, pruritus after the injection of Erenumab
- Minor bleeding or bruising resulting from the blood draw
- Temporary pain or temporary increases in existing pain prompted during the TMD clinical examination or PPT.

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]

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]

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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 TMD 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

Pregnancy will be considered a SAE. 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 TMD 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).

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12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The main objective of the statistical analysis is to estimate change in study endpoints and evaluate the efficacy of Erenumab by testing a priori hypothesis concerning the differences between treatment and placebo.

Erenumab reduces pain and restores function in patients suffering of TMD.

The primary efficacy hypothesis is that Erenumab produces greater change in average pain score (0-100 scale) from Visit 1 to Visit 4 than placebo.

The secondary efficacy hypothesis is that Erenumab produces a greater proportion of patients reaching at least a 50% reduction from baseline in monthly TMD pain days compared to placebo. This will be determined as a change from baseline phase (4 weeks) through the 12 weeks treatment phase (3 cycles) until Visit 4.

Functional measures related to TMJ biomechanics and pain related behaviors:

There is a greater proportion of patients achieving >=30% decrease (score) in limitation of jaw function with the use of erenumab after 12 weeks of treatment compared to placebo.

There is a greater proportion of patients achieving >=30% decrease (score) in oral behaviors with the use of erenumab after 12 weeks of treatment compared to placebo.

There is a greater proportion of patients achieving >=30% increase in value in pressure pain thresholds in temporalis, masseter, trapezius muscles, TMJs and epicondyles with the use of erenumab after 12 weeks of treatment compared to placebo.

There is a greater proportion of patients achieving >=30% decrease in intensity and pain related disability (GCPS) with the use of erenumab after 12 weeks of treatment compared to placebo.

There is a greater proportion of patients achieving >=30% increase in score (impression of improvement/ impression of change/PGIC) with the use of erenumab after 12 weeks of treatment compared to placebo.

There is a greater proportion of patients achieving >=30% decrease (score) in anxiety and depression (change in HADS) with the use of erenumab after 12 Weeks of treatment compared to placebo.

[redacted]

12.2 Sample Size Considerations

The proposed sample size of 60 randomized patients split into two independent groups is based on a 30-50% reduction in TMD pain scores at follow-up, assuming a power of 90%, alpha = 0.05, assuming a 0.5 (medium) effect size. This was calculated using GPower software. This sample size is also based on the conservative assumption of a 15% patient drop out at follow up.

12.3 Planned Interim Analyses (if applicable)

If any interim analyses are to be conducted this will take place without unblinding.

12.3.1 Safety Review

Analysis of adverse events will use the safety sample, defined as all randomized participants who received at least one cycle of study medication.

12.3.2 Efficacy Review

The study's primary aim is to evaluate the effects of Erenumab in reducing pain level and secondary outcomes in participants with chronic TMD. The primary endpoint is change from Visit 0 to Visit 4 in average pain level (0-100) calculated in the month prior to the visit. Secondary outcomes are TMD pain days, jaw function, pain-related disability, and other pain related outcomes.

12.4 Final Analysis Plan

The main goal of the statistical analyses is to estimate change in study primary and secondary endpoints to evaluate efficacy of Erenumab. Intention to treat analysis will be performed using a within-subjects student's pair t-test or repeated measures ANOVA (if more than two time points) to determine significant reduction in pain after drug intervention in each patient. Subsequently, a between-subjects unpaired t-test or two-way mixed designed ANOVA (if more than two time points) will be performed to determine difference between the placebo and erenumab groups. *Post-hoc analysis* will only be conducted following a significant ANOVA test, to protect from Type I errors. We will use a 2-way between subject's repeated measure ANOVA design to determine difference between the Erenumab group and placebo group, or a between-subjects unpaired t-test if two groups only. We will also use student's paired t-test to determine time points of significance. 50% reduction in pain days will be determined as a function of baseline pain days. Where, appropriate similar statistical procedures will be used for secondary endpoints.

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).

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 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 or Oral Surgery 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 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, to assure that participants have the cognitive acuity to understand and adhere to the study procedures. Persons over 65 y/o and children will not be included in the study since Erenumab has not been validated in older patients and children and because TMD 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.

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

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SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- *Site Roster*
- *Manual of Procedures*
- *Laboratory Handling (if applicable)*
- *Case report forms*
- *Quality Management Plan*
- *Data Management Plan*
- *Clinical Monitoring Plan*
- *Statistical Analysis Plan*
- *DSMB or Oversight Committee Charter*

APPENDICES

[redacted]

APPENDIX A: SCHEDULE OF EVENTS

Study Phase	Pre-screening[A]	Screening and Baseline	Randomization and Treatment (12 weeks of treatment/3 cycles of Erenumab)				Follow Up	Early termination
Clinic Visit		V0	V1[B]	V2	V3	V4	V5	ET
Study Day/	0-4 weeks prior to V0	1-3 weeks prior V1	Day 0	Day 28	Day 56	Day 84	Day 112	
Procedures								
Contact Information	X							
Pre-screening interview Script	X							
Informed consent[C]		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 [D]		X	X	X	X	X		
Collect Daily Symptom Diaries [D]			X	X	X	X	X	
Assess compliance with Daily Symptom Diaries			X	X	X	X		
Randomization		X						
Provide study drug injection[E]			X	X	X			

Study Phase	Pre-screening[A]	Screening and Baseline	Randomization and Treatment (12 weeks of treatment/3 cycles of Erenumab)				Follow Up	Early termination
Clinic Visit		V0	V1[B]	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
TMD Examination		X	X	X	X	X	X	
Pressure Pain Threshold Examination		X	X	X	X	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[F]			X	X	X	X	X	X
Jaw functional Limitation Scale[F]			X	X	X	X	X	X
Oral Behaviors Checklist[F]			X	X	X	X	X	X
Hospital Anxiety and Depression Index[F]			X	X	X	X	X	X

Study Phase	Pre-screening[A]	Screening and Baseline	Randomization and Treatment (12 weeks of treatment/3 cycles of Erenumab/placebo)	Follow Up	Early termination

Clinic Visit		V0	V1[B]	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	
Patient Global Impression of Change[F]			X	X	X	X	X	X

[A] Pre-screening can happen by phone or at clinic visit. It may be combined with screening visit and baseline visit (Visit 0).
[B] In the case Visit 1 cannot occur after one week of Visit 0, and the participant is to remain in the study; Visit 0 will be repeated as an unscheduled visit. The timing of visits 2-5 and their windows are established from the date of Visit 1.
[C] Includes consent to participate in the study and HIPPA
[D] Diary symptom diaries are completed electronically but if a participant opted the paper form, they will be dispensed and collected.
[E] The study drug will be administered (S.C.) on Visit 1, Visit 2 and Visit 3.
[F] Questionnaires will be completed electronically a day prior to the scheduled visit or distributed on paper format a previous visit to be returned at the scheduled visit.