Efficacy of Rimegepant Plus Calcitonin Gene-Related Peptide Monoclonal Antibody for Migraine

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Efficacy of Rimegepant Plus Calcitonin Gene-Related Peptide Monoclonal Antibody for Migraine

A Thesis Presented to
The Faculty of the School of Medicine
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LIST OF ABBREVIATIONS

ACS: Acute Coronary Syndrome
AE: Adverse Event
AMY1: Amylin receptor 1
BBB: Blood Brain Barrier
BMI: Body-Mass Index
cAMP: cyclic Adenosine Monophosphate
CGRP: Calcitonin Gene-Related Peptide
CI: Confidence Interval
CLR: Calcitonin Receptor-Like Receptor
DUA: Data Use Agreement
ECG: Electrocardiogram
ePRO Diary: electronic Patient Reported Outcomes Diary
ER: Emergency Room
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
ICHD: International Classification of Headache Disorders
IHS: International Headache Society
IRB: Institutional Review Board
kDa: kilo Dalton
LPN: Licensed Practical Nurse
mAb: Monoclonal Antibody
MBS: Most Bothersome Symptom
MI: Myocardial Infarction
mITT: modified Intention-To-Treat
MSQ: Migraine-Specific Quality of Life Questionnaire
NSAID: Nonsteroidal Anti-Inflammatory Drug
ODT: Oral Disintegrating Tablet
OSA: Obstructive Sleep Apnea
PCI: Percutaneous Coronary Intervention
RAMP1: Receptor Activity-Modifying Protein 1
RCT: Randomized Controlled Trial
RD: Risk Difference
RR: Risk Ratio
RN: Registered Nurse
SAE: Serious Adverse Event
SD: Standard Deviation
TIA: Transient Ischemic Attack
US: United States of America
vs: versus
ABSTRACT

Migraine is a paroxysmal pain disorder managed with abortive therapy during a pain attack, prophylactic therapy to prevent attacks, and often a combination of both. Calcitonin gene-related peptide (CGRP) and its receptor have a role in the provocation of migraines, and therefore have been targeted in the development of both preventive and abortive therapies. However, there is limited research investigating concomitant use of the therapies. This study will examine the safety and efficacy of oral rimegepant when used for acute treatment concomitantly with a monoclonal antibody (mAb) targeting the CGRP ligand or receptor for the preventive treatment of migraine. A biphasic trial with a randomized, double-blind, placebo-controlled Primary Phase and an open label Secondary Phase will assess efficacy as measured by freedom from pain at 2 hours. The results of this study have the potential to improve and expand the management approaches used for migraine patients.
CHAPTER 1: INTRODUCTION

1.1 Background

Migraine is a disabling disorder which is estimated to affect approximately 15% of the global population.\(^1\) Migraine is characterized by a painful unilateral headache attack often associated with nausea, vomiting, photophobia, and phonophobia.\(^2\) An increased frequency of migraine headache days correlates with increased disability and results in decreased quality of life involving both negative social and psychological impacts.\(^3\)

Although the definitive underlying pathophysiology of migraine is unknown, the inflammatory peptide, calcitonin gene-related peptide (CGRP), and its receptor, expressed in both the peripheral and central nervous system including trigeminovascular pathways, have been identified as having a role in the provocation of migraines.\(^4\) This system has been targeted in the search for new efficacious and safe migraine treatments. One of the more promising classes are small molecule CGRP receptor antagonists, also called gepants. Such a small molecule antagonist can either compete with the initial CGRP C-terminal binding event and block the activation of the receptor or potentially displace bound CGRP and deactivate the receptor.\(^5\) One of the gepants, rimegepant (Nurtec-ODT [Biohaven Pharmaceuticals, New Haven, CT]), was found to be significantly more effective than placebo for acute treatment of migraine, as measured by pain freedom and reduction of most bothersome symptom (MBS) two hours after intake.\(^2\) It was approved for acute treatment of migraine by the Food and Drug Administration (FDA) in February 2020 (Biohaven Pharmaceutical Company Holding Ltd., 2020).

The advent and approval of rimegepant was a significant development in the acute treatment of migraine. Although many abortive treatments for migraine are available, their efficacy and tolerability vary greatly among migraine patients. One of the more widely and well-established acute treatments are triptans. Sumatriptan is the most commonly used acute treatment
for migraine attacks in the United States of America (US). However, pain freedom at 2 hours after drug intake, the primary outcome in most clinical trials for acute treatment of migraine, is only experienced by 12-40% of patients depending on the triptan used. Also, triptans are contraindicated in patients with coronary artery disease, uncontrolled hypertension, and cerebrovascular disease. The gepants’ proposed mechanism of action involves the inhibition of vasorelaxant responses to CGRP in the middle meningeal arteries, and they are less potent in antagonizing the vasodilatory responses in the coronary arteries. Therefore, rimegepant may be a suitable alternative for patients who are unable to use or do not currently achieve pain freedom from triptans or other abortive treatments. It continues to be important to consider the natural cardioprotective effects of CGRP as well as any pre-existing cardiovascular or cerebrovascular risk factors when using drugs that target this system.

The CGRP system has also become a target for preventive migraine therapy. Several new preventive interventions have been introduced and are increasingly being utilized by patients with migraine. The primary focus involves monoclonal antibodies (mAbs) that target the CGRP system and unlike other existing preventives, are administered via monthly injection (or quarterly injection for fremanezumab [Ajovy] and eptinezumab [Vyepti]). These FDA approved preventives include erenumab-aooe (Aimovig [Amgen, Thousand Oaks, CA and Novartis, Switzerland]), galcanezumab-gnlm (Emgality [Eli Lilly, Indianapolis, IN]), fremanezumab-vfrm (Ajovy [Teva, Israel]), and eptinezumab-jjmr (Vyepti [Lundbeck Seattle Biopharmaceuticals, Inc., Bothell, WA] which have all demonstrated safety and efficacy in trials. Galcanezumab, fremanezumab, and eptinezumab neutralize some portion of circulating α-CGRP and β-CGRP ligands which prevent it from signaling. Erenumab is unique from the other CGRP preventives in that it blocks the CGRP receptor instead of the peptide itself. Erenumab and fremanezumab
are approved for prevention in adults with either the episodic (<15 migraine days per month) or chronic (>14 migraine days per month) form of migraine. Fremanezumab has also demonstrated efficacy in patients with documented failure of up to four migraine preventive medication classes.\textsuperscript{11} Galcanezumab is approved for migraine prevention in those with at least four migraines per month and it is the only CGRP mAb that is approved for cluster headache prevention.\textsuperscript{13} In contrast to the other CGRP mAbs that are injected subcutaneously, eptinezumab is administered intravenously every 3 months and approved for the episodic or chronic form of migraine.\textsuperscript{12,14} The advent of this new class of preventive treatment in migraine is welcomed by both patients and providers. Existing preventive options for migraine consist of a variety of antihypertensive, antidepressant, and antiepileptic medications, which have numerous side effects and on which less than 50% of patients experience a 50% or greater reduction in their monthly attack frequency.\textsuperscript{4} The CGRP mAbs also have ranged from 43-62\% of patients achieving 50\% reduction, but the ease of intermittent dosing as well as low incidence and mild to moderate severity of reported adverse events make them a desirable alternative.\textsuperscript{4,13} Furthermore, CGRP antibodies show a low risk for drug-drug interactions and hepatotoxicity, which can be important for patients using multiple medications.\textsuperscript{4} Complete remission from migraine is uncommon, even with this breakthrough preventive treatment, and acute migraine attacks will still occur in the majority of patients on CGRP antibody therapy. Although at a reduced frequency and intensity, these remaining attacks are often debilitating and require acute treatment.\textsuperscript{15}

\textbf{1.2 Statement of the Problem}

Given the concomitant development of gepants and mAbs, both of which act on the CGRP system, it begs the questions—Would patients using both experience greater benefit? Is such a
combination safe? Targeting the CGRP system for both acute and prophylactic migraine treatment has the potential to generate a stronger antimigraine effect, however, a possible increase in side effects would have to be thoroughly assessed as well.² Published reports of the concomitant use of oral rimegepant for acute treatment and a mAb for prevention are limited. A small case series demonstrated possible efficacy in treating refractory migraine with concomitant rimegepant and erenumab.¹⁶ Following those promising cases, an open-label sub-study of 13 migraine patients simultaneously using rimegepant with erenumab or either anti-CGRP mAbs, fremanezumab or galcanezumab, showed no serious adverse events; efficacy was not reported, however.¹⁷ Therefore, further study in the form of a randomized controlled trial to investigate the safety and efficacy of rimegepant in the setting of concomitant mAb therapy is necessary. If shown to be effective as well as safe, this therapeutic approach may have clinical implications for migraine treatment. Exploration of concomitant CGRP therapy may provide the best opportunity to expand evidence-based migraine management and to improve quality of life in migraine patients.

1.3 Goals and Objectives

The goal of this study is to investigate the efficacy and safety of rimegepant for acute migraine treatment when used concomitantly with a CGRP ligand- or receptor-targeted mAb compared to use without a mAb. Efficacy will be determined by freedom from pain at 2 hours after administration of rimegepant.

1.4 Hypothesis

When using rimegepant as an abortive intervention, adult subjects on an anti-CGRP or anti-CGRP receptor mAb preventive (subcutaneous or intravenous injection) will have a
different incidence proportion of freedom from pain at 2 hours compared to those who have never used a mAb preventive.

1.5 Definitions

- **Rimegepant**: CGRP receptor antagonist, single dose 75 mg oral dissolving tablet
- **Adult**: ages 18-65 (inclusive)
- **Anti-CGRP or anti-CGRP receptor monoclonal antibody migraine preventives**: erenumab, galcanezumab, fremanezumab, or eptinezumab
- **Freedom from pain**: On a 0 to 3 pain severity numerical rating scale (0=none, 1=mild, 2=moderate, 3=severe), the reduction from moderate (2) or severe (3) at the time of drug administration to no pain (0).
REFERENCES


CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

During the period of July 2020 to July 2021, a comprehensive systematic literature search was conducted using repeated searches of PubMed, Scopus, Web of Science, and clinicaltrials.gov databases. Assistance was much appreciated and provided by the librarians at the Yale School of Medicine. Searches were conducted using the following combination of MeSH terms: “migraine”, “calcitonin gene-related peptide”, “CGRP”, “gepant[s]”, “rimegepant”, “monoclonal antibod[y][ies]”, “erenumab”, “galcanezumab”, “fremanezumab”, “eptinezumab”, and included brand and alternative names for each medication. Reference lists of all studies were looked at to identify additional pertinent literature. In this review, relevant clinical studies (including case series and conference poster presentations), systematic reviews, and meta-analyses were included. Preference was given to articles detailing concomitant use of CGRP monoclonal antibodies (mAbs) and rimegepant, and randomized controlled trials (RCTs) investigating efficacy of rimegepant.

The literature search demonstrates the novelty of concomitant use of rimegepant with CGRP mAb therapy. Empirical studies documenting their use are inherently limited due to being case series. For this reason, RCTs investigating efficacy of the medications and the classes to which they belong to were also included to obtain the maximal amount of information existing around their clinical use thus far. The novelty of the medications establishes opportunities for research, however this also reveals the necessity of designing a study which is both feasible and realistic for the stage at which the drugs can be safely studied. Without advancing to a RCT to investigate the concomitant use of the medications, there will be a lack of data to support clinical benefit, thus justifying the need for the proposed study.
2.2 Mechanisms of CGRP Blockade

Calcitonin gene-related peptide (CGRP) is a vasoactive neuropeptide that binds to a CGRP receptor and causes potent vasodilation, including in cranial vasculature and specifically within the trigeminal ganglion.¹ The peptide is known to be released during migraine attacks and intravenous infusions of CGRP have been shown to induce migraine-like headaches in migraine patients.² It has been proposed that elevated levels of CGRP may lead to sensitization of neuronal circuits such that usual sensory inputs (light, sounds, tastes, odors) are experienced as bothersome.³ The mAbs likely target CGRP and its receptors within the trigeminal ganglion and due to their molecular weight of 150 kilo Daltons (kDa) and structure they are unlikely to cross the blood brain barrier (BBB).¹⁻³ Although gepants weigh 0.2-1 kDa, their main target is also thought to be outside of the BBB since only a small percentage of gepant is detected in cerebrospinal fluid compared to plasma following administration in non-human primates.²

The CGRP receptor is a G-protein-coupled receptor which is formed by calcitonin receptor-like receptor (CLR) and a receptor activity-modifying protein 1 (RAMP1), therefore it is often referred to as CLR/RAMP1 receptor.³ Rimegepant is a small molecule antagonist with two proposed mechanisms: competition with the initial binding of CGRP to its receptor, blocking activation of the receptor, or displacement of bound CGRP, effectively deactivating the receptor.

![Figure 1. Mechanisms of CGRP blockade by a small molecule CGRP Receptor Antagonist (dark blue): competition with the initial CGRP ligand (red) C-terminal binding event, preventing N-terminal agonist insertion (D to F), and displacement of bound CGRP ligand (E to F).³](image)

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In order to achieve efficacy with either proposed mechanism, high enough circulating plasma levels are needed as well as balanced physical properties of receptor affinity, protein binding, pharmacokinetics, and safety. In these regards, rimegepant has been optimized. For example, its standard oral dissolving tablet (ODT) formulation has been shown to accelerate relief of migraine through more rapid exposure, showing difference of effect from placebo as early as 15 minutes following administration and statistically significant by 1 hour for pain relief and return to normal function. From a safety perspective, the increased potency of rimegepant in antagonizing the CGRP receptors in the middle meningeal arteries as compared to the coronary arteries may prevent cardiovascular side effects and allow for a broadened patient population to use them in comparison to triptans.

The migraine preventive mAb, erenumab, binds with high affinity to and antagonizes the CLR/RAMP1 receptor, while galcanezumab, fremanezumab, and eptinezumab bind to the neuropeptide itself, neutralizing some portion of the ligand preventing it from signaling through the CLR/RAMP1 receptor. The mAbs’ high selectivity for either CGRP or the CGRP receptor reduces the risk of off-target effects and possible drug to drug interactions. They also have a very long plasma half-life, allowing for once monthly or quarterly injection. Given that they are tolerated well with infrequent administration, this leads to higher treatment adherence rates compared to other preventives. Also, the long half-life of the monoclonal antibodies may target the high levels of CGRP associated with medication overuse headache, a fairly common problem among migraine patients, and alleviate this as well. Unfortunately, the intended preventive effect varies among patients, where some have no response, some have a small reduction in their number of monthly headache days, and some have a near or actual complete response. In a large trial investigating efficacy of erenumab, 40% of participants achieved >50% reduction in
monthly migraine days, and no participants were rid of migraine attacks entirely. Given this, acute treatment will still be required and herein lies an opportunity to investigate the concomitant use of gepants and mAbs.

2.3 Concomitant Use of Gepants and Monoclonal Antibodies (mAbs)

Especially for difficult-to-treat patients, a possible therapeutic approach has emerged involving the combination of gepants and monoclonal antibodies (mAbs). Acting on the CGRP pathway in two ways, there’s potential for a stronger anti-migraine effect. For example, it’s possible that surges of CGRP during migraine attacks may be better targeted by the small molecule gepants with quicker onset of action and short half-life while the biologic mAbs’ longer half-life offer sustained migraine prevention. The medications offer differentiation in their action and therefore increase coverage for the migraine patient. However, combination treatment may have potential limitations which would need to be considered in the design of the present trial. Not all patients have the same degree of response to receptor or peptide blockade offered by mAb preventives, so it would be plausible to expect similar variation in response to antagonism of the CGRP receptor with rimegepant. To better characterize the response to combination therapy, one stratified analysis would compare the response to rimegepant seen in positive versus less positive responders to preventive mAbs. Another potential mechanistic conflict to consider is that with blocking of the CGRP receptor, CGRP can still bind other receptors (e.g., amylin receptor 1, AMY1) and induce a migraine effect. Conversely, if the CGRP neuropeptide is blocked, it is still possible for other peptides (e.g., adrenomedullin) to activate the CGRP receptor albeit with lower affinity than CGRP. Both proposed conflicts, if true, would preclude optimal migraine management. Lastly, the chronic blockade of the CGRP receptor could result in a compensatory overexpression of CGRP receptors leading to tolerance.
of the medications over time. These possible barriers will not be elucidated in this proposed trial, however being aware of the potential shortcomings, as well as the strengths, of a treatment modality on a molecular level is essential when expanding this area of study.

Two case series exist describing the potential for concomitant use of a CGRP mAb and CGRP receptor antagonist in the treatment of migraine. In this first example, a case series presents two subjects participating in a long-term safety study of rimegepant for acute treatment (after FDA approval); both were started on monthly erenumab in addition to existing rimegepant. Both subjects self-reported decades of medically refractory migraine. While on erenumab, every migraine attack the subjects treated with rimegepant was successfully relieved and no other acute rescue medications were required. More so, no adverse events were experienced by either subject. This study, although purely observational and limited by size, was a breakthrough in that it brought forth the reasonable possibility that CGRP signaling could be targeted acutely (i.e., by a gepant) on a background of chronic inhibition (i.e., by a mAb). It is theorized the 2 agents differ in half life and potency, allowing rimegepant to provide additional benefits to ongoing mAb therapy. The mAbs have a half-life of 27-30 days, whereas rimegepant has a significantly shorter 11 hour half-life. In addition, rimegepant was found to be 16 times more potent than erenumab at antagonism of CGRP-mediated cyclic adenosine monophosphate (cAMP) signaling in whole-cell assays, so combination therapy may provide an additive benefit in blocking the intracellular cascades leading to vasodilatory effects. Additional studies to verify and uncover the sources for the efficacy of combination therapy are warranted.

The second case series reports on 13 subjects with migraine on a stable dose of a CGRP mAb who treated acute attacks with rimegepant. The goal was to assess the rate of on-treatment
adverse events. No subjects had serious adverse events, adverse events leading to
discontinuation, or aminotransferase levels >3x the upper limit of normal. Given that the
combination treatment was well tolerated, the authors called for studies of larger patient
populations to confirm their findings. This study is limited by its open label design and short
duration of follow up. In regards to mechanism, the study proposes a theory that the CGRP
receptor occupancy may decrease between injections of a CGRP mAb, which would lead to
increases in unbound CGRP levels in the plasma. Prior modeling studies have indicated that
during the month following an injection of a ligand targeted mAb (i.e. galcanezumab,
fremanezumab, eptinezumab), CGRP plasma levels first drop then return to baseline with up to
36% to 55% of CGRP unbound with the potential to induce breakthrough attacks by binding to
their receptor. Therefore, rimegepant acting on the receptor itself is likely to provide a targeted
benefit in aborting these acute attacks. In addition, with a progressive rise in CGRP plasma
levels throughout the month, this suggests there may be an optimal period during which patients
would benefit, or conversely, a period where potent blockade poses risk associated with
excessive blockade of CGRP activity.

2.4 Review of Rimegepant Efficacy Trials

Although there are no published RCTs investigating concomitant use of CGRP mAbs and
rimegepant, multiple studies have examined the relationship between rimegepant and freedom
from pain at 2 hours, as well as other secondary variables to be analyzed in this proposed trial.
Two similar randomized, double-blind, placebo-controlled, multi-center phase 3 trials, both with
over 1,000 subjects, demonstrated that a single 75 mg dose of rimegepant was more effective
than placebo in freedom from pain at 2 hours —21% versus (vs) 11%, Risk Difference (RD) 10.4
(95% Confidence Interval (CI) 6.5 to 14.2), p<0.0001 and 19.6% vs 12.0%, RD 7.6 (95% CI
3.3 to 11.9), p<0.001\textsuperscript{16} —and freedom from the most bothersome symptom (MBS) at 2 hours—35\% vs 27\%, RD 8.3 (95\% CI 3.4 to 13.2), p=0.0009\textsuperscript{15} and 37.6\% vs 25.2\%, RD 12.4 (95\% CI 6.9 to 17.9), p<0.001\textsuperscript{16}. There was also a positive response shown at 60 minutes post-dose and continuing through 48 hours post-dose suggesting rimegepant’s duration of effect might provide advantages over triptans and other gepants.\textsuperscript{15} In addition, one randomized dose-ranging trial of rimegepant compared the intervention to placebo with sumatriptan as an active comparator.

Rimegepant was found to be superior to placebo were the percentage of subjects who were pain free at 2 hours were at doses of 75 mg (31.4\%, p=0.002), 150 mg (32.9\%, p<0.001), and 300 mg (29.7\%, p=0.002), compared to placebo with 15.3\% and rates of adverse events, although mild in intensity, were dose dependent.\textsuperscript{17} This trial was not designed with statistical power to allow comparison of the sumatriptan arm against the rimegepant arm, however the trial did demonstrate that sumatriptan was also more effective than placebo with respect to the primary endpoint of pain freedom (35\%, p<0.001).\textsuperscript{17} Furthermore, although the patient numbers were small, 2\% of subjects reported events of chest discomfort, chest pain, and jaw pain all within the sumatriptan-treated arm. Even the highest dose of rimegepant administered in the trial (600 mg) did not incur similar events.\textsuperscript{17} A meta-analysis of 3,827 pooled subjects from four RCTs, including the three discussed above, supported that 75 mg rimegepant led to significant freedom from pain (20.6\% vs 12.5\% for rimegepant vs placebo, Risk Ratio (RR) 1.70, 95\% CI 1.39 to 2.08, p<0.001), pain relief (58.6\% vs 44.6\%, RR 1.34, 95\% CI 1.25 to 1.44, p<0.001), and freedom from MBS (36.0\% vs 25.1\%, RR 1.44, 95\% CI 1.23 to 1.68, p<0.001) at 2 hours post-dose compared with placebo.\textsuperscript{18} Much of the methodology included in this proposal is adopted from the described empiric trials while improving upon the weaknesses and limitations presented by them.
2.5 Review of Methodology

Study Design

In the empiric trials presented above, rimegepant is compared to placebo and subjects treated a single migraine attack with the active intervention.\textsuperscript{15,16} Challenges to this study design emerge on two main accounts with the first being the lack of an active comparator, and the second being the treatment of only a single attack.

These studies have been critiqued for failing to justify the comparison of rimegepant to placebo, as opposed to an active comparator, when other therapeutic interventions exist for migraine. The ethics of the design have been called into question as half of subjects were allowed to experience severe pain, often resulting in an inability to work or perform typical daily activities. However, in the setting of a single migraine attack study, long-term harm from a non-active comparator is unlikely and informed consent can be used to justify the use of a placebo.\textsuperscript{19}

To improve upon ethical standards, this proposed study design includes offering rescue therapies to all participants to be used 2 hours after administering rimegepant or placebo if needed. Also, if at any point unbearable pain is experienced, the rescue medication may be self-administered and will be documented as an intervention failure. Although a non-inferiority design could be used to compare a new medication with established treatment, it’s difficult to put forth any single abortive treatment as standard of care. Even the widely used triptans do not lead to response in 33\% of patients.\textsuperscript{16} Another argument is that demonstrating superiority to placebo rather than an active comparator is more likely to result in positive findings for the medication, but have less of an impact on therapy choices in clinical practice.\textsuperscript{19} One RCT compared rimegepant to placebo, but included sumatriptan (100 mg) as an active comparator. Both rimegepant and sumatriptan were found to be superior to placebo in freedom from pain at 2 hours, however the trial was not
designed with statistical power to allow head to head comparison of the sumatriptan arm against the rimegepant treatment arms. Therefore the addition of sumatriptan as an active comparator without designing the trial with the goal of demonstrating non-inferiority is unlikely to add much strength to the study results when the primary goal is to compare those on or not on a mAb.

The single-attack study design has been criticized for the lack of generalizability that can be applied to the efficacy and safety outcomes of the studies because consistency of response to the medication cannot be assessed. The authors do call for future trials to establish the benefits of rimegepant across multiple attacks, however in defense of this design, studies of single migraine attacks are the global standard for establishing efficacy of acute treatments of migraine and for regulatory approval in the US. Multiple-attack studies can be affected by un-blinding (where patients learn to distinguish active drug from placebo) and carryover effects, so the first attack is used to define primary efficacy endpoints. In order to maintain the randomization and blinding of a single-attack study but also provide an opportunity to extend results beyond that of primary efficacy, the multi-phase trial design is proposed to subvert these critiques. For more detailed information on the proposed study design please refer to 3.1 Study Design.

**Study Population**

The study population from which subjects are to be recruited consists of adults with migraine who have been on a stable dose of a CGRP mAb (erenumab, galcanezumab, fremanezumab, or eptinezumab) for at least 3 months. The CGRP mAbs are administered monthly (or quarterly for fremanezumab and eptinezumab), none are available generically, and therefore the medications incur costs to patients, private insurance companies, and government funded programs. Public paid claims data was used to estimate the number of people in the U.S. who are on a CGRP mAb for migraine prevention. The most recent data available shows that in
2019, Medicaid and Medicare Part D spending totaled $48,010,499 and $119,459,268, respectively, to pay for Aimovig (erenumab-aooe) alone.\textsuperscript{21,22} Using this data, it can be estimated that 7,208 and 16,828 patients were covered by Medicaid and Medicare, respectively, for a year supply of the medication in 2019. With inclusion of those covered for galcanezumab and fremanezumab, the estimated number of Medicaid and Medicare patients on a CGRP mAb in 2019 totals 42,279 patients. Please refer to \textbf{APPENDIX A: Study Population Approximation}, for calculations. This is likely a gross underestimation of the number of patients on a mAb currently, as eptinezumab was not FDA approved until 2020 and the remaining three mAbs were only approved in 2018.\textsuperscript{23} For example, with erenumab, there was a 2\% increase in spending from 2018 to 2019 for both Medicaid and Medicare, and likely continued to increase by 2021.\textsuperscript{21} Also, an even higher growth rate may be expected from 2019 to 2020 in the setting of the Covid-19 pandemic during which a number of patients were transitioned from botulinum toxin therapy to a mAb for migraine prevention as office visits were made limited.

It is necessary to realize this estimate does not include what is expected to make up the majority of the study population– the number of patients who obtain a CGRP mAb through private insurance or a payment assistance program funded by the pharmaceutical company. It is estimated that 75\% of Aimovig prescriptions cost patients $5 or less per month including those where the Aimovig Ally\textsuperscript{TM} Access Card was used (the card is available to those with private insurance). The remaining 25\% of Aimovig prescriptions cost privately insured patients an average of $82 per month.\textsuperscript{24} Although difficult to obtain data to estimate the number of patients enrolled in the payment assistance program or covered by private insurance, the majority of patients’ relatively low copay is supportive that cost would be less of a barrier for most US citizens to be able to access the medication. Based on these data and the calculated estimates
obtained from it, recruiting patients from the study population in this multi-center US based study to satisfy the desired sample size is both realistic and attainable. For more detailed information on recruitment, please refer to 3.4 Recruitment.

**Selection Criteria**

The selection criteria for subjects to participate in this trial is similar to the rimegepant vs placebo RCTs and based on International Headache Society (IHS) Guidelines for controlled trials of acute treatment of migraine attacks in adults. 15-17,25 A complete list of inclusion and exclusion criteria can be referred to in 3.2 Study Population and Sampling.

One of the most notable exclusion criteria is for subjects with a history with current evidence of uncontrolled, unstable, or recently diagnosed cardiovascular disease, cerebrovascular disease, or uncontrolled hypertension. Clinical trials of the mAbs showed cardiovascular safety issues deemed unrelated to treatment. 2 Although no adverse cardiac effects have been observed thus far in rimegepant vs placebo studies or in the concomitant CGRP mAb and rimegepant case series, this exclusion criteria is recommended for the purpose of safety. 10,13,15,16 CGRP is important for maintenance of cardiovascular homeostasis and could possibly prevent cerebral or cardiac ischemia with its induction of vasodilation. 2 The limited data surrounding CGRP blockade by two medications and lack of long-term safety studies make it critical to consider those with preexisting risk factors in order to prevent a cardiovascular-related adverse event. 9 Therefore this population should not be included in this particular study with the knowledge that as results from long-term safety studies of rimegepant emerge, it may support including cardiovascular patients in future studies.
Efficacy Parameters and Outcomes

The primary outcome of freedom from pain at 2 hours and secondary outcomes including freedom from most bothersome symptom (MBS) at 2 hours, time to freedom from pain etc. are all seen in the empirical trials of rimegepant vs placebo discussed earlier.\textsuperscript{15-17} This is fairly standard in that acute migraine treatment trials which are well designed in accordance with IHS Guidelines and all have the same, if not similar, efficacy endpoints.\textsuperscript{25} Where there is variation in the proposed trial is the addition of the Migraine Specific Quality of Life Questionnaire (MSQ) to assess the effect of migraine on daily functioning. The MSQ is a psychometrically valid tool that can be used to reliably measure the impact of migraine among both episodic and chronic migraine patients. It was found that MSQ change scores were higher in magnitude in groups experiencing greater decline in headache frequency, e.g. a >50\% improvement in headache frequency correlated with a 23.3 mean change in MSQ score (Standard Deviation (SD) 24.0), 30-50\% improvement correlated with a 12.6 mean change in MSQ score (SD 20.1), and a <30\% improvement in headache frequency correlated with a 3.0 mean change in MSQ score (SD 14.0) yielding a p-value of <0.001 for between-category comparisons.\textsuperscript{26} Although the proposed trial is focused on acute outcomes from rimegepant intervention, improvements in management of migraine attacks also has broadened impacts on patients’ functioning and overall quality of life. If an acute attack is treated more rapidly and with sustained relief, there will be fewer impacts on daily life activities. Therefore, the inclusion of this questionnaire adds strength to the existing framework of acute migraine treatment trials.

Outcomes for the proposed study are attained from subjects’ self-reporting through the use of an electronic Patient Reported Outcomes diary (ePRO diary). This is recommended by IHS guidelines as an ePRO diary has time-stamp capabilities and also provides an opportunity
for adverse events (AEs) to be communicated with the research team in real time. Simplicity of the electronic report form is of the utmost importance, as the quality of collected data decreases as the quantity increases. The goal is for the form to be as easy as possible for subjects to fill out during attacks. In prior rimegepant studies, an ePRO Diary was exclusively used for outcome reporting. However, to remain inclusive of those subjects with significant photophobia as part of their migraine symptom profile, one may opt for a near-identical paper option so as not to preclude their ability to report outcomes. Also, during the Run-in Period, all subjects will practice documenting their symptoms in the diary with acute attacks. Those who are unable to consistently document, will be excluded from further participation in the trial.

Additionally, participant-reported outcomes come with concerns of report bias. The subjective interpretation of symptoms and pain severity level will inevitably vary from person to person. However, with the simple, standardized numerical pain scale (0 = No pain, 1 = Mild pain, 2 = Moderate pain, or 3 = Severe pain) recommended by IHS guidelines, there is less room for major variations in subject reporting. Furthermore, the open-label secondary phase of the proposed study will allow for within-subject comparisons, wherein subjective pain ratings will be more consistent across multiple attacks for each subject. Lastly, the primary endpoint of freedom from pain is more easily defined than a reduction in pain which involves more subjective judgement (i.e. the difference between no pain and any degree of pain is binary, whereas the difference between mild and moderate or moderate and severe pain is not as explicit). Therefore the efficacy parameters themselves are protective against potential self-report bias.
2.6 Review of Possible Confounding Variables

Demographics Variables

One demographics variable which may exert an effect on the outcome is sex. Migraine is up to 3 times more prevalent in women than in men, and women with migraine have more frequent and severe headache attacks.\(^2\) In rodent models, the application of CGRP to the dura mater induce behavioral responses consistent with headache only in female rats. Females show significantly lower facial withdrawal thresholds at 3, 5, and 24 hours after injection (p < 0.0001).\(^{27}\) This suggests the CGRP receptor itself is implicated in the higher prevalence of migraine in women. The difference may be related to hormonal fluctuations e.g. in estrogen and progesterone, potentially affecting CGRP signaling.\(^2\) Although gepants and mAbs have both been shown as safe and exert an effect in both male and female patients, existing studies lack the statistical power to assess a potential sex difference in efficacy.\(^2\) For the proposed study, a female to male subject ratio that approximates the migraine population will be sought, serving to make the findings from this study generalizable to migraine.

Another factor which raised concern for confounding in previous rimegepant trials is obesity. Women with obesity formed the majority of the study population. This was criticized for the potential effect it may have on pharmacokinetics, however body-mass index (BMI) was not found to predict response to rimegepant.\(^{15,18,20}\) Also, as discussed above, migraine is predominantly a disease of women, and 43% of adults aged 40-59 years are obese.\(^{20}\) For this study, the research pharmacy will attempt to recruit from a more diversified population in terms of sex and weight, especially given the multi-center setting, however it is understood that these imbalances may only account for the natural differences in disease prevalence and thus far have not shown to make a significant prediction of outcomes.
Preventive Medications

In prior rimegepant vs placebo studies, subjects were allowed to have been on a stable dose of a preventive medication for at least 3 months prior to the trial. The results were stratified dichotomously, with participants answering if they were on a preventive (yes/no), however the different types of preventive medications the subjects were on are not described.\textsuperscript{15,16} This could have confounded outcomes in that some prophylactic medications can reduce severity of acute migraine attacks more than others.\textsuperscript{28} This may impact the level of ease with which the migraine is successfully treated. In the proposed study, subjects are intentionally on mAb preventives (and allowed to currently be on one additional non-mAb preventive), and controls are allowed to be on a stable dose of no more than two non-mAb prophylactic medications. Given that 87% of those with episodic migraine take no preventive medications, it will be attempted to balance the number of subjects and controls currently on other preventive treatments in order to minimize the effect of this confounding variable.\textsuperscript{28} However, given the inclusion criteria requiring 2-8 migraine attacks per month in the 3 months prior to screening and maintained during the Run-in Period, as long as the subject is meeting this migraine burden, it is less likely the different preventives will pose an issue of confounding. This also allows the control subjects to be more representative of the episodic migraine population at large and improve generalizability of this study’s results.

Migraine Triggers

In terms of the migraines themselves, subjects may have their own identifiable triggers which tend to induce a migraine, and this is an element which would be difficult to control for in the proposed study. Common triggers involve disturbances in sleep, exercise, diet, and stress, with successful management mitigating migraine burden.\textsuperscript{29} Although subjects will be encouraged
to minimize major changes to their routine and medications while optimizing healthy habits in regards to those four pillars, variation will inevitably exist throughout the study. This may not only influence how often a particular subject has a migraine, but also how hard it may be to treat. Pharmacologic treatment may not impart relief without simultaneous management of the particular trigger (i.e. a subject who is sleep deprived, would likely require sleep in addition medication in order to relieve their migraine).29 Throughout the Secondary Phase of the study, patterns may be recognized within subjects’ reported symptoms and outcomes as they treat multiple attacks with rimegepant. This could reveal to the researcher specific underlying triggers influencing the results. However, it is realized that the differences among subjects in the prophylaxis and management of their triggers, may confound the outcomes in almost all migraine studies.

**Rimegepant Formulation**

With regards to the active intervention, rimegepant is formulated as an oral disintegrating tablet (ODT) which has been recognized for its fast absorption and time to peak plasma concentration.15 This must be considered as it has been associated with relatively rapid onset of relief seen in subjects. Other migraine agents have also prioritized an ODT formulation given that many patients have associated nausea with acute attacks. This is done with the intention of increasing speed of absorption and onset of effect while mitigating the effects of migraine on the gastrointestinal system.30 In the proposed study, the placebo tablet will be designed with the same taste, shape, and disintegrating properties as the active intervention. Also, pain outcomes are to be tracked for 24 hours after self-administering the intervention so that not only the rapid onset but also sustained pain relief is prioritized in the results to demonstrate efficacy.
2.7 Conclusion

This review of the literature demonstrates the novelty of concomitant use of rimegepant with CGRP mAb therapy and the necessity for a RCT investigating their combined efficacy and safety. The studies that investigate the CGRP pathway and potential mechanisms of rimegepant in the context of the mechanisms of mAbs aid the understanding of how their combined use may improve pain outcomes. These studies also lead researchers to consider the potential for adverse events to arise. This information is critical in the design of the proposed study such that it is not only feasible but also safe. Next, the case series reviewed in this chapter reveal promising results for concomitant use of the medications, however they lack the number of subjects, blinding, and randomization to demonstrate efficacy, so each of these areas are addressed in the proposed methods. Also, previous RCTs demonstrating the safety and efficacy of rimegepant are discussed in order to highlight portions of the methodology that are to be either replicated or improved upon to conduct an effective study while reducing bias and confounding where possible. The review identifies the gap in this area of research and utilizes what information is available to fill that gap with a RCT that will generate data for the benefit of both providers and the patients for whom they prescribe migraine therapy.
REFERENCES


CHAPTER 3: STUDY METHODS

3.1 Study Design

This multi-center, biphasic trial will evaluate the safety and efficacy of rimegepant 75 mg ODT for acute migraine treatment with concomitant anti-CGRP or anti-CGRP receptor mAb for migraine prevention. The Primary Phase will consist of a randomized, double-blind, placebo-controlled single-attack study, and the Secondary Phase will be a 2 month open label multi-attack study.

3.2 Study Population and Sampling

The source population from which the study and control populations will be acquired consists of adults ages 18-65 years old with at least a 1 year history of migraine with or without aura. The study population (herein interchangeably referred to as the mAb group) will have been treated with a stable dose of an injectable anti-CGRP or anti-CGRP receptor monoclonal antibody: erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), or eptinezumab (Vyepti) for at least 3 months prior to screening. The control population (herein referred to as the control group) will include those who have never used anti-CGRP or anti-CGRP receptor mAbs. The complete inclusion and exclusion criteria, which have been partially adopted from a previous clinical trial investigation of rimegepant, can be seen below.¹

**Inclusion Criteria:**

1. Adults ages 18-65 years old with at least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, (ICHD-3, 2018)
2. Age at onset of migraine is <50 years old.
3. History of 2-8 migraine attacks per month in the 3 months prior to the Screening Visit and maintains this requirement during the Run-in Period.
4. Less than 15 days with headache (migraine or non-migraine) per month in the 3 months prior to the Screening Visit and maintains this requirement during the Run-in Period.
5. Study subjects: Appropriately administered stable dose of erenumab, galcanezumab, fremanezumab, or eptinezumab for at least 3 months prior to study.
Use of other migraine preventives is permitted. Study subjects may be on a stable
dose of no more than one prophylactic agent, as determined by the investigator,
for at least 3 months prior to the study.
6. Control subjects: naïve to an anti-CGRP or anti-CGRP receptor monoclonal antibody.
a) Use of other migraine preventives is permitted. Control subjects may be on a
stable dose of no more than two prophylactic agents, as determined by the
investigator, for at least 3 months prior to study.
7. All subjects should maintain their preventive regimen and not alter it during the study.
8. Patients with contraindications to use of triptans may be included provided they meet all
other study entry criteria.
9. Have a sitting pulse rate ≥ 45 beats per minute (bpm) and ≤ 100 bpm during the vital sign
assessment at the Screening Visit. Clinical site may perform a maximum of 2 repeats of
vital sign measurements if the initial measurement is out of range.
10. Women of childbearing potential must be using two acceptable methods of contraception
to avoid pregnancy throughout the study in such a manner that the risk of inducing
pregnancy is minimized for the duration of the clinical study and up to 8 weeks after the
study.
   a) Must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L
   or equivalent units of HCG)
   b) Women must not be breastfeeding

**Exclusion Criteria:**
1. Current use of a gepant for acute migraine treatment
2. Previously participated in an investigational study of a gepant
3. Difficulty distinguishing migraine headache from tension-type or other headache types
4. Has a history of menstrual migraine, migraine aura with diplopia or impairment of level
   of consciousness, hemiplegic migraine, retinal migraine, or medication overuse headache
   as defined by ICHD-3
5. Has a current diagnosis of new persistent daily headache, trigeminal autonomic
   cephalalgia (e.g., cluster headache), or painful cranial neuropathy as defined by ICHD-3
6. Required hospital treatment of a migraine attack 3 or more times in the 6 months prior to
   screening
7. Participation in any other clinical investigation using an experimental drug or other
   therapy (e.g. neuromodulatory devices) within 30 days prior to study intervention
   administration
8. Participation in a blood or plasma donation program within 60 or 30 days, respectively,
   prior to study intervention administration.
9. Positive drug screen for drugs of abuse that in the investigator’s judgment is medically
   significant, in that it would impact the safety of the patient or the interpretation of the
   study results. In addition:
   a) Detectable levels of cocaine, amphetamine, barbiturates and phencyclidine (PCP)
      in the drug screen are exclusionary. Patients who are positive for amphetamines
      or barbiturates on the urine drug screen may have their urine samples evaluated
      for further analysis at the investigator’s discretion to rule out a false positive
      result or ask for documentation showing prescribed use (i.e. methylphenidate for
      ADHD)
b) Detectable levels of marijuana in the initial drug screen are not exclusionary, however subjects must have a negative test before initiating the Run-in Period and remain negative throughout the study in order to participate.

10. History of treatment for, or evidence of, alcohol or drug abuse within the past 12 months or patients who have met DSM-V criteria for any significant substance use disorder within the past 12 months from the date of the Screening Visit

11. Patient history of HIV disease

12. Patient history of Polycystic Ovarian Syndrome (PCOS)

13. Patient history with current evidence of uncontrolled, unstable or recently diagnosed obstructive sleep apnea (OSA), cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Patients with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening.

14. Uncontrolled hypertension (high blood pressure), or uncontrolled diabetes (however patients can be included who have stable hypertension and/or diabetes for 3 months prior to being enrolled)

15. Patient has a current diagnosis of major depression, other pain syndromes, psychiatric conditions (e.g., schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the investigator’s opinion, might interfere with study assessments

16. Patient has a history of gastric or small intestinal surgery, or has a disease that causes malabsorption

17. Has a history or current evidence of any significant and/or unstable medical conditions (e.g. congenital heart disease or arrhythmia, known or suspected infection, cervical disease, End Stage Renal Disease, hepatitis B or C, or cancer) that in the investigator’s opinion, might interfere with study assessments or place the patient at higher risk of a significant adverse event.

18. ECG and Laboratory Test Findings
   a) Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 ml/min/1.73m²
   b) Corrected QT interval > 470 msec (QTc by method of Frederica), during the Screening/Baseline Phase
   c) Left Bundle Branch block
   d) Right Bundle Branch Block with a QRS duration ≥ 150 msec.
   e) Intraventricular Conduction Defect with a QRS duration ≥ 150 msec.
   f) Serum bilirubin (Total, Direct and Indirect) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period.)
   g) AST (SGOT) or ALT (SGPT) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period.)
   h) Neutrophil count ≤ 1000/µL (or equivalent).

19. Prohibited concomitant medication prior to randomization and during the course of the study or as specified.
   a) St. John’s Wort should not be taken 14 days prior to randomization and throughout the study.
b) History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months

b) History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 months

c) Use of narcotic medication, such as barbiturates, heroin, opium in the form of morphine and codeine, oxycodone and hydrocodone for at least 2 days prior to randomization.

d) Use of acetaminophen or acetaminophen containing products after randomization is prohibited, except as rescue medication as described in protocol. Any use of acetaminophen or acetaminophen containing products during screening must be stopped at least 2 days prior to randomization.

e) Use of acetaminophen or acetaminophen containing products after randomization is prohibited, except as rescue medication as described in protocol. Any use of acetaminophen or acetaminophen containing products during screening must be stopped at least 2 days prior to randomization.

3.3 Subject Protection and Confidentiality

Written informed consent must be obtained from the patient in accordance with requirements of the study center’s institutional review board (IRB) or ethics committee, prior to the initiation of any protocol-required procedures. The consent forms will be available in English, Spanish, and translated into additional languages as necessary. The consent form contains a study description, explanation of the purpose of the research, duration of participation, potential risks and benefits, methods of protecting confidentiality, a clear statement that participants may withdraw at any time, and a statement that the investigators reserve the right to terminate a subject’s involvement at any time. All subjects will be informed if significant new findings develop during the course of the study that may affect whether they are willing to continue participation. The consent form will be explained to each subject individually and privately by research personnel and participants will be given the opportunity to ask questions and discuss concerns prior to issuing consent (APPENDIX B: Sample Informed Consent Form).

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential 4-digit subject number beginning with 0001, 0002, 0003, etc. for identification throughout the study. This subject number must not be reused for any other participant in the
study. Each subject will be provided with an electronic Patient Reported Outcomes (ePRO) Diary on a secure handheld electronic device to ensure stored data is only shared with the research team throughout the study. The device will be returned at the trial’s conclusion for proper de-identification and disposal of subject data. The method of blinding investigators and subjects as well as the collection and storage of health information obtained both in clinic and electronically will comply with all relevant privacy standards and regulations as written in the Health Insurance Portability and Accountability Act (HIPAA). All study personnel will complete HIPAA training.

The study protocol is written in accordance with the most recently updated Guidelines of the International Headache Society (IHS) for controlled trials of acute treatment of migraine attacks in adults: fourth edition. This ensures the protection of subjects as the guidelines were created to allow for a safe, standardized, and evidence-based approach to the conduct of randomized controlled trials within this specific discipline.

3.4 Recruitment

Subjects will be recruited through outpatient offices, online advertising, and word of mouth. At sites involved with the study, healthcare providers will provide a brochure and refer potential participants to contact the research coordinator, who will arrange for a phone screening based on the inclusion and exclusion criteria (see APPENDIX C: Phone Screening Questions). Eligible candidates will be brought in for in-person screening and if they continue to meet the remaining criteria, they will be given the opportunity to enroll in the study and provide written informed consent. Participants will be continuously enrolled until reaching the target sample size, and participants will begin the study as recruitment ensues.
3.5 Timeline and Resources

Based on previous studies involving similar populations with more subjects, the enrollment period is expected to span approximately 12 months to achieve the target sample size including both subjects on a CGRP mAb and control subjects who have never used a CGRP mAb. For each enrolled subject, a Run-in Period of 4 weeks, the Primary Phase of 1 to 8 weeks, and the Secondary Phase of 8 weeks, totals a 13-20 week time commitment. Accounting for enrollment and the length of data collection, study completion will be within 2 years.

Study materials and personnel required to carry out the study include:

- Co-primary investigators, 2 research assistants
- Site coordinator, 1 research assistant, and 1 LPN or RN (for each site)
- Research pharmacy responsible for balancing demographics variables during recruitment, use of randomization software, and blinded allocation of intervention in blister packs
- Informational brochure for recruitment (see APPENDIX D: Recruitment Brochure)
- Electronic Patient Reported Outcomes ePRO Diary, a secure hand held electronic device for each subject with instructions for use (or alternative paper version of reported outcomes diary)
- Laboratory kits and laboratory manual
  - Safety laboratory, plasma, serum, instructions for all specimens collected will be provided by a designated central laboratory.
- ECG Machine, electronic blood pressure monitor, thermometer, scale
  - Equipment, supplies, instructions, and training materials will be supplied by a centralized medical supplies vendor.
3.6 Study Protocol and Intervention

Run-in Period

Subjects who have been screened and consented will enter a Run-in Period for 4 weeks during which migraine frequency will be monitored with a requirement of 2-8 migraine attacks during the period in order to continue on in the study. They will also have baseline safety measurements assessed: Physical examination, vital signs/physical measurements, clinical safety laboratory testing, ECG, assessment of migraine history (signs and symptoms), and pregnancy test (See APPENDIX F: Safety Assessments). To document each migraine attack during the Run-in Period, the participant will use a provided electronic Patient Reported Outcomes (ePRO) Diary via secure handheld electronic device with time stamping capability which will prompt documentation of pain, symptoms, and adverse events in the same way it will during the study. Subjects may use their personal standard of care abortive treatments for each attack. This will allow the participants to adjust to using the ePRO Diary and assess procedural compliance. Non-compliant subjects and those who do not meet the required number of migraine attacks will be excluded from further participation in the study. Those who will go on to randomization and allocation will be administered a baseline Migraine-Specific Quality of Life Questionnaire (MSQ)
(MSQ). The MSQ is a self-administered, migraine-specific, 14-item instrument assessment of quality of life that was developed to assess the effect of migraine on daily functioning (see APPENDIX E: Migraine Specific Quality of Life Questionnaire (MSQ)).

**Intervention**

The intervention is single dose (75 mg) oral disintegrating rimegepant (Nurtec-ODT [Biohaven Pharmaceuticals, New Haven, CT] for abortive treatment of migraine attacks of moderate or severe intensity. The placebo is an oral disintegrating tablet identical in appearance, taste, and dissolution quality as the rimegepant tablet. Subjects will be educated on how to properly allow the tablet to dissolve orally and no more than one tablet may be administered every 24 hours.

**Randomization and Assignment of Intervention**

For the Primary Phase of the study, subjects in both the mAb group and the control group will be randomly assigned by a computer program in a 1:1 ratio to rimegepant or placebo for treatment of a single migraine attack of moderate or severe pain intensity. Both investigators and participants will be blinded as to their assignments. A blister pack containing a single tablet (rimegepant or placebo) will be provided to each subject by the research pharmacy. This phase extends for a maximum of 8 weeks, and those who do not have a migraine attack during that period will be excluded from further participation in the study. Those who treat their single attack prior to the 8 week mark may advance to the Secondary Phase.

For the Secondary Phase of the study, beginning after the subject treats their first attack, all subjects in both groups will receive rimegepant to treat multiple migraine attacks of moderate or severe pain intensity over an 8 week period. A blister pack containing twelve 75 mg rimegepant tablets will be provided initially. Some subjects may have more frequent attacks than
others and require more medication, so they will be instructed to notify the research pharmacy when they have four tablets remaining and an additional allotment of four tablets can be shipped to them, with a maximal allotment of 16 tablets total for the 8 week period (accounting for a maximum of 8 migraine attacks per month).

Table 1. Study Protocol Timeline

<table>
<thead>
<tr>
<th>Group</th>
<th>Run-in Period 4 weeks</th>
<th>Primary Phase (Blinded) 1 migraine attack</th>
<th>Secondary Phase (Open Label) 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Rimegepant</td>
<td>Rimegepant</td>
<td>Rimegepant</td>
</tr>
<tr>
<td>Monoclonal Antibody</td>
<td>Rimegepant</td>
<td>Rimegepant</td>
<td>Rimegepant</td>
</tr>
</tbody>
</table>

3.7 Data Collection

At the time of a migraine attack, subjects will begin documentation in their ePRO Diary. The first question will be to rate their pain on a numerical rating scale from 0-3, where 0 is no pain, 1 is mild pain, 2 is moderate pain, and 3 is severe pain. If a subject rates their pain a 2 or 3 (moderate or severe) one will be asked additional questions via the ePRO Diary regarding specific symptoms (see Table 2) before being prompted to self-administer the allocated tablet to treat the attack. If a subject rates their pain a 1 (mild), one will be asked to refrain from self-administering the allocated treatment and only if the pain increases to a 2 or 3 will the patient restart the documentation process in the ePRO Diary and proceed with treatment. If a subject takes their own medication (i.e. ibuprofen, acetaminophen etc.) at the time where pain was a level 1 and has now increased to a 2 or 3, they are not to administer the allocated treatment and this migraine attack cannot be included in the study.

Once the subject has self-administered the allocated treatment, the ePRO Diary will prompt to reevaluate symptoms and pain at 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours,
4 hours, 8 hours, 12 hours, 24 hours (see Table 2). There will be an option to report adverse events at any time during the study (and within 30 days of discontinuation of the trial). This will include documentation of event severity (mild, moderate, severe), time of onset (ePRO Diary will automatically timestamp entry), and time of resolution. In addition, subjects will be instructed to directly contact study personnel for any adverse event with potentially serious implications (e.g., chest pain, uncontrolled vomiting) within 24 hours. Subjects will be provided a 24/7 contact telephone number to call for such events. All adverse events deemed to be serious, as determined by the study investigator, will be followed to resolution or stabilization. All serious adverse events (SAEs) will be reported to the IRB within 72 hours (see APPENDIX F: Safety Assessments).

To maintain ethical standards, subjects who do not experience freedom from pain 2 hours after administering the allocated treatment during either phase of the trial will be allowed to use an approved rescue medication. Permissible rescue medications are aspirin, ibuprofen, naproxen, other nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (up to 1000 mg/day), antiemetics (e.g. metoclopramide or promethazine), triptans, or baclofen. Other rescue medications may be deemed acceptable by the co-primary investigators on a case by case basis at the start of the trial. If a subject experiences unbearable pain prior to 2 hours and uses a rescue medication, this will be considered a treatment failure. If needed, after 48 hours of administering the study medication, patients may take their standard of care abortive medication(s) (including triptans if not contraindicated). Use of a rescue medication must be documented in the ePRO Diary at the time of administration.

After a subject has treated their first migraine attack with the allocated intervention (rimegepant or placebo), one will return to clinic for safety assessment evaluation within the
week of treatment (see APPENDIX F: Safety Assessments). If safety is assured, subjects will move on to the Secondary Phase and be given their blister pack of twelve 75 mg rimegepant tablets. Once again, subjects are only to treat migraine attacks of moderate or severe pain with one tablet and will document in their ePRO Diary as they did during the first attack with each subsequent attack. For the purposes of this study, 48 hours of freedom from moderate (2) or severe (3) pain between migraine attacks treated with rimegepant or a rescue medication is required.

Throughout the Secondary Phase, a period of 8 weeks total, subjects will be monitored for adverse events continuously via the ePRO Diary and as described above, all adverse events that might potentially be serious must be reported directly to study personnel. Subjects will return to clinic for safety endpoint measurements at 2 weeks, 4 weeks, and 8 weeks. A Migraine-Specific Quality of Life Questionnaire (MSQ) will be administered electronically at 4 weeks and 8 weeks (see Table 3). Adherence to ePRO Diary reporting and questionnaire response will be monitored throughout the study and additional reminders will be delivered electronically to those subjects who are consistently failing to report data.

Table 2. ePRO Diary Prompts and Time Points

<table>
<thead>
<tr>
<th>eDiary Prompts</th>
<th>Before intervention</th>
<th>30 minutes</th>
<th>60 minutes</th>
<th>90 minutes</th>
<th>2 hours</th>
<th>3 hours</th>
<th>4 hours</th>
<th>8 hours</th>
<th>12 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain rating (0-3)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Identify most bothersome symptom</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonophobia (0-3)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia (0-3)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (0-3)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Outcome Tracking

<table>
<thead>
<tr>
<th>Outcome Tracking</th>
<th>Run-in Period 4 weeks</th>
<th>Primary Phase (Blinded) 1 migraine attack</th>
<th>Secondary Phase (Open Label) 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ePRO Diary</td>
<td>w/ attacks</td>
<td>w/ attack</td>
<td>w/ attacks</td>
</tr>
<tr>
<td>MSQ</td>
<td>End of week 4</td>
<td></td>
<td>End of weeks 4 and 8</td>
</tr>
<tr>
<td>Safety Endpoints</td>
<td>Screening (Day -1)</td>
<td>After attack</td>
<td>End of weeks 2, 4, and 8 (formally); potentially serious adverse events reported any time</td>
</tr>
</tbody>
</table>
3.8 Outcome Measures

The primary outcome is freedom from pain at 2 hours after the intervention dose. Freedom from pain will be defined by the presence of no pain (0) in a person who had pain of moderate (2) or severe (3) intensity immediately prior to administration of the dose. Incidence proportions will be analyzed with a chi-square. A secondary outcome will be time to freedom from pain, defined in the same way, and analyzed with a Kaplan-Meier test. Operationalization and statistical analysis of all primary and secondary outcomes are shown in Table 4.

Several additional secondary outcomes will be measured for all subjects. One secondary outcome is freedom from most bothersome symptom (MBS) at 2 hours with the MBS having been identified just prior to administration of the dose. Another set of secondary outcomes include pain relief at 2 hours and time to pain relief where pain relief is defined as mild (1) or no pain (0) in a subject who had pain of moderate (2) or severe (3) intensity just prior to administration of the dose. In addition, total migraine freedom at 2 hours which is defined as having no pain, nausea, photophobia, and phonophobia at the 2 hour time point will be measured in all subjects regardless of their initial endorsement of each individual symptom. Use of a rescue medication after 2 hours and use of a rescue medication before 2 hours (treatment failure) are also secondary outcomes. Also, MSQ scores will be compared and used as a secondary outcome.

The following secondary outcomes will be measured conditionally, depending on the responses of the subject in their ePRO Diary. Specific migraine symptoms will be assessed with freedom from phonophobia at 2 hours, freedom from photophobia at 2 hours, and freedom from nausea at 2 hours. These will be measured in those who marked the symptom as moderate (2) or severe (3) prior to dose administration and after 2 hours mark the symptom as absent (0). Sustained pain freedom will also be measured in those who had pain freedom at 2 hours, and
defined as remaining pain free from 2 to 24 hours after administering treatment without use of a rescue medication.

*Table 4. Operationalization and Planned Statistical Analysis of Primary and Secondary Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Operationalization</th>
<th>Type of Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from pain at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Time to freedom from pain</td>
<td>Continuous</td>
<td>Kaplan Meier</td>
</tr>
<tr>
<td>Freedom from MBS at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Pain relief at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Time to pain relief</td>
<td>Continuous</td>
<td>Kaplan Meier</td>
</tr>
<tr>
<td>Freedom from phonophobia at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Freedom from photophobia at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Freedom from nausea at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Total migraine freedom at 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Use of rescue medication after 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>Use of rescue medication before 2 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>(treatment failure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained pain freedom from 2-24 hours</td>
<td>Dichotomous</td>
<td>Chi-square</td>
</tr>
<tr>
<td>MSQ Scores</td>
<td>Continuous</td>
<td>Between group minimally</td>
</tr>
<tr>
<td></td>
<td></td>
<td>important differences</td>
</tr>
</tbody>
</table>

**3.9 Sample Size Calculation**

One RCT found that the incidence proportion of freedom from pain at 2 hours was 10.9% of those who had taken placebo and 21.2% in those who had taken 75 mg of rimegepant. The effect size (absolute difference of effect) is 10.3%. With a 2-sided significance level of 0.05 (α), and 80% power, a minimum sample size of 420 participants was calculated. This yields a sample of 210 in the mAb group and 210 in the control group. The projected minimum sample size will further consider the anticipation of drop out and discontinuation during the study. The previously mentioned trial had a dropout and discontinuation rate of 7.1%. To account for anticipated loss during the study period, a sample size of 450 subjects will be sought: 225 subjects in the mAb group and 225 subjects in the control group. (See APPENDIX G: Sample Size Calculation)
3.10 Analysis

Variables to describe the population at baseline will be balanced between the mAb group and the control group. This will include age, sex, race, ethnicity, and BMI. This will also include migraine type in terms of with aura or without aura. Dichotomous variables will be represented with counts and percentages. Continuous variables will be summarized with univariate statistics (e.g., n, mean, standard error, median, minimum and maximum).

Several populations will be analyzed. Enrolled subjects include those who sign an informed consent form and are assigned a subject identification number. Randomized subjects are enrolled subjects who receive a randomization treatment assignment during the Primary Phase (rimegepant or placebo). Treated subjects are enrolled subjects who receive study therapy (rimegepant or placebo). Modified Intent to Treat (mITT) subjects are randomized subjects that take any amount of study therapy and provide at least one efficacy measurement.

Analysis will be performed with a modified intention-to-treat method. Results will be statistically significant if $p \leq 0.05$. The primary outcome is freedom from pain at 2 hours, analyzed via chi-square statistical test between mAb and control groups. Secondary outcomes, both dichotomous and continuous variables, and their appropriate statistical tests for analysis are listed in Table 4.

Exploratory analysis will be performed within subjects who were randomized to receive placebo during the Primary Phase and then subsequently administered rimegepant in the Secondary Phase. A McNemar’s test will be used to compare outcomes within the same subject. The same test will be used to analyze each subject’s consistency of response to rimegepant over the course of the Secondary Phase. Lastly, a stratified analysis will compare the response to rimegepant seen in positive versus less positive responders to preventive mAbs.
REFERENCES


CHAPTER 4: CONCLUSION

4.1 Advantages and Disadvantages

The primary advantage of the proposed study is well defined in the statement of the problem as it fills the gap in the investigation of concomitant use of rimegepant with a CGRP mAb through a randomized controlled trial. The proposed methods are valid as they were written in accordance with International Headache Society (IHS) guidelines and mirror previous rimegepant vs placebo RCTs, however improvements have also been made in the proposed study design. With its unique biphasic design, this trial is able to maintain a phase with blinding and randomization to investigate a single migraine attack while also meeting ethical guidelines in a separate phase allowing the investigation of rimegepant’s effects in the acute treatment of several migraine attacks over time. Furthermore, the addition of the Migraine-Specific Quality of Life Questionnaire (MSQ) provides a more comprehensive measurement of the medication’s impact on patients’ overall migraine management. The study is powered appropriately and the sample size is sufficient in comparison to previous rimegepant vs placebo RCTs. Compared to the case series for concomitant rimegepant and CGRP mAb, the sample size is significantly larger. Lastly, a strength of this study is its generalizability. Although the selection criteria are necessarily strict because rimegepant is still a fairly new medication, the recruitment of subjects such that the sample emulates the study population at large is highly prioritized. The generalizability is also improved by the multi-attack phase of the study, where consistency of response to rimegepant may be analyzed. This may also be helpful in its application to studies of other members of the gepant class for treatment of acute migraine attacks in the future.

A potential disadvantage of this study is the confounding variables it poses which are difficult to control for. These include patient specific migraine triggers and environmental changes, which are present in any migraine treatment study, and therefore expected to arise in this trial.
However, an emphasis to patients about maintaining their routines is all that can be realistically achieved to address this variable. Second, variability in the types of preventives the control subjects are taking poses a potential confounding variable, however in order to maintain the external validity of the study it is necessary to include subjects on preventives for their migraines. Lastly, the proposed study does not include an active comparator, with rimegepant being compared to placebo. It might be argued that the inclusion of an active comparator (e.g. a triptan) would strengthen the clinical implications of the study results, however it is beyond the scope of this trial which is primarily focused on comparing the effects and safety of the drug in those taking vs not taking a CGRP mAb. Depending on results from this study, the inclusion of an active comparator in similar future studies might be warranted.

4.2 Clinical and Public Health Significance

The findings from this study have the potential to impact patients and their providers as well as lead to public health benefits. Both preventive and abortive treatment of migraine are addressed in this trial, which are the two pillars of migraine management. The main objective is to determine the efficacy of rimegepant with outcome measures focused on pain and symptom freedom in the acute setting, however it is the incorporation of the medication in long-term migraine management that expands the impacts of this study. Patients’ quality of life is implicated since an improved migraine treatment regimen leads to less time in pain, fewer disability work days, and less time spent being treated in a healthcare setting. This also has impacts on the healthcare system at large, as the total estimated cost of migraine headache amounts to $78 billion per year in the US.\(^1\) The estimated mean cost for migraine-related care per outpatient visit was $139.88, per Emergency Room (ER) visit was $775.09, and per inpatient hospitalization was $7,317.07.\(^2\) It is cost saving to both the patient and to the health system when
there are fewer visits to the ER and fewer hospitalizations related to migraine care. The proposed study’s results may expand evidence based management options which would help patients treat their migraine attacks at home, decreasing the need for emergency visits and inpatient stays.

Given the increasing use of mAbs for preventive therapy, understanding the efficacy and safety of rimegepant in patients taking such preventives is an important consideration. This study will provide data helping to elucidate where rimegepant best fits in migraine management and for which subset of patients a benefit is likely to be achieved. With the potential to improve the lives of patients, providers will be able to refer to data from a randomized controlled trial before prescribing their patients concomitant rimegepant and CGRP mAb to understand the likely benefits, and risks, associated with their use.
REFERENCES

APPENDIX A: Study Population Approximation

Calculations approximating study population using paid claims data from Medicaid and Medicare Part D spending reports:

**Aimovig (erenumab-aooe)**

<table>
<thead>
<tr>
<th></th>
<th>Medicaid</th>
<th>Medicare Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total spending in 2019:</td>
<td>$48,010,499</td>
<td>$119,459,268</td>
</tr>
<tr>
<td>Average spending per dosage unit:</td>
<td>$559.84</td>
<td>$591.54</td>
</tr>
<tr>
<td>Doses per person, in one year:</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
| Total 
spending in 2019 divided by average 
spending per dosage unit: | $559.84                                      | $91.54                                 |
| Doses per person, in one year:     | 85,758 divided by 12: | $7,146 patients                      |
|                                           | 201,946 divided by 12: | $16,828 patients                     |

**Emgality (galcanezumab-Gnlm)**

<table>
<thead>
<tr>
<th></th>
<th>Medicaid</th>
<th>Medicare Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total spending in 2019:</td>
<td>$23,788,338</td>
<td>$40,700,935</td>
</tr>
<tr>
<td>Average spending per dosage unit:</td>
<td>$554.80</td>
<td>$588.61</td>
</tr>
<tr>
<td>Doses per person, in one year:</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
| Total 
spending in 2019 divided by average 
spending per dosage unit: | $554.80                                      | $588.61                              |
| Doses per person, in one year:     | 42,877 divided by 12: | $3,573 patients                      |
|                                           | 69,147 divided by 12: | $5,762 patients                     |

**Ajovy (fremanezumab-Vfrm)**

<table>
<thead>
<tr>
<th></th>
<th>Medicaid</th>
<th>Medicare Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total spending in 2019:</td>
<td>$12,806,446</td>
<td>$28,888,525</td>
</tr>
<tr>
<td>Average spending per dosage unit:</td>
<td>$373.95</td>
<td>$393.51</td>
</tr>
<tr>
<td>Doses per person, in one year:</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
| Total 
spending in 2019 divided by average 
spending per dosage unit: | $373.95                                      | $393.51                              |
| Doses per person, in one year:     | 34,246 divided by 12: | $2,853 patients                      |
|                                           | 73,412 divided by 12: | $6,117 patients                     |

**Total number of patients covered by Medicaid or Medicare Part D in 2019 for a year supply of CGRP mAb migraine preventive**

\[
7,146 + 16,828 + 3,573 + 5,762 + 2,853 + 6,117 = 42,279 patients
\]
APPENDIX B: Sample Informed Consent Form

COMPOUND AUTHORIZATION AND CONSENT FORM FOR PARTICIPATION IN A RESEARCH STUDY
YALE UNIVERSITY
YALE UNIVERSITY SCHOOL OF MEDICINE, PHYSICIAN ASSOCIATE PROGRAM

Study Title: EFFICACY OF RIMEGEPANT PLUS CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODY FOR MIGRAINE

Principal Investigator(s): [Names here]

Introduction

You are being asked to join a research study. The following information will explain the purpose of the study, what you will be asked to do, and the potential risks and benefits. You should ask questions before deciding whether you wish to participate, or at any time during the course of the study.

Purpose

The purpose of this research study is to investigate the effectiveness of rimegepant (a medication indicated for treating acute migraine attacks) in the setting of use of a calcitonin gene-related peptide (CGRP) monoclonal antibody (erenumab, galcanezumab, fremanezumab, or eptinezumab; indicated for the prevention of migraine attacks).

Procedures

This study involves 6 in-person visits over a 13-20 week time period. The first visit will include Safety Assessments: a physical examination, vital sign/physical measurements, blood draws, an electrocardiogram (ECG), pregnancy test (if applicable), and questions about your migraine history of signs and symptoms. Then a Run-in Period (4 weeks) will begin during which you will use an electronic Patient Reported Outcomes (ePRO) Diary which will prompt you to document pain, symptoms, and adverse events at the time of a migraine attack (detailed explanation below). You may use your personal standard of care abortive treatments for each migraine attack during this period. Subjects who are unable to document appropriately may be excluded from further participation in the study.

Preparation and Primary Phase

The second visit you will be asked to complete a Migraine-Specific Quality of Life Questionnaire (MSQ), a 14 item assessment that was developed to assess the effect of migraine on daily functioning. You will be randomly assigned to receive either a single dose (75 mg) of oral disintegrating rimegepant (Nurtec-ODT) or an identical placebo in a blister pack to be used to treat a single migraine attack of moderate or severe pain intensity. You and the researchers will not know which treatment you are assigned. This first phase of the study extends for a maximum of 8 weeks. Those who do not have a migraine attack during that period will be
dismissed from further participation in the study. Those who treat their single attack prior to the 8 week mark may advance to the Secondary Phase.

**Secondary Phase**
The third visit, after your first treated migraine attack, you will return for Safety Assessments. In the Secondary Phase of the study, you will receive rimegepant to treat multiple migraine attacks of moderate or severe pain intensity over an 8 week period. A blister pack containing twelve 75 mg rimegepant tablets will be provided initially. Some subjects may have more frequent attacks than others and require more medication, so you will be instructed to notify the research pharmacy for more tablets if needed. You will have in-person visits at the end of weeks 2, 4, and 8 during which Safety Assessments will be repeated and the MSQ will be administered at the 4 and 8 week visits.

**ePRO Headache Diary**
At the time of a migraine attack, you will begin documentation in your ePRO Diary. The first question will be to rate your pain on a rating scale from 0-3, where 0 is no pain, 1 is mild pain, 2 is moderate pain, and 3 is severe pain. If you rate your pain a 2 or 3 (moderate or severe) you will be asked additional questions via the ePRO Diary regarding specific symptoms (most bothersome symptom, nausea, light sensitivity, and sound sensitivity) before being prompted to take your pill (rimegepant or placebo) to treat the attack. After you take the pill, the ePRO Diary will prompt you to reevaluate your symptoms and pain at 30 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 8 hours, 12 hours, 24 hours. There will be an option to report side effects or other adverse events at any time during the study (and in the 30 days after you complete the study) and you will be encouraged to document them at the times they start and end (ePRO Diary will automatically timestamp the entries).

Subjects who do not experience freedom from pain at 2 hours after taking the treatment or have unbearable pain prior to 2 hours will be allowed to use an approved rescue medication. This must be documented in the ePRO Diary at the time you take it.

**Potential Risks**
There are some risks associated with participation in this study. These risks include (1) rimegepant, (2) phlebotomy, and (3) confidentiality.

(1) Rimegepant

Although uncommon, documented adverse reactions to rimegepant include nausea (2-3%), abdominal pain (< 2%), dyspepsia (< 2%), and <1% risk of skin rash, hypersensitivity reaction, or dyspnea.¹

*Minimizing risk:* Patients with serious medical conditions are not permitted to take part in the study.

(2) Phlebotomy
Possible risks associated with blood draws (as part of Safety Assessments) include pain, bleeding, fainting, bruising, infection, and/or hematoma at the injection site.

**Minimizing Risk:** Only trained professional phlebotomists and nursing staff will perform blood draws.

(3) Confidentiality

Taking part in any research study places you at risk for loss of confidentiality. Several procedures are in place to reduce this risk (see below).

1Nurtec ODT (rimegepant) [prescribing information]. New Haven, CT: Biohaven Pharmaceuticals Inc.; May 2021.

**Potential Benefits**

This research may benefit you directly in the treatment of your acute migraine attacks. Even if you do not directly benefit from taking part in the study (e.g., if you get placebo or rimegepant is not effective for you), the results will serve to improve our understanding of the effectiveness of rimegepant in migraine patients.

**Privacy/ Confidentiality**

To protect your confidentiality, your name and other identifying information will not be recorded on any study documents. At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, you will be assigned a unique 4-digit subject number for identification throughout the study. The method of blinding investigators and subjects as well as the collection and storage of health information obtained both in clinic and electronically will comply with all relevant privacy standards and regulations as written in the Health Insurance Portability and Accountability Act (HIPAA). We will only collect information that is needed for research. Only the researchers involved this study and those responsible for research oversight will have access to the information you provide. Examples of information that we are legally required to disclose include certain reportable diseases and Serious Adverse Events.

**Research Authorization:** Except as permitted by law, your health information will not be released in an identifiable form outside of the Yale University research team. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Note, however, that your records may be reviewed by those responsible for the proper conduct of research such as the Yale University Human Research Protection Program, Yale University Human Subjects Committee. The information about your health that will be collected in this study includes: age, gender, weight, height, race, admission diagnosis, medical comorbidities, length of hospital stay, infectious disease history, antibiotic use history and presence of indwelling devices. Information may be re-disclosed if the recipients are not required by law to protect the privacy of the information. At the conclusion of this study, any identifying information related to your research participation will be destroyed. By agreeing
to participate in this study, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes. This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Regardless of the choice you make, you will not lose access to your medical care or give up any legal rights or benefits. The researcher also has the right to discontinue your participation in the study at any time. Take as much time as you need before you make your decision. Ask the research staff any questions or to clarify items you do not understand. Once you have an understanding, you will be asked if you wish to participate, and if so, you will have to sign this form.

Questions

You have read the above description of the research study. You have read the risks and benefits involved, at this point please ask any further questions you have.

If you have any further questions later or if you have a research-related problem, you may contact the Principal Investigator(s) at 203-xxx-xxxx.

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Board at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to participate in this study. You will be provided with a copy of this form.

___________________________  ________________________________  ______
Participant Printed Name         Participant Signature          Date

___________________________  ________________________________  ______
Person Obtaining Consent Printed Name  Person Obtaining Consent Signature  Date
Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only. If the interpreter is affiliated with the study team, the signature of an impartial witness is also required.

Print name of interpreter: __________________________
Signature of interpreter: __________________________ Date: ______

An oral translation of this document was administered to the participant in __________________ (language) by an individual proficient in English and __________________ (language).

Print name of impartial witness: __________________________
Signature of impartial witness: __________________________ Date: ______
APPENDIX C: Phone Screening Questions

“We would like to ask you some general information to determine whether you might qualify for this study. This information will only be used to determine your eligibility to participate in research. This information will be stored in secure research files. If you do not want any information about you stored, we will terminate this interview now. If you agree to proceed ahead with this preliminary interview and seem to be eligible to participate in this study, we may invite you for a face to face meeting. Would you like to continue?”

YES/NO

1. Verification of patient identifiers (name, date of birth)
2. How old were you diagnosed with migraine?
3. How many migraine attacks do you have per month? How many migraine attacks have you had per month for the last 3 months?
4. Do you currently take or have you ever taken any of the following medications: erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), or eptinezumab (Vyepti)?
   a. If answer is yes:
      i. How long have you been taking the medication?
      ii. Has your dose changed in the past 3 months?
      iii. Do you use any other migraine preventives? How many?
      iv. What other medications or treatments do you take?
   b. If answer is no:
      i. Do you use any migraine preventives? How many?
      ii. What other medications or treatments do you take?
5. Do you currently take a gepant (i.e. rimegepant, ubrogepant) to treat migraine attacks?
6. Have you ever participated in an investigational study of a gepant?
7. Have you participated in any other clinical investigation using an experimental drug or other therapy in the past 30 days?
8. Women of childbearing potential
   a. Are you currently pregnant or breastfeeding?
   b. Are you planning to become pregnant in the next 6 months?
9. May we have your verbal consent to access your medical records in order to further assess your eligibility for participation in this study?

In addition to the phone screening questions above, the potential subjects’ medical records will be reviewed to determine eligibility based on inclusion/exclusion criteria. If met, they will be brought in for an in-person Screening Visit to determine if enrollment in the study will be offered to them.
DO YOU HAVE MIGRAINES?

Do you take erenumab, galcanezumab, fremanezumab, or eptinezumab for migraine prevention?

OR

Have you NEVER taken erenumab, galcanezumab, fremanezumab, or eptinezumab?

Volunteers Needed for Participation in a Research Study
(read on for additional information)

**Study Purpose:** To investigate the effectiveness of rimegepant (a medication for treating migraine attacks) with use of a CGRP monoclonal antibody (erenumab, galcanezumab, fremanezumab, or eptinezumab; for the prevention of migraine attacks).

**Who can participate?**

Adults (age 18-65 years) with at least 1 year history of migraine and treated for at least 3 months with injectable anti-CGRP or anti-CGRP mAb: erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), or eptinezumab (Vyepti)

OR

Adults (age 18-65 years) with at least a 1 year history of migraine who have never taken a CGRP mAb for migraine prevention.

**What will be asked of me?**

- You will be asked to take rimegepant (or placebo) to treat acute migraine attacks
- Document your migraine symptoms in an electronic diary (or paper equivalent)
- 6 in-person visits over a 13-20 week time period
- Receive Safety Assessments: a physical examination, vital sign/physical measurements, blood draws, an ECG, pregnancy test (if applicable), and answer questions about your migraine history of signs and symptoms.

If you are interested in participating or have any questions, please do not hesitate to contact us at:
203-xxx-xxxx or xxxxxx@yale.edu
APPENDIX E: Migraine Specific Quality of Life Questionnaire (MSQ)

PATIENT INSTRUCTIONS:
Please fill out this questionnaire. It will help us understand the effects of migraine headache on your daily activities. The questionnaire has been designed so that it can be completed quickly and easily. Please check only one answer for each question. You should answer every question. Thank you for your time.

While answering the following questions, please think about all migraine attacks you may have had in the past 4 weeks

PLEASE SELECT ONLY ONE RESPONSE TO THESE QUESTIONS:

1. In the past 4 weeks, how often have migraines interfered with how well you dealt with family, friends and others who are close to you?
   (Select one response)
   - None of the time
   - A little bit of the time
   - Some of the time
   - A good bit of the time
   - Most of the time
   - All of the time

2. In the past 4 weeks, how often have migraines interfered with your leisure time activities, such as reading or exercising?
   (Select one response)
   - None of the time
   - A little bit of the time
   - Some of the time
   - A good bit of the time
   - Most of the time
   - All of the time

3. In the past 4 weeks, how often have you had difficulty in performing work or daily activities because of migraine symptoms?
   (Select one response)
   - None of the time
   - A little bit of the time
   - Some of the time
   - A good bit of the time
   - Most of the time
   - All of the time

4. In the past 4 weeks, how often did migraines keep you from getting as much done at work or at home?
   (Select one response)
   - None of the time
   - A little bit of the time
   - Some of the time
   - A good bit of the time
   - Most of the time
   - All of the time
5 In the **past 4 weeks**, how often did migraines **limit** your ability to concentrate on work or daily activities?

*(Select one response)*

- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

6 In the **past 4 weeks**, how often have migraines **left you too tired** to do work or daily activities?

*(Select one response)*

- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

7 In the **past 4 weeks**, how often have migraines **limited** the number of days you have felt energetic?

*(Select one response)*

- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

8 In the **past 4 weeks**, how often have you had to **cancel** work or daily activities because you had a migraine?

*(Select one response)*

- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

9 In the **past 4 weeks**, how often did you **need help** in handling routine tasks, such as everyday household chores, doing necessary business, shopping, or caring for others, when you had a migraine?

*(Select one response)*

- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

10 In the **past 4 weeks**, how often did you have to **stop** work or daily activities to deal with migraine symptoms?

*(Select one response)*

- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time
11. In the past 4 weeks, how often were you not able to go to social activities such as parties or dinner with friends because you had a migraine?

(Select one response)
- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

12. In the past 4 weeks, how often have you felt fed up or frustrated because of your migraines?

(Select one response)
- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

13. In the past 4 weeks, how often have you felt like you were a burden on others because of your migraines?

(Select one response)
- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

14. In the past 4 weeks, how often have you been afraid of letting others down because of your migraines?

(Select one response)
- None of the time
- A little bit of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time
APPENDIX F: Safety Assessments

Safety Assessments will be performed at the Screening Visit (Day -1), prior to the Run-in Period, after the first treated migraine attack in the Primary Phase, and at the end of weeks 2, 4, and 8 during the Secondary Phase.

1) Physical Examination
2) Vital Signs/Physical Measurements
   a. Height will only be captured at the Screening Visit.
   b. Weight (BMI), body temperature, respiratory rate, blood pressure, orthostatic change in blood pressure and heart rate will be collected at all indicated time points.
3) Clinical Safety Laboratory Testing
   a. Hematology
   b. Blood chemistry/electrolytes
   c. Lipid panel
   d. LFTs, bilirubin
   e. eGFR
   f. Urinalysis
   g. Urine drug screen
4) Electrocardiogram (ECG)
5) Assessment of Migraine History (Signs and symptoms)
6) Pregnancy Test
   a. A serum pregnancy test will be completed at the Screening Visit and at the conclusion of the Run-in Period (if appropriate).
   b. Confirmatory urine pregnancy test for Women of Child Bearing Potential (WOCBP) should be completed during remainder of indicated time points.
7) Adverse Event (AE) and Serious Adverse Event (SAE) Assessment
   a. Definitions
      i. Serious Adverse Event (SAE)- any event that meets any of the following criteria: death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect in the offspring of a subject who received rimegepant, others may be considered an SAE when, based upon medical judgement, jeopardize the subject and may require medical or surgical intervention
      ii. Non-Serious Adverse Event (AE)- any unfavorable and unintended sign (e.g. abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not it is considered related to the investigational product
   b. SAEs are reported from the time of informed consent and non-serious AEs are reported from the time of first dose. All ongoing non-serious AEs and SAEs will be followed until resolution or until investigator deems there will be no further
status change. SAE and AE’s that occur during the treatment period should be reported to the site directly or via ePRO Diary.
c. SAEs, whether related or not related to study drug, and pregnancies must be reported within 24 hours of the site’s knowledge of the event
APPENDIX G: Sample Size Calculation

The sample size was calculated* using the following parameters:

Alpha: 0.05 (tails = 2)
Beta: 0.20
Power of 80%
Effect Size for proportions: 21.2% - 10.9% = 10.3%
Factoring in a 7.1% drop out rate, the final sample size is 450 subjects, 225 in mAb group and 225 in control group.

BIBLIOGRAPHY


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