PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Fremanezumab, Migraine and Sleep**
Principal Investigator	**Rami Burstein, PhD**

B1. PURPOSE OF PROTOCOL

The main goal of this study is to determine whether there is a relationship between fremanezumab's ability to prevent migraine and improved sleep quality in migraine patients (fremanezumab is a FDA-approved humanized anti-CGRP monoclonal antibody for the treatment of migraine).

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Significance:

In 2019, the FDA approved the use of a class of drugs that inhibit CGRP signaling for the prevention of migraine. Surprisingly, although migraine is considered a brain disorder, anti-CGRP-monoclonal antibodies (CGRP-mAb) appear to act mainly outside the central nervous system as they cannot cross the blood brain barrier (BBB). The premise of this proposal is that because the BBB is relatively open in the hypothalamus, fremanezumab (an anti-CGRP-mAb) can attenuate some classical sleep disturbances by modulating the activity/functioning of hypothalamic neurons that regulate the sleep-wake cycle. This premise was based on the widely-accepted notions that poor sleep quality is one of the most common migraine triggers and drugs that improve sleep quality can help reduce migraine frequency. Unraveling a mechanism (neural substrate) of action for this new class of migraine preventive drugs is critical to our ability to learn how to best use it in the clinic.

Background:

Background about neurons that regulate the sleep-wake cycle: Recent advances in understanding neuronal networks that promote wakefulness point to brainstem cholinergic neurons in the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LTD). The input from these areas to relay thalamic nuclei is thought to facilitate thalamocortical transmission (Celesia and Jasper, 1966), and serotoninergic neurons in the dorsal (DR) and median (MN) raphe, noradrenergic neurons in locus coeruleus (LC), dopaminergic neurons in ventral periaqueductal gray (vPAG) (Lu et al., 2006), histaminergic neurons in the tuberomammilary nuclei (TMN) and potentially glutamatergic neurons in the lateral parabrachial nuclei (LPB) whose extensive input to the hypothalamus, basal forebrain and cerebral cortex is thought to facilitate cortical processing of thalamic input (Saper et al., 2005, 2010, Lee and Dan, 2012). These cholinergic and monoaminergic neuronal circuits, which constitute the ascending arousal system, are regulated by wake-promoting lateral hypothalamic neurons that contain orexin (ORX) and cholinergic neurons in the horizontal limb of the diagonal band nucleus (HDB) and by sleep-promoting hypothalamic melanin-concentrating hormone (MCH) neurons and ventrolateral preoptic area (VLPO) neurons containing γ-aminobuteric acid (GABA) and galanin (Saper et al., 2005, 2010, Lee and Dan, 2012). While synthesizing these multiple brain areas into a coordinate network that regulates the transition between sleep and wake states, Saper and colleagues (Saper et al., 2001. 2005) have conceived the idea that the transition between these states is mediated by a flip-flop switch, whereby the wake-promoting neurons converge on and inhibit the sleep-promoting neurons and vice versa.

Background about migraine and sleep: Most patients believe that many of their migraine attacks are triggered by sleeping too little, sleeping too much, have their sleep interrupted too many times during the night, poor sleep quality, not feeling well-rested in the morning hours after the sleep, etc. These common complains gave rise to the notion that sleep disturbances are some of the most common triggers of migraine. Moreover, sleep disturbances may be a risk factor for chronification of migraine, the transformation of migraine from episodic to chronic form. If sleep disturbances can trigger migraine attacks or lead to its chronification, it is tempting to propose that drugs that prevent migraine may have an ability to restore normal sleep or attenuate certain aspects of sleep disturbances and by doing so, prevent the initiation of an attack by preventing or modifying its trigger.

Background on fremanezumab and the hypothalamus: Fremanezumab is an anti-CGRP monoclonal antibody and belongs to a class of drugs that effectively prevents migraine. In principle, the size of CGRP (about 150 kD) does not allow it to cross the blood brain barrier (BBB) and enter the brain. It is therefore believed to achieve its preventative effects by acting outside the brain. An exception to this thinking is the hypothalamus, a brain area where the BBB is relatively open and as a result, large molecules may gain some access to its neurons.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Overview:

This is a within-person study design that examines treatment effects (changes) using high-resolution assessments. To complete the study, each participant will be observed using daily assessments of **migraine** and **sleep** outcomes before treatment (baseline: 0 to 30 days), and at 1, 2, and 3 months after treatment (injection 1: days 31-60, injection 2: days 61-90, injection 3: days 91-120). In essence, this creates an interrupted time-series design where repeated interventions are introduced at fixed intervals.

Methods:

The study involves 5 visits. The first and last visit will take place at the headache clinic, while the middle three will occur at the Clinical Research Center:

In clinic visit 1 (day 0), subjects will learn about the study and if they agree to participate, will be consented and screened for eligibility. Those deemed to be eligible will be asked to fill a headache questionnaire and then taught how to fill, at home, a daily e-diary for sleep and a daily e-diary for headache via REDCap. The electronic headache diaries are being collected to allow us to determine how the treatment affects migraine frequency, intensity, and duration. We will also administer a QST procedure prior to starting subjects on study treatment.

In clinic visit 2 (day 30), subjects will visit the CRC to review their e-diaries and receive the first treatment. The treatment is 225 mg (dissolved in 1.5 ml solution) fremanezumab. Fremanezumab (Ajovy) is a monthly dosed anti-CGRP mAb subcutaneous injection. Prior to being started on the study treatment, subjects of child-bearing potential will undergo pregnancy testing.

In clinic visit 3 (day 60), we will review participants' headache and sleep diaries 1 month after receiving the 1st injection and administer the 2nd injection.

In clinic visit 4 (day 90), we will review participants' headache and sleep diaries 1 month after receiving the 2nd injection and administer the 3rd injection.

In clinic visit 5 (day 120), participants will return to the headache clinic to summarize their experience, review their 120-days e-diaries, and provide any feedback they may have about their experience with fremanezumab. We will also do a follow up QST procedure to complete the end of subjects' study participation.

Quantitative Sensory Testing (QST):
QST will be done in a quiet room away from noise and distraction. Patients will be able to choose their most comfortable position (sitting on a chair or laying in bed) during the sensory testing. In each testing session, pain thresholds to hot and mechanical stimulation will be determined in the skin over the site to where the pain is referred to. This site includes most commonly the periorbital and temporal regions. Heat skin stimuli will be delivered through a 30x30 mm^2 thermode (Q-Sense 2016, Medoc) attached to the skin at a constant pressure and their pain thresholds will be determined by using the *Method of Limit*. The equipment used for quantitative sensory testing has an FDA approval. It imposes no risk or discomfort, and since the patient controls it, stimuli can be stopped at any time.

To determine pain thresholds, the skin will be allowed to adapt to a temperature of 32°C/89.6°F for 5 minutes and then warmed up at a slow rate (1 °C/sec) to a maximum of 50°C/122°F or until pain sensation is perceived, at which moment the subject stops the stimulus by pressing a button on a patient response unit. If the subject does not stop the heat stimulus before it reaches 50°C/122°F, the device will automatically shut off and return the heat stimulus to a temperature of 32°C/89.6°F within a second. This will prevent burns from occurring to the subjects, as a 50°C/122°F should not cause a burn, even if it stays at this temperature for 30 seconds. Heat stimuli will be repeated three times each and the mean of recorded temperatures will be considered threshold. Pain threshold to mechanical stimuli will be determined by using a set of 20 calibrated von Frey hairs (VFH, Stoelting). Each VFH monofilament is assigned a scalar number in an ascending order (1 = *0.0045g*, 2 = *0.023g*, 3 = *0.027g*, 4 = *0.07g*, 5 = *0.16g*, 6 = *0.4g*, 7 = *0.7g*, 8 = *1.2g*, 9 = *1.5g*, 10 = *2.0g*, 11 = *3.6g*, 12 = *5.4g*, 13 = *8.5g*, 14 = *11.7g*, 15 = *15.1g*, 16 = *28.8g*, 17 = *75g*, 18 = *125g*, 19 = *281g*). Because a linear relationship exists between the log force and the ranked number, mechanical pain thresholds are expressed as VFH numbers (#) rather than their forces (g). Each monofilament will be applied to the skin 3 times (for 2 sec) and the smallest VFH number capable of inducing pain at two out of three trials will be considered threshold. Skin sensitivity will also be determined by recording patient's perception of soft skin brushing, which is a dynamic mechanical stimulus, as distinguished from the VFH, which is a static mechanical stimulus.

Primary Outcome Measures:

Fremanezumab and sleep
This primary outcome measures improvement in sleep quality during the treatment period as compared to the pre-treatment period. Sleep quality will be measured using the Insomnia Severity Index. This index scores requires subjects to answer 7 questions by depicting a number (between 0 and 4) that represents best their answer. The scale of the Insomnia Severity Index is 0-28. The total score categories are as follows: 0-7 = No clinically significant insomnia, 8-14 = Subthershold insomnia, 15-21 = Clinical insomnia (moderate severity), 22-28 = Clinical insomnia (severe).

Fremanezumab and migraine

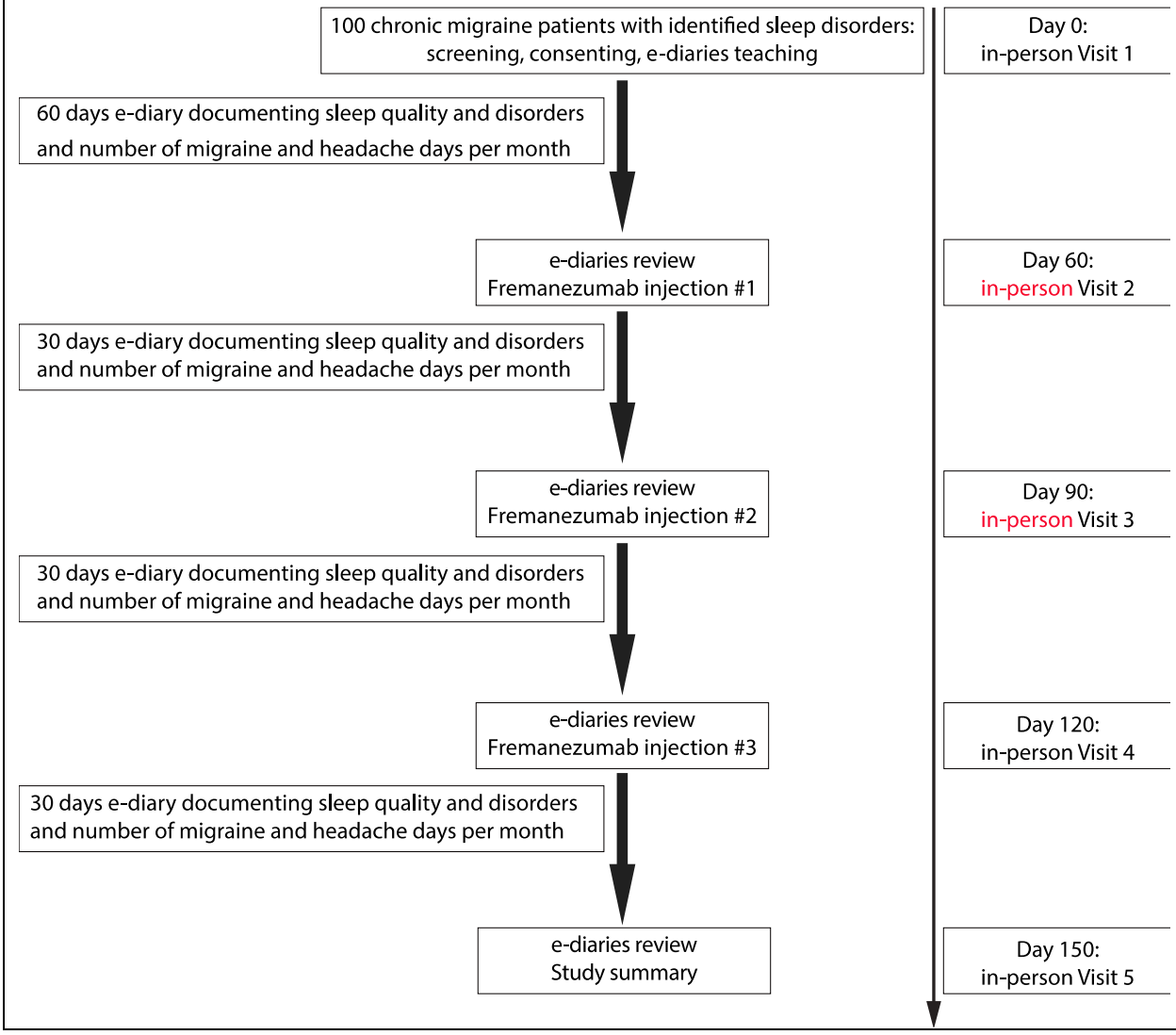
This primary outcome measures changes in number of migraine days per month before and during treatment. The number of migraine days per month will be captured using a validated headache questionnaire and scores as follows: 0-8 migraine days per month = low frequency episodic migraine, 9-14 migraine days per month = high frequency episodic migraine, 15-30 migraine days per month = chronic migraine.

Assessments of headache and sleep:

At screening (visit 1), headache severity and impact will be assessed based on patients' interviews and HIT-6. Sleep quality will be assessed using the Insomnia Severity Index. (https://cbtscience.files.wordpress.com/2014/02/insomniaseverityindex.pdf).

On days 30, 60, 90 and 120, baseline and treatment impact on headache and sleep will be assessed using the Headache e-diary and the consensus sleep diary [Carney et al., (2012) *The consensus sleep diary: Standardizing prospective sleep self-monitoring,* Sleep Vol.35, No.2, pp.287-302], the latter of which captures total sleep time, sleep latency, wake after sleep onset, number of awakenings, quality, sleep efficiency, and trouble staying awake.

Study flow chart



B. Statistical Considerations

Sample Size Justification:

Although precise sample size calculations are difficult given the novelty of the hypotheses and hierarchical structure of the data, a simulation was created using the "SIMR" package in R and R-Studio. Enrolling N = 100 with 4 measurement occasions (baseline, M1, M2, M3) that are created by aggregating the daily measurements from each month provides sufficient power to detect even small associations between changes in sleep and migraine activity. For example, fitting a linear mixed effects model assuming a random intercept, a modest association between intercept and slope (r = -0.50), unit variances for the fixed and random effects (i.e., z-scores), and alpha = 0.05, this sample size will provide 95% power (95%CI: 75.1% to 99.9%) to detect correlations between slopes (i.e., changes in migraine and sleep) as small as r = 0.15. Differences smaller than this magnitude are unlikely to be clinically meaningful.

Data Analysis:

To fulfill the study's purpose, 4 hypothesis are being proposed:

Hypothesis 1 – temporal relationship I: Fremanezumab partially prevents migraine by restoring some aspects of sleep disturbances. If this hypothesis is correct, fremanezumab-induced improvement in sleep disturbances will precede the improvement in headache (i.e., the reduction in migraine days per month).

Hypothesis 2 – temporal relationship II: Fremanezumab-induced improvement in sleep disturbances is secondary to the reduction in migraine days per month. If this hypothesis is correct, fremanezumab-induced reduction in migraine or headache days per month will precede the onset of improvement in sleep quality and quantity.

Hypothesis 3 – principle III: The prevention of migraine leads to improved sleep and reduced sleep disorders. If this hypothesis is correct, only fremanezumab responders will experience improved sleep or sleep disturbances whereas fremanezumab non-responders will not experience improvement of sleep disturbances. If this hypothesis is incorrect, sleep quality or quantity will not improve in fremanezumab responders.

Hypothesis 4 – principle IV: Fremanezumab-Improved sleep disturbances lead to reduced migraine or headache days per month. If this hypothesis is correct, only persons with improved sleep disturbances will experience reduction in number of migraine or headache days per month. If this hypothesis is incorrect, patients with improved sleep disturbances may be migraine treatment responders.

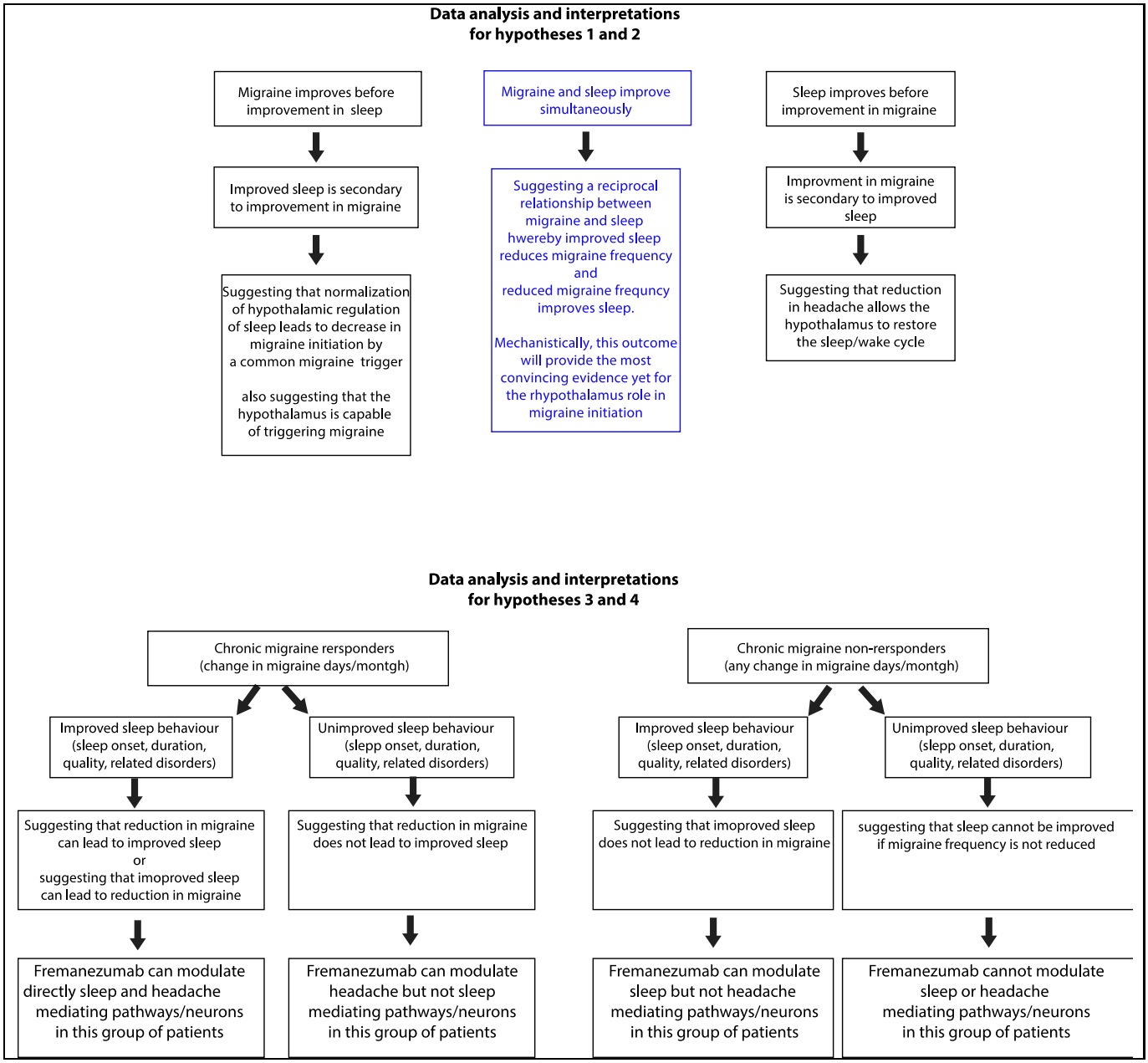
The primary analyses are designed to estimate the elements of the competing hypotheses (i.e., temporal changes in migraine and sleep). To contrast these hypotheses, we will employ multivariate multilevel regression models as summarized by MacCallum et al.[73] and Goldstein.[74] This approach to modeling within-person change does not have the limitations of a change score approach (i.e., unreliability of residualized change scores), or percentage change approaches (i.e., floor effects, heterogeneous variances) where predictors and outcomes are reduced to differences among measurement occasions. A multivariate modeling approach will allow a direct test of all study hypotheses while maintaining a conservative Type-I error rate. Briefly, parsimonious models will be specified for outcomes and lagged (Y_{t-1}) and synchronous (Y_t) representations of each of the proposed mechanisms modeling time with both linear and quadratic change parameters. This model form will

capture the expected substantial early-treatment changes in mechanisms (emerging via reductions in daily headache probability and/or increased sleep quality), or more gradual changes that may occur over the full treatment period. The pre-treatment values and change parameters will be specified as individual-level random effects; this effectively allows a unique trajectory to be specified for each individual and for each outcome. These trajectories will then be aggregated using a series of fixed main effects and interactions that directly correspond to each of our specific hypotheses.

In hypothesis 1, lagged sleep trajectories (t-1, t-2, and t-3) are hypothesized to exhibit statistically significant associations with headache probability such that greater increases in sleep are associated with greater reductions in migraine activity. The opposite is assumed in hypothesis 2 where lagged headache trajectories are hypothesized to exhibit statistically significant associations with sleep such that greater reductions in migraine activity are associated with greater increases in sleep. The best fitting model, using lags of either/both will be estimated using nested models and likelihood ratio tests to evaluate the best fitting hypothesis.

Secondary analyses: In addition to testing primary hypotheses, this study will provide a rich source of data to examine effects on other mechanisms. First, analyses will consider questions of "for whom does treatment work?" We will test whether pre-treatment levels of outcomes lead to differential response to treatments (ie, association between intercepts and slopes), which could provide preliminary evidence that, for instance, individuals with worse sleep respond best to treatment. Second, we will estimate the primary models using additional dichotomizations such as 'responders' for both sleep and migraine activity (> 50% change). For these analyses, treatment phase (baseline, treatment) and responder (no, yes) will be fixed factors with associations between response groups evaluated using frequency counts and odds ratios (95%CI). In a final set of models, we will use three treatment phases (baseline, early treatment, late treatment) to examine the cross-lagged association of responders and non-responders by treatment phase.

Sensitivity to Missing Data: We will strive to reduce the extent of missing data by using daily diaries with low burden. Further, our estimation techniques, based on maximum likelihood, utilize all available data, and as such produce unbiased estimates when the data are missing at random (MAR). The trajectory-based approach should be robust to embedded missing data and the models include many of the factors that might produce an increased drop-out rate (e.g., lack of treatment response). Nevertheless, we will examine estimates in the context of sensitivity analyses utilizing multiple imputation procedures under a variety of assumptions, including a pain drop-out model (ie, lingering pain is associated with increased drop-out) recently implemented by Dr. Houle.



C. Subject Selection

Potential study subjects will be provided an informed consent form (ICF) to review. Those who are interested in participating will provide informed consent and then be screened for eligibility (inclusion/exclusion criteria). Individuals screened as potential study subjects must meet all the following inclusion criteria and none of the following exclusion criteria.

INCLUSION CRITERIA

1. Between the ages of 18 and 65 years
2. Been previously diagnosed with migraine (with or without aura), in accordance with the ICHD-3 criteria
3. Experiences between 8 to 25 headaches days per month (during the last 3 months), with at least 8 of them being migraine days during which the migraines lasted more than 4 hours if untreated
4. Onset of migraine at age 50 years or younger

5. Agrees to refrain from initiating or changing the type, dosage, or frequency of any prophylactic medications for indications other than migraine that may interfere with the study objectives (e.g., antidepressants, anticonvulsants, beta-adrenergic blockers, etc.)
6. Able to provide written informed consent

EXCLUSION CRITERIA

1. Currently on a regimen of 1 or more migraine preventative therapy
2. Other significant pain problem (e.g., cancer pain, fibromyalgia, other head or facial pain disorder) that may confound the study assessments
3. Known or suspected severe cardiac disease (e.g., symptomatic coronary artery disease, prior myocardial infarction, congestive heart failure)
4. Known or suspected cerebrovascular disease (e.g., prior stroke or transient ischemic attack, symptomatic carotid artery disease, prior carotid endarterectomy or other vascular neck surgery)
5. Abnormal baseline electrocardiogram (ECG) within the last year (e.g., second or third-degree heart block, prolonged QT interval, atrial fibrillation, atrial flutter, history of ventricular tachycardia or ventricular fibrillation, clinically significant premature ventricular contraction)
6. Uncontrolled high blood pressure (systolic >160 mm HG, diastolic >100 mm Hg) after 3 measurements within 24 hours
7. Known history or suspicion of secondary headache
8. Known history or suspicion of substance abuse or addiction (within the last 5 years)
9. Preventative use of marijuana (including medical marijuana) or cannabidiol oil within the last 1 year
10. Currently takes simple analgesics or NSAIDs >15 days per month or triptans, ergots, or combined analgesics >10 days per month for headaches or other body pain
11. Currently takes prescription opioids for headaches or body pain
12. Undergone nerve block (occipital or other) in the head or neck within the last 3 months
13. Received botulinum toxin or anti-CGRP-mAb injections within the last 6 months
14. Nursing, pregnant, or thinking of becoming pregnant during the study period, or of childbearing years and unwilling to use an accepted form of birth control
15. Participating in any other therapeutic clinical investigation or has participated in a clinical trial in the preceding 30 days
16. Belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with the follow-up requirements, or provide self-assessments is compromised.
17. A relative of or an employee of the Investigator or the clinical study site
18. Psychiatric or cognitive disorder and/or behavioral problems that, in the opinion of the clinician, may interfere with the study
19. BMI of 30 or greater

B4. POSSIBLE BENEFITS

It is not guaranteed or promised that patients will receive any benefit from being in this study. Information from this study may help others in the future as a result of knowledge gained from the research.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions such as rash, urticaria, and dyspnea have been reported with fremanezumab in clinical trials. If a serious or severe hypersensitivity reaction occurs, treatment with fremanezumab will be discontinued and the subject will treated with an appropriate therapy.

ANTICIPATED ADVERSE EVENTS

The most common adverse reaction of fremanezumab is injection site reactions. In a phase 3, randomized, double-blind, placebo-controlled REGAIN study in CM and EVOLVE-2 study in EM , there were no clinically meaningful differences between 120 mg monthly dose of fremanezumab and placebo on any safety or tolerability outcomes with exception of injection site reaction, pruritus and swelling.

REPORTING ADVERSE EVENTS

The investigator being the sponsor of the study has sole responsibility for reporting of adverse events to the FDA, IRBs and/or investigators. For informational purposes any correspondence to the FDA regarding adverse events or other safety issues will be simultaneously copied to the Company via email (us.clinops.sae@tevapharm.com) or facsimile (215-795-4243). The Investigator will communicate the occurrence of any serious adverse events which he or she believes to be definitely, likely, possibly or probably related to the Study Product, and any exposure of a pregnant study participant to the Study Product, within 24 hours of becoming aware of the event.

The reporting period begins when a patient signs the informed consent, and ends 30 days after the discontinuation of dosing or completion of the patient's participation in the study.

IMMUNOGENICITY

There is a potential for immunogenicity because fremanezumab is a therapeutic protein. In controlled studies with fremanezumab up to 3 months the incidence of anti-fremanezumab antibody was 0.4%. 1 of 6 fremanezumab-treated patients had neutralizing antibodies at Day 84. In a 12 month open-label study, 1.6% of patients developed anti- fremanezumab antibodies. 17 of 30 anti-fremanezumab positive patients had neutralizing activity in their post-dose samples.

Although these data do not demonstrate an impact of anti-fremanezumab-vfrm antibody development on the efficacy or safety of fremanezumab in these patients, the available data are too limited to make definitive conclusions.

Migraine is a common and disabling neurological disease. Migraine has been ranked as the seventh highest among specific causes of disability globally. Unfortunately, a large percentage of individuals with migraine are not successfully treated, and their pain and associated symptoms of photophobia,

phonophobia, and nausea do not subside. Prior to introduction of anti-CGRP-mAb, the preventive treatment armamentarium was nonspecific and included anti-depressants, anti-epileptics and anti-hypertensive medications. The adherence rates with these classes of medications have been low (35%–50%) due to unsatisfactory efficacy and side effects. According to available safety and efficacy data from Phase 2 and 3 trials in episodic migraine (EM) and CM, fremanezumab has been shown to be safe and efficacious in preventing migraine in EM and CM patients, and reduced disability and functional impairment. Fremanezumab was also shown to be tolerable with low discontinuation rates in the clinical trials. As a potential alternative treatment for prevention of migraines, subjects recruited for study participation will be offered fremanezumab. Investigators believe that subjects with symptoms associated with migraine may benefit from monthly regimen of fremanezumab. Considering that the target migraine population is often refractory to standard-of-care treatment and has few low-risk options for prevention of migraines, investigators believe that the potential risks of treatment with fremanezumab in this study are acceptable given the potential benefits of treatment.

QST PROCEDURE

The QST is designed to test a person's pain limit, so while the participant may feel discomfort as the heat stimulus increases at a slow rate from 32 to 50°C/89.6 to 122°F, they can stop the heat at any time and are in complete control of how hot the stimulus gets during the test. At this temperature range and for this duration of time, there is minimal risk of a burn.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

The potential participants will be recruited largely from the investigator's (Dr. Ashina) own patient population, as well as other providers in the headache clinic. Patients will either be informed about the study directly from the investigator in headache clinic in the BIDMC Headache Center or if they express interest in the study they may be contacted by phone by the study coordinator in order to explain more about the study.

ResearchMatch.org will also be used as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository.

The text posted on ResearchMatch will be as follows: You are being contacted by a team of researchers at the BIDMC Comprehensive Headache Center who are studying the possibility that a new FDA-approved migraine drug may also help with sleep. The study is titled "Fremanezumab, migraine and sleep" and is available to you through ResearchMatch. This study lasts for 4 months and involves 5 visits to the hospital: an enrollment visit that lasts 1.5-2.0 hours, followed by 3 monthly visits (30 min each) where you will receive the fremanezumab injections, and a study summary visit. Throughout the study, you will be asked to fill an online daily combined headache and sleep diary that should take no more than 5 minutes to complete. If you are interested in participating, please click "Yes, I'm interested."

We will also be utilizing the migraine data repository established in IRB protocol #2011P000149 to reach out to individuals who have previously expressed interest in participating in future migraine research. Individuals in the repository will be contacted by their preference of either email or postal mail.

We will be utilizing the services of Eruptr to run a 2-month campaign for the study, in which targeted ads will be posted on Facebook. Individuals who click on the provided links will be directed to a landing page that provides information on the study. Those who are interested in participating can provide their name and contact info, which will be received by the study coordinator. The coordinator will then reach out to the potential participant to schedule them for a baseline visit.

Consent

Potential research subjects will be consented either before the screening visit in clinic or on the day of their Screening Visit. This will happen in one of two locations in the BIDMC Pain Center at 1 Brookline Place: the PI's designated research room on the first floor in room 123 or Dr. Ashina's primary clinic location in Suite 406. The

study will be explained by the primary investigator, or by another one of the qualified investigators and the Study Coordinator. Detailed information relating to the study drug and study procedures, along with information about the risks and benefits of participating in any research study and in this specific study, will be provided to the participant. The consenting process will be documented on a consent checklist and notes will be taken about any questions asked by the participant.

Subject Protection

There will be no coercion or undue influence placed on patients. They will be informed of the study and given the freedom to participate or not, and this will not influence any care provided to them.

B7. STUDY LOCATION

Privacy

Conversations with potential study subjects will be done in the BIDMC Pain Center at 1 Brookline Place, either in room 123 or Suite 406. Conversations over the phone will be done in offices within the hospital so that sensitive information cannot be overheard by anyone other than study staff.

Study procedures will be performed in standard patient rooms in the Clinical Research Center on Gryzmish 8 of Beth Israel Deaconess Medical Center. The location will provide protection against study subjects being witnessed and conversations overheard by anyone other than study staff.

Physical Setting

The proposed study will take place in the BIDMC Comprehensive Headache Center at 1 Brookline Place and the Clinical Research Center on Gryzmish 8 of Beth Israel Deaconess Medical Center as outpatient visits. The PI's research room and the study physicians' clinic are located in the Pain Center and the study visits require very few procedures.

B8. DATA SECURITY

We will store electronic data in a password-protected directory on a secure server behind the BIDMC firewall. All paper records will be stored in a locked room that will be accessed only by members of the study team. Only the study team will have access to identifiable information.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

This is not a multi-site study

B10 Dissemination of Research Results

Subjects will be thanked for their participation at the completion of their study and follow-up procedures. Upon request, the sponsor will provide copies of publications that result from this project. Publications will also be printed in publicly available journals.