A Randomized, Double-Blinded, Single Site Study to Evaluate the Efficacy of Erenumab for Treatment of Idiosyncratic Facial Pain Mimicking Rhinosinusitis

National Clinical Trial (NCT) Identified Number: pending

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EXECUTIVE SUMMARY

Approximately 30 million Americans each year are diagnosed with rhinosinusitis and over 80% of these are prescribed antibiotics, often repeatedly. However, studies suggest that a large proportion of these patients do not have rhinosinusitis. We hypothesize that they have an idiosyncratic facial pain condition related to migraine. Because of the overlapping symptoms, in addition to the lack of effective treatment options for this idiosyncratic facial pain condition, patients could be inappropriately prescribed antibiotics and other unnecessary treatments including sinus surgery. The advent of erenumab in the treatment of migraine headaches offers a unique opportunity to investigate its efficacy in the treatment of idiosyncratic facial pain mimicking rhinosinusitis. Such an indication for erenumab would have a widespread impact in the treatment of a common condition with very few treatment options, as well as for mitigating antibiotic overuse.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator/Sponsor-Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Food and Drug Administration (FDA), if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all amendments to the protocol will be submitted to FDA prior to implementation. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from actively enrolled participants, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Randomized, Double-Blinded Single Site Study to Evaluate the Efficacy of Erenumab for Treatment of Idiosyncratic Facial Pain Mimicking Rhinosinusitis

Study Description:

Objectives:

Primary Objective: To compare change from baseline in mean number of days per month with significant pain or pressure between treatment and placebo groups at 4 to 6 months.

Secondary Objectives:

1. To compare change from baseline in mean number of days per month with significant pain or pressure between treatment and placebo groups at 1 month and 3 months.
2. To compare mean number of days per month with significant pain or pressure comparing baseline to 1, 3, and 4 to 6 months within each group (intragroup analysis)
3. To compare change from baseline between treatment and placebo groups at 1, 3, and 4 to 6 months for the following:

    a. Sinonasal Outcome Test-22 (SNOT-22)
    b. Migraine Functional Impact Questionnaire (MFIQ)
    c. Mean number of days per month with significant nasal congestion and rhinorrhea.
    d. Doses of rescue pain medications taken
    e. Mean daily pain score

Study Population: Patients presenting with at least three months of chronic or episodic midfacial pain or pressure referred for evaluation of sinusitis and found to have no endoscopic or radiographic evidence of sinusitis

Phase: IV

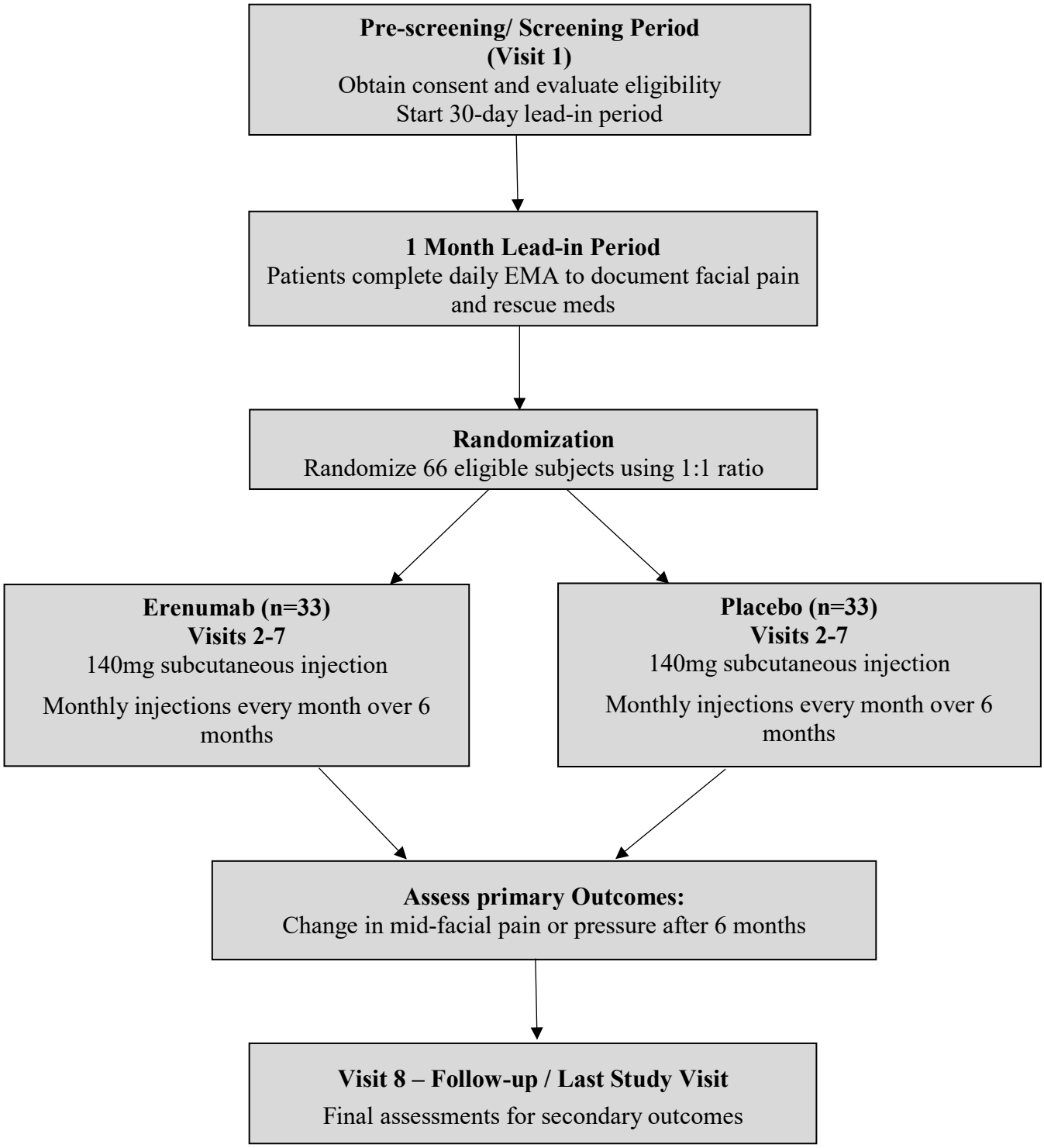
Description of Sites/Facilities Enrolling Participants: Duke University Health System

Description of Study Intervention: Erenumab vs. Placebo

Study Duration: 34 months

Participant Duration: 7 months

1.2 SCHEMA



1.3 SCHEDULE OF EVENTS (SOE)

Procedures	Screening / Lead-in Period	Baseline / Randomization & Initial Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Follow-up / End of Study visit	Unscheduled Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Unscheduled
	Day -30 to -1	Day 0 (+6 days)	Day 30 (+/- 6 days)	Day 60 (+/- 6 days)	Day 90 (+/- 6 days)	Day 120 (+/- 6 days)	Day 150 (+/- 6 days)	Day 180 (+/- 6 days)	N/A
Informed Consent	x								
Demographics	x								
Medical History	x								
Randomization		x							
Study drug Administration		x	x	x	x	x	x		
Concomitant medication review	x	x	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x	x	x
Home BP Monitoring (BP checks daily x 7 days following first dose of drug administration, then weekly and when symptomatic throughout duration of study)		→							
Sinus CT Scan[1]	x								
Pregnancy test[2]	x	x	x	x	x	x	x		
Endoscopy[3]	x								
Review subject pain and blood pressure diary compliance and instruct subject on daily use	x	x	x	x	x	x	x	x	x
Migraine Assessment Tool (MAT)	x								

Procedures	Screening / Lead-in Period	Baseline / Randomization & Initial Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Follow-up / End of Study visit	Unscheduled Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Unscheduled
	Day -30 to -1	Day 0 (+6 days)	Day 30 (+/- 6 days)	Day 60 (+/- 6 days)	Day 90 (+/- 6 days)	Day 120 (+/- 6 days)	Day 150 (+/- 6 days)	Day 180 (+/- 6 days)	N/A
Sinonasal Outcome Test questionnaire (SNOT-22)	x				x			x	
Migraine Functional Impact questionnaire (MFIQ)	x				x			x	
Pain Location Diagram	x								
Adverse event review and evaluation	x	x	x	x	x	x	x	x	x
Subject Compensation (clincard)	x	x	x	x	x	x	x	x	

1 - Most recent Sinus CT scan obtained as SOC should be within 12 months of the screening visit. If > 12 months then repeat for study purposes if not clinically indicated.

2 - Serum pregnancy test at screening, then urine pregnancy test on subsequent visits

3 - Endoscopy at screening as standard of care (SOC). If not done as SOC within 3 months of the screening visit, then complete it as a research procedure and charged to the study. Repeat only as clinically indicated.

1.4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary:	
To compare change from baseline in mean number of days per month with significant pain or pressure between treatment and placebo groups at 4-6 months.	Change in mean number of days per month with significant midfacial pain or pressure (defined as greater than 4/10) from baseline to 4-6 months
Secondary:	
To compare change from baseline in mean number of days per month with significant pain or pressure between treatment and placebo groups at 1 month and 3 months.	Change in mean number of days per month with significant midfacial pain or pressure (defined as greater than 4/10) from baseline to 1 month and 3 months.
To evaluate the efficacy of erenumab in reducing mean number of days with facial pain (intragroup change)	Change in mean number of days per month with significant pain or pressure comparing baseline to 1, 3, and 4-6 months within each group.
To evaluate the efficacy of erenumab in reducing burden of rhinosinusitis symptoms	Change in 22-Item Sinonasal Outcomes Test (SNOT-22) questionnaire score from baseline to 1, 3, and 6 months
To evaluate the efficacy of erenumab in improving functional impact of migraine-related facial pain	Change in each of the five domains of the Migraine Functional Impact Questionnaire (MFIQ) from baseline to 1, 3, and 6 months
To evaluate the efficacy of erenumab in improving associated symptoms of nasal congestion and rhinorrhea	Change in average number of days per month with significant nasal congestion or rhinorrhea (defined as greater than 4/10) from baseline to 1, 3, and 4-6 months
To evaluate the efficacy of erenumab in reducing pain medication usage	Change in doses of rescue pain medications taken from baseline to 1, 3, and 4-6 months
To evaluate the efficacy of erenumab in reducing daily pain severity	Change from baseline in mean daily pain score from baseline to 1, 3, and 4-6 months

2 RATIONALE AND BACKGROUND

2.1 STUDY RATIONALE

Patients with midfacial pain or uncomfortable pressure are often presumed to have rhinosinusitis. Despite treatment for sinusitis, a significant number of patients continue to complain of facial pain without clear etiology, which can be frustrating for both the patient and clinician. If this facial pain is not due to a presumed diagnosis of "sinusitis" as assessed by failure to respond to medical management, a negative endoscopic evaluation and no significant radiologic evidence of sinusitis, then the patient has idiosyncratic facial pain unrelated to but mimicking sinusitis. One possible etiology for patients with an ongoing complaint as described above is migraine-related facial pain. Changing the paradigm as to how these sinus patients are both evaluated and treated could have important public health benefits.

There can be significant overlap between the symptoms of migraine disease and those of rhinosinusitis, which results in misdiagnosis and unnecessary treatments.[1-3] Several studies indicate that the majority of patients with self-perceived sinus headache satisfy the diagnostic criteria for migraine. A study of 2991 patients by Schreiber et al found that 88% of patients with self-reported or physician-diagnosed sinusitis met diagnostic criteria for migraine.[4] Similarly, Eross et al reported in a study of 100 patients that 88% with self-perceived sinus headaches met criteria for migraine and other primary headache disorders.[5] Another study of 130 patients with migraines and no evidence of sinusitis found that 81.5% were misdiagnosed with sinusitis.[6]

Consideration and institution of migraine-specific treatment in patients who have midfacial pain or pressure mimicking rhinosinusitis could have a significant public health impact. This impact would include reduction of unnecessary treatments such as repeated or prolonged antibiotics and endoscopic sinus surgery [7, 8], and improved quality of life and cost savings for the patient and stakeholders supporting health care. Calcitonin gene-related peptide receptor (CGRPR) antagonists have demonstrated clinical efficacy in migraine prevention.[9, 10] Erenumab, a monoclonal antibody binding to the CGRP receptor, was FDA approved in 2018 for the prevention of migraines. Therefore, erenumab has the potential to be an effective treatment option for this patient population.

2.2 BACKGROUND

Approximately 30 million adult Americans, or 12% of the US population, are diagnosed with rhinosinusitis (RS) annually and antibiotics are prescribed in 82% of associated office visits. This includes patients with acute rhinosinusitis (ARS), in which symptoms last <4 weeks, recurrent acute rhinosinusitis (RARS), in which a patient has 4 or more acute episodes in a year, and chronic rhinosinusitis (CRS), in which symptoms last >12 weeks [6]. However, several studies suggest that many of these patients have no objective evidence of sinusitis on endoscopy or imaging, but rather meet criteria for migraine or other

primary headache disorder.[1, 5-8] This leads to ineffective treatments and associated morbidity, such as antibiotic resistance, persistent symptoms, and unnecessary surgery.

Patients with idiosyncratic facial pain may actually have chronic upregulation of any one or more branches of the trigeminal nerve leading to the perception of facial pressure and pain with secondary autonomic symptoms such as nasal congestion, rhinorrhea, tearing, and facial swelling. In other words, they may have a complex spectrum of nervous system dysfunction that can mimic RS. Despite this, studies have demonstrated that patients undergo invasive sinus procedures at least in part due to the lack of effective treatments for idiosyncratic facial pain.[11] Medications commonly prescribed for migraine prevention, such as valproate or topiramate, are often ineffective or poorly tolerated. Moreover, patients often are not candidates for such medications because they do not have a classic presentation of migraines.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

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 most common adverse reactions (incidence ≥ 2% and at least 2% greater than placebo for either 70 mg or 140 mg doses) in Phase 3 trials were injection site reactions (5-6%), constipation (3%), and cramps/muscle spasms (2%). 1.3% of patients in these trials withdrew from treatment because of adverse events. The most frequent injection site reactions were pain, erythema, and pruritus.

Hypersensitivity reactions, including rash, angioedema, and anaphylaxis, have been reported with erenumab in post-marketing experience. Most hypersensitivity reactions were not serious and occurred within hours of administration, although some occurred more than one week after administration.

Constipation with serious complications has also been reported in the postmarketing setting. The majority of cases occurred after the first dose of erenumab. There were cases that required hospitalization with or without surgery.

Antibodies against erenumab have been seen in clinical studies. The incidence of antibody development was 6.2% in patients receiving 70 mg once a month and 2.6% in patients receiving 140 mg once a month. No side effects associated with these antibodies were observed. The side effects of using erenumab in combination with other drugs are unknown at this time.

Constipation with serious complications has been reported following the use of Aimovig® in the postmarketing setting. There were cases that required hospitalization, including cases where surgery was necessary. In a majority of these cases, the onset of constipation was reported after the first dose of Aimovig®; however, patients have also presented with constipation later on in treatment. Patients

who take medications that decrease the movement of the stomach and intestines may have a higher chance of developing constipation and related complications such as stool impaction and bowel perforation.

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

We will monitor patients treated with Aimovig® for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of Aimovig® is warranted if evaluation fails to establish an alternative etiology.

The pre-filled syringe may cause pain or discomfort in addition to bleeding, bruising, redness, warmth, itching, swelling, infection, or firmness of the skin near the injection site. Additionally, the pre-filled syringe contains a dry natural rubber that is derived from latex, which may cause an allergic reaction. Subjects who have a known allergy to latex will be excluded.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential benefits of erenumab include an improvement in severity and frequency of facial pain and other sinus-type symptoms in adults, leading to significant improvements in quality of life. This is based on randomized trials demonstrating the efficacy of erenumab.[9, 10, 12] Anecdotally, patients presenting to the otolaryngologist with idiosyncratic facial pain without rhinosinusitis have improvement in facial pain and other sinonasal symptoms with erenumab. Notably, the degree of improvement in facial pain was comparable to that of headache.[2, 13]

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Large randomized trials have demonstrated the positive safety profile and efficacy of erenumab versus placebo.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is a Phase IV, randomized, double-blinded, placebo-controlled single center trial of erenumab versus placebo in patients with mid-facial pain or pressure without evidence of sinus disease. Sixty-six eligible subjects will be randomized in a 1:1 ratio to receive subcutaneous injections of either 140 mg erenumab or placebo every 30 days for 6 months (last injection at day 150), followed by a final follow-up visit at day 180.

3.2 EVALUATION BY STUDY VISIT

See Section 1.3, Schedule of Events

3.2.1 SCREENING/LEAD-IN PERIOD (VISIT 1)

Subjects will undergo a screening visit to determine eligibility to proceed with the one month (30-day) lead-in period. The screening visit may be combined with a standard of care visit for patients already being evaluated for rhinosinusitis and/or facial pain. This study will be explained in lay language to each potential participant. Each participant will sign an informed consent before committing to any study-related tests or procedures. The screening visit will occur at least 30 days before Visit 2 and will include the following assessments:

1. Written informed consent
2. Assessment of prior & current concomitant medications
3. Record demographics
4. Complete medical history physical exam. Only perform if not previously done as SOC in the 30-day screening period.
5. Vital signs, height and weight
6. Endoscopy. If performed as SOC within 3 months prior to enrollment, it may be used. If a SOC endoscopy was performed more than 3 months before enrollment or was never performed, it will be performed for study purposes.
7. Complete sinus CT scan and nasal endoscopy if not completed as standard of care within 12 months of randomization
8. Pregnancy test (serum), if applicable
9. Completion of questionnaires
    a. Migraine Assessment Tool (MAT)
    b. 22-Item Sinonasal Outcomes Test (SNOT-22)
    c. Migraine Functional Impact Questionnaire (MFIQ)
    d. Pain Location Diagram

10. Review pain diary with subject [ecological momentary assessment (EMA)] - how and when to complete.
11. Discuss compensation with subject.
12. Collect baseline adverse event information, if applicable.

During the screening visit, eligible subjects will receive instructions and training on use of the ecological momentary assessment (EMA) via mobile phone. If for any reason they cannot complete the EMA via a mobile phone, a paper copy will be available to the participant. During the 30-day lead-in period, subjects will be expected to score on a scale of 1 to 10 their symptoms of pain/pressure, nasal congestion, and rhinorrhea as well as any rescue medicines taken for pain each day. Subjects will be instructed to return to the site at the end of the 30-day lead-in period for Visit 2. During the 30-day lead-in period, subjects must record a minimum of 20 (67%) daily diary entries to be eligible for randomization during visit 2. This will be evaluated through the review of the EMA daily data log. The coordinator may call subjects to remind them to complete the log during this time period. Subjects who do not have a minimum of 20 daily entries will be considered a screen failure and removed from the study.

3.2.2 BASELINE/RANDOMIZATION (VISIT 2)

At the end of the 30-day lead-in period, subjects will return to the study site for visit 2. Eligibility criteria will be reviewed, including review of the EMA data during the lead-in period. If study participant meets eligibility based on review of baseline assessments, then subjects will be randomized and receive the first dose of erenumab or placebo.

Assessments to be performed during visit 2:

1. Concomitant medication review
2. Physical exam
3. Vital signs, height and weight
4. Pregnancy test (urine) if applicable
5. Review of data from EMA with instructions for continued use
6. Randomization
7. Administration of placebo or IP

Subjects will be given a portable home blood pressure monitoring device. Instructions for use of this device will be provided at the time of the first dose of the study drug. Subjects will record their blood pressure every day for seven consecutive days after the first dose. Thereafter, they will record their blood pressure once per week and when symptomatic throughout the entire duration of the study. Subjects will enter their blood pressure information through redcap or twilio. This data will be reviewed monthly by the PI or within 24 hours if immediate intervention is required. In addition, patients will be educated on the symptoms of high blood pressure and, at any time in the study, if symptomatic, the patient should check their blood pressure and notify the study coordinator. The coordinator may call the subject to remind them to record their blood pressure during their study participation.

For patients with normal baseline blood pressure (at or below 120/80), if subjects find that their blood pressure equals or exceeds 140 mm Hg systolic *or* 90 mm Hg diastolic on two consecutive readings within thirty minutes, they will notify the study coordinator and seek medical attention. For patients who have abnormal baseline blood pressure, if subjects find that their blood pressure equals or exceeds 160 mm Hg systolic *or* 100 mm Hg diastolic on two consecutive readings within 30 minutes, they will notify the study coordinator and seek medical attention. Subjects will be asked to repeat the pressure the following day. If persistently elevated for three consecutive days, subject will be removed from the study and referred for evaluation and treatment.

If a blood pressure is found to be greater than or equal to *180 mm Hg systolic or 120 mm Hg diastolic, and confirmed on a second measurement within 30 minutes, subjects will seek medical attention immediately. In addition to weekly monitoring,* subjects will be instructed to measure their blood pressure immediately if they develop any symptoms associated with hypertensive crisis, *such as chest pain, shortness of breath, headache, numbness/weakness, change in vision, difficulty speaking*, confusion, or nausea/vomiting. Subjects who develop hypertensive crisis at any point during the study will be removed from the study.

3.2.3 STUDY VISITS 3 THROUGH 7

During the treatment period, subjects will return to the study site every 30 days (+/- 6 days) and will undergo assessments and procedures listed in the schedule of events in section 1.3. Subjects will complete the patient-oriented outcome questionnaires noted in the schedule of events. Study medication (erenumab or placebo) will be administered per protocol. A review of the EMA data and concomitant medications (including over the counter medications) between each visit will occur. Subjects will be reminded to continue to record their symptom severity and rescue medicine intake each day through their mobile phone or via paper if not feasible. Subjects will also be reminded to continue blood pressure monitoring weekly and when symptomatic. The coordinator may call the subject to remind them to record their daily diary and blood pressure.

3.2.4 FOLLOW-UP/END OF STUDY VISIT (VISIT 8)

Subjects will be asked to return for follow-up one month after the last study drug administration and undergo assessments and procedures listed in the schedule of events in section 1.3. Daily symptom and rescue medication data logs will be reviewed, and questionnaires completed. However, the study drug/placebo will not be administered.

3.2.5 UNSCHEDULED VISITS

If a subject returns for an unscheduled visit (i.e., adverse event, adverse event follow up), the subject will undergo the assessments and procedures listed in the schedule of events table in section 1.3.

3.3 EXPLORATORY ANALYSIS

In addition to the daily pain assessment and rescue medication intake obtained through the EMA at the end of the day, subjects' pain/pressure will be assessed on a scale of 1 to 10 at one other random time throughout the day. This will allow for collection of data from subjects in real time in their natural environments.[14, 15]

3.4 JUSTIFICATION FOR DOSE

The recommended dosing per the approved drug package insert provided by the manufacturer is 70mg or 140mg once monthly. Improved efficacy with similar adverse effect profile has been demonstrated for the 140 mg dose versus the 70 mg dose based on the STRIVE trial.[9]

3.5 END OF STUDY DEFINITION

The study will end when the last subject completes the last study visit on Day 180.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

1. Adults 18 years of age or older presenting to Duke Head & Neck Surgery and Communications Sciences clinic for evaluation of rhinosinusitis and/or facial pain or pressure.
2. Symptoms are present at least 10 days a month for the last 3 months as reported by subject.
3. Symptoms must include midfacial pain or uncomfortable pressure (may be unilateral or bilateral), which is defined as pain in the regions overlying the maxillary, ethmoid, frontal sinuses either together or individually.
4. Nasal endoscopy in the last three months shows no signs of inflammation (i.e. thick drainage, polyps, watery edema in the middle meatus or spheno-ethmoid recess (mild edema permitted).
5. Sinus CT scan or MRI within 12 months of enrollment during a symptomatic period shows no more than scattered minimal mucosal edema or mucous retention cyst with patent infundibula bilaterally. For subjects with a CT scan more than 12 months old or just an MRI, a CT will be repeated for study purposes. For patients with CT scans less than 12 months old, a CT will be repeated for study purposes if the subject has changes in symptoms suggestive of sinusitis.
6. Ability to read/write English.
7. Has a smart phone and access to the internet.

4.2 EXCLUSION CRITERIA

1. Hypersensitivity to erenumab or to any of the drug components (acetate, polysorbate, and sucrose).
2. Previous exposure to erenumab or any other -CGRP inhibitor in the six months prior to enrollment.
3. Allergy to latex.
4. Inability to differentiate facial pain from other headaches.
5. Non-English speaking or unable to provide written informed consent.
6. On a preventative migraine medication (see below) during the 30 day lead-in period:
   - Category 1: Divalproex sodium, sodium valproate
   - Category 2: Topiramate
   - Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, ebivolol, pindolol, propranolol, timolol)

- Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Category 6: Flunarizine, verapamil
- Category 7: Lisinopril, candesartan

7. Received botulinum toxin (Botox) to the head and neck for migraines in the last four months.
8. More than one major open surgery of the nose or sinuses for sinonasal cancer.
9. History of uncontrolled or unstable blood pressure.
10. History of liver failure.
11. History of metastatic malignancy in the last five years or actively undergoing treatment for cancer.
12. Active seizure disorder or other significant neurological conditions other than migraine.
13. Myocardial infarction (MI), stroke, transient ischemic attack (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening.
14. History or evidence of any other unstable or clinically significant medical condition that in the opinion of the sponsor-investigator/ Principal Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.
15. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records or patient self-report.
16. Pregnant or breastfeeding, or expecting to conceive during the study, including through 16 weeks after the last dose of investigational product or placebo
17. Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with investigational product or placebo through 16 weeks after the last dose of investigational product. Female subjects not of childbearing potential are defined as any female who is post-menopausal by history, defined as:
    - Age ≥ 55 years with cessation of menses for 12 or more months, OR
    - Age < 55 years but no spontaneous menses for at least 2 years, OR
    - Underwent bilateral oophorectomy, bilateral salpingectomy, or hysterectomy
18. Unlikely to be able to complete all protocol required study visits or procedures.
19. Currently receiving treatment in another investigational device or drug study.

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4.3 SCREEN FAILURES

Screening will occur at the baseline visit. Up to twenty screen failures are anticipated. The reason for screen failure will be documented.

Screen Failures are defined as:

a) Patients who are not compliant with EMA or daily diary for more than 33% of triggered queries during the 30-day lead-in period.
b) Patients who do not report at least 10 days of significant pain or pressure during the 30-day lead-in period.
c) Patients needing prophylactic migraine medicine (meds listed under exclusion # 6) during the 30 day lead-in period.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited from Duke otolaryngologists and other clinicians who mainly treat sinus disease or facial pain. Clinic schedules will be pre-screened by the study coordinator several days in advance to ascertain potential subjects being seen for rhinosinusitis and/or facial pain. The study coordinator will alert providers of patients who appear potentially eligible based on pre-screening. If a patient is deemed eligible based on the exam and clinical findings, the study will be introduced by the provider when discussing treatment options for non-RS related facial pain. Referrals from outside clinics will also be taken and those patients will be assessed for eligibility. Recruitment brochures or flyers will be developed and posted in the waiting rooms of participating clinics and may be emailed to potential participants. Social media may be used to engage potential subjects outside of Duke. Once enrolled, subjects will be compensated $100 for study visits 1 and 8, $50 for visits 2-7, or $500 for the entirety of the study.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Erenumab is a monoclonal antibody blocking the calcitonin gene-related peptide receptor. It is FDA-approved for the preventative treatment of migraine in adults. It is administered subcutaneously in the abdomen, thigh, or upper arm at a standard dose of 140 mg once a month.

5.1.2 DOSING AND ADMINISTRATION

Either erenumab 140 mg or placebo will be administered by a nurse in the Duke Otolaryngology clinic via subcutaneous injection in the abdomen, thigh, or upper arm. Study participants will receive monthly injections for six months. Prior to subcutaneous administration, study drug will sit at room temperature for at least 30 minutes protected from direct sunlight.

Currently, erenumab is not available in 140mg single dose syringes for this study. Subjects will receive either two 70mg erenumab injections for a total dose of 140mg of erenumab, or two injections of placebo.

5.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

5.2.1 ACQUISITION AND ACCOUNTABILITY

Erenumab and matching placebo will be manufactured and supplied by Amgen, Inc. Study drug will be shipped directly from Amgen to the Duke Investigational Drug Service Pharmacy (IDS). Investigational product and placebo accountability including receipt, dispensation, and destruction will be recorded by IDS pharmacy using the electronic reporting system, Vestigo.

5.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Erenumab injection is a clear to opalescent, colorless to slightly yellow solution for subcutaneous administration. Erenumab for this study will be supplied as single dose pre-filled syringes containing 70 mg/mL solution. Placebo and active erenumab will be packaged in identical Type 1 glass syringes with attached stainless steel needle and labeled according to their contents. The unblinded IDS pharmacist or designee will dispense erenumab or matching placebo according to subject randomization schedule. Dispensed syringes will be indistinguishable in appearance and labeling to maintain the study blind.

5.2.3 PRODUCT STORAGE AND STABILITY

Erenumab for injection is stored at 2-8℃ in the original carton to protect from light until time of use. If removed from the refrigerator, erenumab is stable for 7 days at room temperature 15-25℃. Erenumab syringes should not be frozen or shaken.

5.2.4 PREPARATION

Duke IDS pharmacist or designee will receive subject randomization number and match it to treatment assignment on unblinded randomization scheme. On day of dosing, IDS pharmacist will dispense assigned treatment (erenumab or placebo) with blinded labeling to study team for administration.

5.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

At the conclusion of the screening/lead-in period, eligible subjects will be randomly assigned to receive either erenumab 140 mg or placebo in a 1:1 allocation ratio based on a computer-generated randomization schedule supplied by the Duke IDS pharmacy. The subject, investigators, nurse, and study coordinator will be blinded.

5.4 STUDY INTERVENTION COMPLIANCE

Subjects will be administered the study drug or placebo each month in clinic by designated nurses. The nurse and study coordinator will monitor compliance at the time of medication administration. The study coordinator will review instructions on completing the daily log at each study visit. Reminder calls and/or messages via MyChart will be sent prior to each visit.

5.5 CONCOMITANT THERAPY

5.5.1 RESCUE MEDICINE

Rescue medicine for facial pain will be permitted. Recommendations by the principal investigator may consist of over-the-counter medications such as antihistamines, non-steroidal anti-inflammatory drugs, decongestants. Antibiotics and steroids may be indicated if clinical evidence for sinusitis exists. Patients will be referred to their primary care provider (PCP) for prescription medications including triptans, opiates, tramadol, acetaminophen-containing medications, butalbital. These medications are not commonly prescribed by otolaryngologists, and therefore, should be managed by the PCP. Subjects will be instructed to record rescue medicine intake in their EMA data log. The study coordinator or study team member will review all recorded rescue meds and query the patient regarding any rescue meds prescribed by another health care provider. The study coordinator or study team member will verify the rescue medications, by either review of the pill bottle or call to the PCP.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Intervention will be discontinued in the event of a serious adverse reaction to the drug.

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects will have the option of withdrawing from the study at any time for any reason. Reason and date for withdrawal, as well as any adverse events and concomitant medications since the last study visit will be documented.

The Principal Investigator may discontinue a subject from study treatment, or withdraw a patient from the study. Reasons for study treatment discontinuation or withdrawal may include but are not limited to the following:

- Adverse event or hypersensitivity reactions thought to be related to study drug (rash, angioedema, anaphylaxis, hypertensive crisis, persistently elevated blood pressure, constipation with serious complications).
- Patient voluntarily decides to withdraw.
- Patient non-compliance with the study protocol.
- Intercurrent disease, which in the opinion of the patient's treating physician, would affect the ability of the patient to continue on the clinical study.
- Patient lost to follow-up.

All subjects who received at least one dose of study drug or placebo will be requested to complete Visit 8, regardless of whether they completed the study, were withdrawn by the investigator or chose to withdrawal from the study.

Withdrawn and/or discontinued patients will be included in the data analysis by an intention to treat analysis.

6.3 LOST TO FOLLOW-UP

Subjects not appearing for their study visit will be contacted via telephone and, if necessary, by mail. A 10% dropout rate due to adverse events and loss of follow-up will be anticipated.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 EFFICACY ASSESSMENTS

Drug efficacy will be assessed through a smart-phone based app that queries daily symptoms and rescue medication use through EMA. Efficacy will also be assessed through disease-related questionnaires.

7.2 SAFETY AND OTHER ASSESSMENTS

Subjects will undergo history and physical exam at every visit to ensure drug safety. In addition, subjects will be asked specifically about the common adverse effects associated with erenumab, which include injection site reaction, constipation, and muscle spasm/cramps. Subjects will also be queried for hypersensitivity reactions and asked to monitor their blood pressure daily for 7 days after the first injection, weekly thereafter, and when symptomatic. The PI will assess the adverse events monthly or as needed for immediate intervention. A list of concomitant medications will also be recorded at each visit.

7.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is any untoward medical occurrence in a clinical study subject. No causal relationship with the study drug or with the clinical study itself is implied. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, including abnormal results of diagnostic procedures and/or laboratory test abnormalities, which are considered AEs if they

- result in discontinuation from the study
- require treatment or any other therapeutic intervention
- require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 6 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

7.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A Serious Adverse Event (SAE), as defined by the FDA, will be any adverse event that in the opinion of either the sponsor-investigator results in any of the following outcomes:

1) Death
2) Life-threatening adverse drug experience
3) Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)
4) Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) Congenital anomaly/birth defect

Of note, an Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

7.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Unanticipated (Unexpected) Adverse Event:
An AE, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure) for an unapproved investigational product or package insert/summary of product characteristics for an approved product.

Adverse Event Associated With the Use of the Drug:
An AE is considered associated with the use of the drug if the attribution is possible, probable or definite.

7.3.3.1 SEVERITY OF EVENT

Assessment of Severity
The investigator will assess the intensity of the AE and rate the AE as mild, moderate, or severe using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5, which can be accessed at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

The CTCAE classifies AEs as below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

  Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

In addition, information pertaining to duration, treatment, and possibility of causality to study drug will be documented.

7.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The investigator's assessment of an AE's relationship to study drug will be part of the documentation process, but will not be a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The investigator will assess the relationship or association of the study drug in causing or contributing to the AE, which will be characterized using the following classification and criteria:

Definite: Adverse events that, after careful medical evaluation, are considered definitely related to the study drug, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Probable: Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the study drug. The following characteristics will apply:

- A reasonable temporal relationship exists between the event and exposure to the study drug, and
- The event is a known reaction to the study drug that cannot be explained by an alternative cause commonly occurring in the population/individual, or
- The event is not a known reaction to the study drug but cannot be reasonably explained by an alternative cause.

Possible: Adverse events that, after careful medical evaluation, do not meet the criteria for a definite or probable relationship to the study drug, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after exposure to the study drug, and
- There is a reasonable temporal relationship to the application, but the event is not a known reaction to the study drug and could be explained by a commonly occurring alternative cause, or
- In the absence of a reasonable temporal relationship, the event cannot be explained by an alternative cause.

Unlikely: Adverse events that, after careful medical evaluation, do not meet the criteria for a possible, probable or definite relationship to the study drug and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the study drug, or
- The event may have been produced by environmental factors, and
- There is no apparent pattern of response to the study drug.

Not related: Adverse events in this category will have either of the following characteristics:

- The event occurs before exposure to the study drug, or
- The event does not have a reasonable temporal relationship to study drug administration and can be explained by a commonly occurring alternative cause.

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7.3.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

AE review and evaluation will occur at every study visit prior to drug administration once a month, including the final visit, which will be one month after the final medication dose is administered.

7.3.4 ADVERSE EVENT REPORTING

AEs will be reported by the patient throughout the entire study period study, including during study visits. All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, will be recorded using medical terminology in the source document and on the case report form (CRF). Whenever possible, diagnoses will be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators will record on the CRF their opinion concerning the relationship of the AE to study therapy and/or device (pre-filled syringe).

Any non-serious AE that occurs after the dose of study drug will be documented on a CRF page and followed until resolution, stabilization, or the End-of-Study Visit at Day 180 (Visit 8). Any SAE that occurs after the dose of study drug (regardless of relationship to study drug) will be followed until the event resolves, stabilizes, or becomes non-serious. The description of the AE will include type of event, date and time of onset, date and time of resolution, blinded investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome.

7.3.5 SERIOUS ADVERSE EVENT (SAE) REPORTING

All serious AEs (SAEs) during the study period will be documented and reported to Amgen within 72 hours using Amgen’s electronic reporting form, in addition to being reported to the Duke University Health System IRB and other institutional regulators, as applicable. Furthermore, changes in an already

reported serious AE will be reported to Amgen within 72 hours. The investigator will not be responsible for AEs occurring after the study period. Appendix A contains Amgen's Safety Data Exchange Requirements.

The sponsor-investigator will report suspected unexpected serious adverse reaction to the FDA in accordance with 21 CFR 312.32. The FDA will be notified of any unexpected fatal or life-threatening suspected adverse reactions no later than 7 calendar days after notification. Any other SAE that is possibly related and unexpected will be reported to the FDA no later than 15 calendar days upon notification of the event.

The FDA Medwatch Form 3500A will be used to report all SAEs. The MedWatch 3500A form is available at:

- https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Instructions for the MedWatch 3500A form are available at:
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM295636.pdf

SAEs will be reported to the Duke University Health System Institutional Review Board (IRB) per their policy, "Problems or Events that Require Prompt Reporting to the IRB".

7.3.6 REPORTING EVENTS TO PARTICIPANTS

Subjects will be informed of any adverse events that may affect their rights, welfare and/or decision to continue study participation via the consent process and signing the consent (all subjects will receive a signed/dated copy of the consent form).

7.3.7 REPORTING OF PREGNANCY

Pregnancies occurring after the first dose of investigational product will be reported as a serious adverse event and will result in unblinding. The investigator will report within one working day of knowledge of the pregnancy to the IRB. Following delivery or termination of pregnancy, a follow-up pregnancy report will completed. Spontaneous abortions will be reported as SAEs.

7.3.8 UNBLINDING

In the event of an SAE that requires unblinding of the patient to determine whether they are on the active study drug, the PI or coordinator will contact the IDS Pharmacy for emergency unblinding at *IDS.pharmacy@duke.edu*.
The subject will be removed from the study at that point.

7.4 UNANTICIPATED PROBLEMS

7.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An unanticipated problem (UP) is defined as an adverse event that is unexpected given the information currently known about the medication and, to a reasonable extent, may be related to participation in the study. Moreover, an UP can potentially indicate greater risk to all participants than was initially anticipated.

7.4.2 UNANTICIPATED PROBLEM REPORTING

UPs will be reported to Amgen within 24 hours and to the investigator's IRB. Changes may be made to the research protocol and informed consent document, or the study may be suspended based on an UP.

7.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

After review by Amgen and the investigator's IRB, subjects may be notified of UPs as well as any changes in the protocol that warrant a change to the consent form.

7.4.4 STUDY MONITORING

The study will be monitored by Duke University Department of Surgery staff in accordance to the Duke "Clinical Quality Management Plans" Policy.

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
    - To compare change from baseline in mean number of days per month with significant pain or pressure between treatment and placebo groups at 4 to 6 months.

Null Hypothesis: In subjects with idiosyncratic facial pain mimicking rhinosinusitis, the erenumab treatment group is the same as placebo, in terms of the reduction from baseline in mean monthly days with significant pain at months 4 to 6.

Alternative Hypothesis: In subjects with idiosyncratic facial pain mimicking rhinosinusitis, the erenumab treatment group is different than placebo, in terms of the reduction from baseline in mean monthly days with significant midfacial pain at months 4 to 6.

- Secondary Efficacy Endpoint(s):

- To compare change from baseline in mean number of days per month with significant pain or pressure between treatment and placebo groups at 1 month and 3 months.
- To compare change in mean number of days per month with significant facial pain between baseline and 1, 3, and 4-6 months within each group
- To compare change in 22-Item Sinonasal Outcomes Test (SNOT-22) between treatment and placebo groups at 1, 3, and 6 months
- To compare change in the Migraine Functional Impact Questionnaire (MFIQ) and its five subdomains between treatment and placebo groups at 1, 3, and 6 months
- To compare change in reduction of rescue medication use between treatment and placebo groups at 1, 3, and 4-6 months
- To compare change in the mean number of days per month with significant congestion and rhinorrhea between treatment and placebo groups at 1, 3, and 4-6 months.
- To compare reduction in mean pain score between treatment and placebo groups at 1, 3, and 4-6 months

8.2 SAMPLE SIZE DETERMINATION

The primary endpoint is the change from baseline to 4-6 months in the average number of days per month with significant mid-facial pain. Assuming a treatment effect compared to placebo of -3.0 and a common standard deviation of 3.5, a sample size of 33 subjects per group would provide 90% power using a two-sample t-test with a 2-sided significance level of 0.05. An assumed 10% dropout is factored into the sample size calculation.

8.3 POPULATIONS FOR ANALYSES

The complete analysis dataset includes all subjects randomized in the study. Summaries of demographic data, baseline disease characteristics, and subject disposition will utilize this dataset.

The efficacy dataset will be used to carry out analyses of all primary and secondary endpoints. This dataset includes all randomized patients who received at least one dose of the randomly assigned treatment regimen and had at least one post-baseline measurement for mid-facial pain days per month.

8.4 STATISTICAL ANALYSES

8.4.1 GENERAL APPROACH

The primary objective of this study is to evaluate the efficacy of erenumab compared to placebo on the change from baseline in mean monthly days with significant facial pain, in subjects with midfacial pain or pressure mimicking rhinosinusitis.

The primary analysis will be performed when the last randomized subject completes the 6 month (day 180) study visit assessment or is discontinued from the study.

Subjects will be analyzed based on their randomized treatment group assignment. This will be an intention to treat analysis.

Descriptive statistics by treatment group will be tabulated at each study visit. For continuous endpoints, descriptive statistics include: number of subjects, mean, median, standard deviation, standard error, lower and upper quartiles, minimum and maximum. For categorical endpoints, frequency and percentage will be provided.

8.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The change in the number of days with facial pain or pressure from baseline to completion of the six-month treatment administration period will be analyzed using a linear mixed-effects model including treatment group, baseline value, scheduled visit, and the interaction of treatment with scheduled visit. Imputation is not planned. If applicable, a first-order autoregressive covariance structure is assumed. Least squares means for each treatment group, standard errors, associated 95% confidence intervals as well as the treatment difference, associated 95% confidence intervals and p-values will be reported. A two-sided significance level of 0.05 is assumed.

Additionally, we will compare the change in the mean number of days per month with significant idiosyncratic facial pain between the treatment group versus the placebo-controlled group from baseline to intermediate time points at one and three months.

8.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

- The mean number of days per month with significant pain or pressure

This will be compared between baseline and 1, 3, and 4-6 months within each group. This represents an intragroup analysis as opposed to comparing treatment and placebo groups.

- 22-Item Sinonasal Outcomes Test (SNOT-22)

The change in mean scores from baseline for the SNOT-22 survey will be compared at 1, 3, and 6 months. The SNOT-22 is the most widely-used validated sinonasal questionnaire in the otolaryngologic literature.[16] Respondents rate the severity of twenty-two symptoms from a scale of 0 (no problem) to 5 (severe as can be) over the previous two weeks, for a score ranging from 0 to 110. It is self-administered and includes symptoms pertaining to multiple domains, including nasal, extranasal, sleep, and psychological. A minimal clinically important difference has been determined to be 9.[17] Analysis of the SNOT-22 will allow the assessment of changes in specific sinonasal symptoms, such as drainage and congestion, which are thought to be associated with idiosyncratic facial pain.

- Migraine Functional Impact Questionnaire (MFIQ)

The change in mean scores from baseline for each of the five subdomains of the MFIQ will be compared at 1, 3, and 6 months. The MFIQ is a self-administered 26-item questionnaire assessing the impact of migraine on five domains over the previous seven days: physical functioning (5 items), usual activities (10 items), social functioning (5 items), emotional functioning (5 items), and overall functioning (1 item).[18,19] Each item is rated on a 5-point scale, with 5 representing the greatest impact. The scores for each domain will be calculated as the sum of the items.

- Change in number of doses of rescue medication use for facial pain

The change in number of doses of rescue medication use from baseline to 1, 3, and 4-6 months will be compared. The daily data log will enable analysis of frequency, type, and numeric dose of the following rescue medications: triptans, opiates, tramadol, acetaminophen-containing medications, butalbital, antihistamines, non-steroidal anti-inflammatory drugs, decongestants, antibiotics, and steroids. The frequency (number of doses) of rescue medication use will be compared between the two groups at baseline and 1, 3, and 4-6 months

- Mean daily pain score

The change in mean daily pain score (scale of 0 to 10) will be compared between the treatment and control groups from baseline to 1, 3, and 4-6 months.

- Mean number of days per month with significant congestion and rhinorrhea

Significant congestion and rhinorrhea will be defined as symptom score greater than 4 out of 10. The change in mean number of days per month with significant congestion and rhinorrhea from baseline to 1, 3, and 4-6 months will be compared for treatment and control groups.

Analysis of the secondary endpoints will be performed using the same methods as the primary endpoint.

8.4.4 SUB-GROUP ANALYSES

The primary and secondary endpoints will be assessed in subgroups based on facial pain/pressure severity, as measured by frequency of facial pain/pressure days. We hypothesize that subjects with greater severity (definition to be determined) will show greater benefit with the study medication.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

All potential study participants will be given a copy of the IRB-approved informed consent to review. The principal investigator, study coordinator, or authorized key personnel will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. No study procedures will be conducted without prior written informed consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Study participants will be given a copy of the written informed consent, along with instructions for who to call with questions or potential adverse reactions. Instructions will also be given for completing questionnaires and the daily pain and medication log.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Documentation of the consent process will be entered in the study participant's electronic health record.

9.1.2 DISCONTINUATION AND STUDY STOPPING RULES

Subjects will be given the opportunity to withdraw from the study at any time. Every effort will be made to obtain follow-up information. Subjects who discontinue prematurely will be asked to return for a final follow-up visit either in person or by phone.

In the event of serious adverse events felt to be possibly related to erenumab and occurring in more than 3 study patients, the study will stop enrollment and the FDA will be notified for review and feedback. A single patient death possibly related to erenumab will also stop the study.

9.1.3 CONFIDENTIALITY AND PRIVACY

Study records that identify subjects will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). Anonymized data may be shared with the maker of erenumab in accordance with the executed agreement.

Participant confidentiality is strictly held in trust by the sponsor-investigator, sub-investigators, study staff, and their agents. This confidentiality is extended to cover use of medical records related to medical history images in addition to any study information relating to participants.

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

Electronic data will be stored in a private folder housed in a secure server behind the Duke University Medical Center firewall. Paper documents including but not limited to CRFs, questionnaires and original signed ICFs will be kept in a locked file in the HNSCS Research Office, which is locked when not in use. Research data such as the data dictionary and de-identified 3D imaging data and analysis will be stored on a secure, password-protected desktop computer at Duke University. Only study staff listed as key personnel will have access to study data.

This project uses the REDCap Twilio integrated functionality. This module enables a research study to make and receive voice calls and SMS text messages, both to and from survey respondents. A REDCap and Twilio account are linked together. When a user indicates that an SMS (text) or a call should be sent to a cell phone, REDCap requests that action through Twilio. When a user responds, Twilio relays that information back to REDCap. The data is stored in the REDCap database. Twilio does not store any data nor does it keep a log of its actions.

It is important to understand that this feature utilizes the third-party service Twilio.com, which means that all voice calls and SMS messages will be routed through Twilio's servers. However, REDCap goes to great length to ensure that voice call records and SMS transcriptions do not stay in Twilio's logs but are removed shortly after being completed. This is done for security and privacy concerns (e.g., HIPAA), in which your survey participants' phone numbers and their survey responses do not get permanently logged on Twilio's servers but instead remain securely in REDCap.

The REDCap Twilio module is managed by the Biomedical Informatics group in the Institute for Clinical and Translational Science at the University of Iowa. Twilio uses two-factor authentication to access the application administratively. The integrated module can only be turned on by a REDCap Administrator. Twilio configuration is managed by a REDCap administrator. The integration requires ‘inspectors’ be turned off at the Twilio level to ensure no logging data is retained.

This study uses the **Survey as SMS conversation** functionality. When participants take an SMS survey, questions are asked one at a time as an SMS text message conversation/thread. Participants may respond with any kind of alpha-numeric text for SMS survey. Survey as a SMS text conversation is not encrypted communication. HIPAA information will not be collected via this method, unless a special exception is granted. The data being collected using this method reflects what is included in the protocol submission and approved. Appropriate language will be included in the subject consent to

inform subjects of the potential risk of unencrypted communication. Only REDCap administrators are allowed to enable the Twilio option to initiate a survey as an SMS conversation.

This study will also use the **Survey invitation link via SMS** which allows for encrypted communication. Once the participant clicks on a link to the survey, they fill out that survey in a secure environment (https) on the mobile device, just as they would on a desktop or laptop browser. HIPAA information may be collected using this method. The data being collected using this method reflects what is included in the protocol submission and approved by the IRB.

During data collection, subject identifiers and relevant data elements will be recorded. Then, study-specific identification numbers will be assigned to each subject. Prior to dissemination of any data beyond the Duke secure servers or firewall, all identifiers will be stripped from the database and data will only be referenced by the study-specific identification numbers. A master log, which links the study-specific identification number to the study subject, will be generated. The master log will be stored in the study-specific, private electronic folder and will be accessible only to key personnel.

9.1.4 FUTURE USE OF STORED DATA

Data may be available for future research provided the data is de-identified and has obtained sufficient IRB approval for use. The IRB approved ICF will include language alerting subjects that de-identified data collected as part of this study may be used for future research.

9.1.5 STUDY RECORDS RETENTION

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator for the longer of a period of:

- at least two years after the date on which a New Drug Application is approved by the FDA
- at least two years after formal withdrawal of the IND associated with this protocol
- at least six years after study completion

9.1.6 PROTOCOL DEVIATIONS

Protocol deviations will be reported to the IRB, in compliance with 21 Code of Federal Regulations (CFR) 312.60.

9.1.7 PUBLICATION AND DATA SHARING POLICY

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

9.1.8 REFERENCES

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APPENDIX A: INVESTIGATOR-SPONSORED STUDY – SAFETY DATA EXCHANGE REQUIREMENTS

For Interventional studies with Amgen IMP*:

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Sent to Amgen at time of regulatory submission
Serious Adverse Events (SAEs)	Not required, unless contractually specified per study
Adverse Events not meeting serious criteria	Not required, unless contractually specified per study
Events of Interest	Not required, unless contractually specified per study
Pregnancy/Lactation	Within 10 calendar days of Sponsor awareness
Event listing for reconciliation	As specified per contract

*Specific requirements are to be outlined in the Research Agreement

Aggregate reports*(as applicable):

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

*Specific requirements are to be outlined in the Research Agreement