A placebo controlled, randomized clinical trial of galcanezumab for vestibular migraine: The INVESTMENT study

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Study Protocol

Title:
A Pilot Trial of Galcanezumab for Vestibular Migraine

Short Summary:

Vestibular migraine (VM) has been recognized a distinct subtype of migraine that causes dizziness as the predominant symptom. Criteria for diagnosis have been adopted by the Barany Society. Previous epidemiological research from my team has shown that it affects 2.7% of the adult population of the United States. Yet, despite its high prevalence, there is very little data upon which to guide treatment decisions. A Cochrane review in 2015 concluded that there were no placebo-controlled trials in VM, and none have been done since then. Our team recently developed and validated a patient reported outcome tool for VM, called VM-PATHI (VM-Patient Assessment Tool and Handicap Inventory). Anecdotal evidence suggests that CGRP antagonists, such as Galcanezumab, may be effective in reducing or eliminating symptoms in VM. Therefore, we propose a pilot study of changes in VM-PATHI scores, comparing active treatment (Galcanezumab) to placebo arms.

Hypothesis:

Galcanezumab will result in greater in a greater reduction of scores on the VM-PATHI (Vestibular Migraine Patient Assessment Tool and Handicap Inventory) than placebo, when comparing scores at baseline to scores after three months of treatment, between active treatment and placebo arms.

Study Objectives:

Primary:

To assess the efficacy of galcanezumab in treating vestibular migraine, as assessed by VM-PATHI (Vestibular Migraine Patient Assessment Tool and Handicap Inventory) score change between baseline (month 0) and after three months of treatment (month 4), comparing active treatment and placebo arms.

Secondary:

To assess the efficacy of galcanezumab in treating vestibular migraine, as assessed by baseline definitive dizzy days (month 0 to 1), compared to during the third month of treatment (months 3 to 4), between active treatment and placebo arms. Definitive dizzy days will be assessed by a daily query via text message, and consist of any day where dizziness is rated as a 2 (moderate) or higher.

To assess the response rate of subjects to galcanezumab in vestibular migraine, as measured by a 100%, 75%, 50%, and 25% reduction in definitive dizzy days, comparing baseline data (month 0 to 1), to after treatment data (months 3-4), comparing between active treatment and placebo arms.

To assess the time course of response to galcanezumab in vestibular migraine, measured by definitive dizzy days per month, comparing active treatment and placebo arms, from months 0 to 4.

To assess the efficacy of galcanezumab in treating vestibular migraine, as assessed by DHI (Dizziness Handicap Inventory) score change between baseline (month 0) and after three months of treatment (month 4), comparing active treatment and placebo arms.

To assess the efficacy of galcanezumab in treating quality of life in vestibular migraine, comparing the change in baseline PROMIS SF v1.2- Global Health scores to scores after 3 months of treatment (at month 4), across active treatment and placebo arms.

Study Endpoints:

Primary:

VM-PATHI (Vestibular Migraine Patient Assessment Tool and Handicap Inventory) score.

Secondary:

Definitive dizzy days, measured with a daily text message, with any day where dizziness is rated as a 2 (moderate) or higher counting as a definitive dizzy day.

Response rates, as measured by percentage of subjects in each arm experiencing a 100%, 75%, 50%, 25%, 0% reduction in definitive dizzy days.

Dizziness Handicap Inventory

PROMIS SF v1.2- Global Health

Statistical Methods:

Primary Endpoint:

VM-PATHI score changes between baseline and after treatment (month 4) will be compared between active treatment and placebo arms using a paired two-tailed t-test.

Secondary Endpoint:

Definitive dizzy days/month, comparing baseline to after treatment, between active treatment and control arms, will be assessed using a paired two-tailed t-test.

Response rates will be reported per category (100%, 75%, 50%, 25%, and 0%) for both active treatment and control arms. Number of subjects who experience 50% or better reduction in dizziness days will be compared using chi squared test.

Dizziness Handicap Inventory will be compared between active treatment and control arms, looking at change in score from baseline to month 4, using a paired two-tailed t-test.

PROMIS scores, comparing subdomain score changes from before (month 0) and after (month 4) treatment, across active and placebo arms, using paired t-test

Subject Selection:

Inclusion criteria:

- Adult age 18 to 75
- Diagnosis of definite or probable vestibular migraine per Barany society criteria
- Baseline (SV1) and SV2 VM-PATHI score > 25
- Baseline (month 0 to 1) definitive dizzy days > 4

- Fluency in English
- 80% adherence or better to daily SMS during baseline phase
- Written informed consent
- Access to email, and cell phone

Exclusion criteria

- Vestibular hypofunction (unilateral or bilateral)
- History of ear surgery (other than ear tubes)
- Other vestibular diagnosis (excluding treated BPPV- Benign Paroxysmal Positional Vertigo).
- Failure of treatment with > 4 prophylactic migraine medications
- Prior or current treatment with a CGRP medication
- Pregnant/breastfeeding if female
- History of serious medical or psychiatric disease, at the discretion of the treating physician (including significant coronary artery disease, peripheral vascular disease, cerebrovascular disease, kidney disease, liver disease, and uncontrolled psychiatric disease or past psychiatric hospitalization)
- Unwilling to use approved form of birth control during the study
- Ok if on up to 2 migraine prophylactic medications (prescribed for that purpose), dose must be stable for 2 months prior to study start.

Study design: Interventional
Randomization Radio: 1:1 placebo: 120 mg galcanezumab (with 240 mg loading dose at month 1)
Comparator Description: Subjects will be compared between active treatment and placebo groups
IND: exempt
Off Label: no
Sample size: 25 per arm, or 50 total
Sample size justification: This is intended to be a pilot study, as there is currently no data available. Therefore, one main aim of this study is to better inform sample size calculations for a larger study. We have chosen 50 subjects, or 25 per arm, as a reasonable number that should help provide data to inform whether or not a larger study would be useful, assuming a 10-20% drop out rate.

Scientific Justification and background:

The objective of this study is to address whether galcanezumab is more effective than placebo at reducing dizziness in patients with vestibular migraine. Vestibular migraine is a distinct subtype of migraine that causes episodic vertigo/dizziness, sometimes with headache, and sometimes without. However, unlike traditional migraines, patients generally seek out care because of dizziness, and not because of headache. Therefore, these patients are cared for by a variety of providers who treat dizziness, including otolaryngologists, and neurologists. Lifetime prevalence of vestibular migraine in the general population is estimated at 2.7%, and at least 10% of patients in a tertiary care vestibular clinic have vestibular migraine.[1,2] Furthermore, it has been shown to decrease quality of life in multiple domains, including overall health, mental health, and emotional health. Since testing and imaging are usually normal, diagnosis can only

be made on clinical grounds. Recently, consensus criteria for diagnosis was published by the Barany Society and the International Classification of Headache Disorders.[3]

Galcanezumab is a calcitonin gene related peptide (CGRP) antagonist, and is approved by the FDA for treatment of episodic and chronic migraine. Its effects with regards to vestibular migraine have not been formally studied. However, there is ample evidence to suggest that aberrant trigeminovascular inflammation may be integral to the pathophysiology of vestibular migraine, similar to migraine in general. Furman and colleagues provide an excellent review of shared pathophysiology between vestibular migraine and migraine, including the overlap of migraine circuits and central vestibular processing, and trigeminovascular reflex innervation of the inner ear.[4] Vass et al. showed that stimulation of the trigeminal ganglion caused neurogenic plasma extravasation within cochlear blood vessels.[5] They hypothesized that this relationship accounts for the frequent complaints of ear fullness, tinnitus, and vertigo that frequently are seen with vestibular migraine. Furthermore, given the strong phenotypic resemblance of migraine and vestibular migraine, and the similar responses to migraine treatments, it is reasonable to assume they share a pathophysiologic link.

We propose to study the efficacy of galcanezumab for treating vestibular migraine with a pilot double blinded randomized controlled clinical trial. Since the clinical question is a basic one about efficacy of a specific pharmacologic agent, a randomized clinical trial should be effective at answering this question. Furthermore, double blinding of both subjects and treating physicians, and allocation concealment will be performed to minimize bias. Bias is common in vertigo/dizziness studies, including a "regression to the mean" bias, where patients seek treatment during their worst periods of symptomatology, and then improve over time regardless of treatment, and this limits the ability to draw causal inference from cohort studies. Because there is no currently accepted standard of care medication, it would be considered ethical to randomize patients to either placebo or treatment. Given available data, we would first propose to perform a smaller, single institution pilot study, with the intention of gathering data regarding treatment effect sizes for planning a larger, multi-institutional study.

To date, there have been no randomized clinical trials comparing a drug to placebo for treating vestibular migraine. In 2015, Salviz et al. published a randomized clinical trial comparing propranolol to venlafaxine, and concluded that the two drugs were similar in efficacy.[6] However, there was no placebo arm. In 2002, Reploeg and Goebel published a retrospective review of different treatments for vestibular migraine, using a step-wise approach of dietary changes, tricyclic antidepressant, and finally other migraine prophylactic agent.[7] Of 81 patients, 13 (16%) were reported to respond to dietary changes alone. 31 went on to treatment with nortriptyline and of those 12 (39%) had complete resolution of symptoms, 12 (39%) had at least a 75% reduction in symptoms, 6 (19%) had less than 75% reduction in symptoms, and 1 (3%) experienced no response. In 2012, Mikulec published a retrospective cohort study that looked at the effects of caffeine cessation and nortriptyline on vestibular migraine. They found that 47% of patients with vestibular migraine found nortriptyline to be effective at treating symptoms, in a group that failed caffeine avoidance as primary treatment.[8] Finally, Lepcha studied flunarizine, a calcium channel blocker, for vestibular migraine.[9] In that 2013 study, subjects were allocated to a group that included treatment with flunarizine, betahistine, and paracetamol, or a second group that just included treatment with betahistine and paracetamol. However, no placebo was used, and furthermore the primary outcome measure was an unvalidated symptom score. 26 subjects were included in each arm of the study. Subjects in the

flunarizine arm showed improvement in vertigo frequency and severity, but not improvement in headache frequency and severity.

As confirmed with a recent Cochrane review, to date there has been no randomized clinical trial looking at the effectiveness of pharmacotherapy in vestibular migraine.[10] This is despite the fact that it may in fact be the most common reason for recurrent dizziness in the United States, affecting approximately 6.1 million Americans. Based on several observational studies, pharmacotherapy for vestibular migraine may indeed be effective. There is ample scientific evidence to suggest that treatment of vestibular migraine with CGRP antagonists is reasonable. I have personally been using CGRP antagonists to treat recalcitrant cases of vestibular migraine, with good results. However, without a randomized clinical trial, we simply have no data on which to base treatment decisions for a very common cause of dizziness. This equates to clinical equipoise, and therefore necessitates an RCT to better understand if CGRP blocking medications are effective for vestibular migraine.

Study Design:

This will be a single center, randomized double-blinded placebo-controlled trial comparing galcanezumab to placebo for treatment of vestibular migraine. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Patients in the galcanezumab arm will receive 240 mg via subcutaneous injection with a pre-loaded syringe at month 1, followed by 120 mg at month 2, and 120 mg at month 3. Those in the placebo arms will receive subcutaneous injections at the same time intervals of placebo. This will be a single institution study, and randomization will occur through the hospital research pharmacy. Allocation concealment will be ensured; study participants will be given an envelope from a folder of sequentially ordered identical envelopes that will contain study instructions and the allocated drug. The master file linking study ID with allocation will be created by a third party and kept secret until after data analysis is complete. This will ensure that both providers and participants are adequately blinded. Blocking will be used in increments of 10 subjects to ensure equitable distribution of subjects into the two treatment arms. In addition, stratification by sex and definite versus probable vestibular migraine status will be used to ensure equal allocation. Total duration of subject participation will be five months. Total duration of the study is expected to be 2 years.

Inclusion Criteria

1. Male or female aged 18 to 75 years of age at Study Visit 1.
2. Documentation of a vestibular migraine or probable vestibular migraine diagnosis according to the following criteria determined by the Barany Society:
    - Vestibular migraine
        - A: At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 hours
        - B: Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)
        - C: One or more migraine features with at least 50% of the vestibular episodes:

        - headache with at least two of the following characteristics: one sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
        - photophobia and phonophobia
        - visual aura
    - D: Not better accounted for by another vestibular or ICHD diagnosis
- Probable vestibular migraine
    - At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 hours
    - Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
    - Not better accounted for by another vestibular or ICHD diagnosis

3. Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.
4. Baseline (SV1) and SV2 VM-PATHI score > 25
5. Baseline (month 0 to 1) definitive dizzy days > 4
6. Fluency in English
7. 80% adherence or better to daily text message during baseline phase
8. Written informed consent
9. Access to email, and cell phone

a. <u>Exclusion Criteria</u>

1. Pregnant, breastfeeding, or unwilling to use approved form of birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3. Allergy to galcanezumab
4. Prior treatment with galcanezumab
5. History of ear surgery (other than ear tubes)
6. Other vestibular diagnosis (excluding treated BPPV- Benign Paroxysmal Positional Vertigo). This includes Meniere's disease, superior canal dehiscence syndrome, vestibular neuritis, persistent postural perceptual dizziness, unilateral or bilateral vestibular loss, cerebellar or brainstem disease, multiple sclerosis, Mal de Debarquement, Third window syndrome, vestibular paroxysmia, vestibular schwannoma, psychiatric dizziness, central dizziness, multifactorial dizziness, dizziness due to cerebrovascular disease, post-concussive dizziness, and cervicogenic dizziness.
7. Failure of treatment with > 4 prophylactic migraine medications
8. Prior or current treatment with a CGRP medication

9. Pregnant/breastfeeding if female
10. History of serious medical or psychiatric disease, at the discretion of the treating physician (including significant coronary artery disease, peripheral vascular disease, cerebrovascular disease, kidney disease, liver disease, Raynaud's disease, uncontrolled psychiatric disease or past psychiatric hospitalization)
11. History of mania, psychosis, or suicidal ideations
12. Ok if on up to 2 migraine prophylactic medications (prescribed for that purpose), dose must be stable for 2 months prior to study start.

Rationale:

These inclusion/exclusion criteria were chosen so that the study has as much real world applicability as possible, while also minimizing risks to subjects. Based on our preliminary data, we believe that with these inclusion and exclusion criteria, and accounting for subjects who don't want to participate and also dropout, we will still be able to recruit enough subjects to meet our recruitment goals within 2 years.

Sample Size:

We have specifically designed this as a pilot study due to lack of data to help inform sample size calculations. However, hypothesizing a difference between VM-PATHI scores between groups of 7 points, and using the standard deviation from the validation of the instrument, we with 50 subjects total, or 25 per arm, we will have 90% power to detect a significant difference at the 0.05 level between groups to assess the efficacy of galcanezumab for vestibular migraine. If we assume a 10% dropout rate in the trial we will still have greater than 80% power to detect a difference.

Clinical Sites:

We will perform this study as a single center. We will be recruiting subjects from both the Otolaryngology-Head and Neck Surgery and Neurology departments. In a previous study where we developed the VM-PATHI, we were able to recruit around 80 subjects with vestibular migraine in a little over 1 year.

Study Visit Timeline:

The study visits will be scheduled within +/- 4 days of the expected timeline. This flexibility is based on the clinic availability dates of the PI and other providers.

- Study Visit 1 (SV1) = Day 0 / Month 0
- Study Visit 2 (SV2) = Day 30 / Month 1
- Study Visit 3 (SV3) = Day 60 / Month 2
- Study Visit 4 (SV4) = Day 120 / Month 4

Re-Enrollment Policy:

For participants who met all inclusion criteria AND none of the exclusion criteria (except for not having the minimum required VM-PATHI score and/or definitive dizzy days), they can

re-enroll in the study at a later date when they feel their symptoms are worse. At that time, the participant would have to start over from Day 0 and undergo screening again.

Randomization:

This will be a single institution study, and randomization will occur through the hospital research pharmacy. The pharmacy research contact is Edward Lin and Monica Lee, and Helen Wu is the pharmacy supervisor. Edward Lin will be unblinded and will have access to the randomization schedule. Dr. Isabel Allen will remain blinded throughout the study. Therefore, the randomization schedule will be created by a second biostatistician, so that Dr. Allen can stay blinded. Allocation concealment will be ensured as well, and study participants will be given an envelope from a folder of sequentially ordered identical envelopes that will contain study instructions and the allocated drug. The master file linking study ID with allocation will be created by a third party and kept secret until after data analysis is complete. This will ensure that both providers and participants are adequately blinded. Blocking will be used in increments of 10 patients to ensure equitable distribution of subjects into the two treatment arms. In addition, stratification by sex will be used to insure equal allocation of each sex into each arm of the study. Subjects will also be stratified by diagnosis- either dVM or pVM. Total duration of subject participation will be five months.

- **Blinding:**

  b. Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments.

- Access to the randomization code will be strictly controlled- and this will reside with Edward Lin, PharmD and Monica Lee, PharmD. They will not be blinded. All the members of the clinical team, and Dr. Allen, will be blinded.
- Randomization will be done based on meeting final study criteria at SV2. So, if two patients are seen on the same day for SV1 and SV2, it would be the order of patients being seen at SV2. This would only come into play if the patients are part of the same randomization schedule (i.e. same sex and diagnosis). If however, two or more patients in the same randomization strata are seen for SV2 on the same day, given that the prescription is picked up in the AM, if the first patient does NOT meet study criteria, then we will keep the order of randomization (because the drugs are prelabelled for each patient)- but subsequent to that the next subject in that strata who is randomized should take the place of the subject who didn't meet criteria, so as to avoid disruptions to the randomization strategy.
- Packaging and labeling of test and control treatments will be identical to maintain the blind.
- Each subject will be given an identical study packet, containing their assigned drug, along with study information.
- The study blind will be broken on completion of the clinical study and after the study database has been locked. Investigators will be made aware of their subjects' treatment designations only after all the data has been collected and analyzed.
- During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the

Investigator should discuss the emergency with the Medical Monitor prior to unblinding. If it is determined that it is medically necessary to break the blind, the medical monitor will inform the investigator about the study status of that subject. That will be considered a protocol violation, and that subject will be removed from the study.

Intervention:

The study drug will be administered with a subcutaneous injection of galcanezumab or placebo. The first dose (at month 1) will be a loading dose of two injections, or 240 mg in total. After that, at month 2, and month 3, each subject will get either a subcutaneous injection of galcanezumab 120 mg or placebo. The injections will be with a pre-loaded syringe containing either galcanezumab or placebo.

Quality Assurance:

Subjects will self-administer the drug with the pre-loaded syringe. Drugs will be supplied for the full study duration by the site investigator at the second study visit. There will be detailed instruction included in the study packet on how to take the study drug. In addition, the clinical trial coordinator will provide verbal instructions. At the end of the study, the syringes will be examined and counted to ensure compliance.

- **Primary Efficacy Endpoint:**

The primary efficacy endpoint will be the VM-PATHI (Vestibular Migraine Patient Assessment Tool and Handicap Inventory). This is a recently developed and validated outcome measure for vestibular migraine from our group. It has been shown to be highly reliable and valid, and responsive to treatment changes. At this point, it is the only disease-specific outcome measure for vestibular migraine. Scores are between 0 and 100, with 100 indicating higher levels of disease-related suffering.

- **Secondary Efficacy Endpoints:**

Definitive dizzy days: This will be assessed by a daily text message, and subjects will have to answer "Over the last 24 hours, what level of dizziness have you experienced?" The answers are (0) no dizziness, (1) mild dizziness, (2) moderate dizziness, and (3) severe dizziness. Answers (2) and (3) will be considered a definitive dizzy day. This will help us understand the temporal nature of response to treatment. In addition, it will make the data analogous to the migraine headache trials. If participants respond with a "1," "2," or "3," then a follow-up text message will ask about any symptomatic medications used for their dizziness. Participants will be able to type out their responses on the text message. At the end of the study, the study team will code the participants' symptomatic medications into specific categories (e.g., benzodiazepines). Participants will be asked to notify the CRC if a mistake is made in their response to the daily text message.

Dizziness Handicap Inventory (DHI): This is the most widely used measure of dizziness severity, and consists of 25 questions. Questions ask about problems related to dizziness, and are scored as no (0 points), sometimes (2 points), or always (4 points). Total score is between 0 and 100, with higher scores indicating more disability. While subjects with vestibular migraine suffer

from a variety of symptoms, dizziness is clearly the predominant feature. Furthermore, this will help us compare data to other studies that involve causes of dizziness.

PROMIS SF v1.2- Global Health: This is a widely used and validated quality of life measure. It is quick and simple to administer. There are 10 questions on this scale, each with a score of 1-5. Higher scores correspond to a greater extent of the concept measured (e.g., more fatigue, more pain). Two summed scores are generated, one for global mental health (question #3, 6, 7, 8) and one for global physical health (question #2, 4, 5, 10). The remaining 2 questions are analyzed separately. Summed scores for global physical health and global mental health are converted into T-score values using the "HealthMeasures Scoring Service" (https://www.assessmentcenter.net/ac_scoringservice). The T-scores for physical health and mental health can then be grouped into excellent, very good, good, fair, and poor categories. The cut points for each category is determined by calculating the midpoint between 2 adjacent means. For example, if the mean mental health T-score for “Excellent” is 61 and the mean mental health T-score for “Very Good” is 51, then the cut point for these categories would be a T-score of 56.

Data Collection:

Data collection will be performed by the clinical research coordinator during each study visit. This data will be entered into the REDCap database by the research coordinator. VM-PATHI, DHI, GAD-7, PHQ-9, PROMIS SF v1.2- Global Health, and HIT-6 will be administered electronically via REDCap to the subject during the study visit. The schedule of collection of each data point is reviewed in appendix 1. The data collection instructions are contained within appendix 2.

Stopping Rules:

There will be no stopping rules for this trial, given the short duration of the study. Each adverse effect and serious adverse effect will be reviewed by the data safety monitoring team, and subjects may be unblinded and/or the study will be stopped early for serious safety concerns.

- **Early Discontinuation of Study Drug:**
    - A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject’s best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

c. Analysis of Primary Endpoint:

d. For the primary endpoint, which is the change in VM-PATHI scores between month 1 and month 4 as compared between the galcanezumab arm and the placebo arm, a paired two-tailed Student's t-test will be used, provided the data is normally distributed. This will conducted with an intent-to-treat analysis. Significance will set at alpha of 0.05.

e. Analysis of Secondary Endpoints:

Definitive dizzy days/month, comparing baseline (month 0 to 1) to after treatment (month 3-4), between active treatment and control arms, will be assessed using a two-tailed t-test.

Response rates will be reported per category (100%, 75%, 50%, 25%, and 0% reduction in definitive dizziness days, comparing month 0 to 1 to month 3 to 4) for both active treatment and control arms. Number of subjects who experience 50% of better reduction in dizziness days will be compared using Chi Squared test.

Dizziness Handicap Inventory will be compared between active treatment and control arms, looking at change in score from baseline to month 4, using a two-tailed t test.

PROMIS scores comparing active and placebo arm score changes from before (month 0) and after (month 4) treatment using a paired t-test.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

Initially data will be summarized overall, by patient, and by treatment and control groups. Plots of each outcomes will be displayed graphically over longitudinal time points. Univariate summaries of all variables overall, by patient, and by subgroup will include means and standard deviations for continuous variables and counts and percentages for categorical variables.

Bias:

Bias will be minimized by using a double-blinded study design, with allocation concealment. This will limit selection, performance, and detection bias. In addition, this will help control for potential confounding variables. In addition, by including a placebo control group, we will minimize regression to the mean bias. Finally, by collecting information prospectively, we will minimize reporting bias.

Missing Data:

We will minimize missing data by having the clinical trial coordinator present to help the study subject fill out all data. We anticipate a 15-20% loss to follow up, and have accounted for that in our sample size calculations. Outliers and non-compliant subjects will be included in the analysis. We will perform an intent-to-treat analysis.

Trial Duration:

We estimate that this trial will take approximately 2 years to complete, once subject recruitment is able to begin. That includes 1.5 years for subject recruitment and data collection, and 6 months for closeout and data analysis. If recruitment is slower than expected, we will plan on keeping the trial open for a longer period of time. This seems unlikely based on our prior experience with recruitment in this patient population.

Pharmacy/Study Drug:

The active drug and placebo will be managed through the research pharmacy at UCSF. The drug and placebo will be supplied by Eli Lilly and Company. Study drugs will be given to patients on the day of randomization (month 1), so any failure of subjects to take the study drugs will just be considered a violation of protocol, but they will be included in the intent to treat analysis.

Packaging:

Study drug will be supplied in preloaded syringes, each with a dose of 120 mg or placebo. Subjects will first receive the first month's supply (240 mg or placebo) at study visit 2, and then will receive a two-month supply at study visit 3. So, at study visit 2 and 3, each participant will get two pre-filled syringes. They will also get an insulated bag with a cold pack to keep the drug cool until it can be refrigerated at home.

Labeling:

Each carton (kit) of study drug will be labeled with the required FDA warning statement, the protocol number, a treatment number, the name of the sponsors, and directions for patient use and storage.

Dosage:

The study drug will be administered in fixed dose of 120 mg. The first administration, at month 1, will be a loading dose of 240 mg. Each subsequent injection (month 2 and 3) will be 120 mg dose. There will be no dose adjustment for weight, age, or any other factors

Dispensing of Study Drug:

Drugs will be administered in a packet with a 1-month supply by the site investigator at study visit 2. They will then get the second 2-month supply at study visit 3.

Administration of Study Drug:

Subjects will self-administer the drug, with a pre-filled syringe, into an acceptable area of the body. This is typically the thigh, but also includes the abdomen, buttocks, or back of the upper arm. Study personnel will monitor with first and second injection to ensure compliance and proper administration. A note will be placed into the medical record confirming the time, date, and location of the injection (part of the body). For the third injection, the CRC will reach

out to the patient to confirm injection, and then record time, date, and anatomic site of the injection. Adherence to the injection will be confirmed by asking participants to send the CRC a picture of the empty syringe. This picture will be uploaded to the REDCap record.

Storage of Study Drug:

Study drug should be stored at 36 to 46 degrees Fahrenheit. It should not be frozen. If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the PI and captured as a deviation. Subjects will be instructed to store the medication in original packaging to protect it from light until usage.

Study Drug Contents:

Active ingredient: galcanezumab-gnlm. Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80, Sodium Chloride, and Water for Injection, USP.

Study Drug Accountability:

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded by the clinical research coordinator.

Measures of Treatment Compliance:

Subjects will be asked to bring all study materials, including unused drug and containers, to each study visit. This will be used to calculate compliance.

Participant Payment:

Each participant will be provided with a modest payment for their time, parking, and travel expenses. Payment will be provided in the form of a prepaid debit card worth $100 at the second and fourth study visits (total $200). Participants will be asked to contact the study coordinator with any questions.

COVID-19 Screening Protocol

Study personnel will comply with the required screening tool to be cleared for onsite work each day. Please note the screening protocols may change according to the latest UCSF guidelines. High-touch surfaces and frequently used objects, including onsite computers, will be disinfected at the beginning and end of each study visit. Participants will be screened for COVID-19 symptoms by phone 48 hours prior to their time of arrival onsite as follows:

In the last 30 days, have you been diagnosed with COVID-19? [YES / NO]
In the last 14 days, have you had unprotected close contact with someone diagnosed with COVID-19 (such as a household contact)? [YES / NO]
Close contact = within 6 feet for 15 minutes or longer, live with a person diagnosed
Unprotected = without a face covering or without appropriate PPE at work if a healthcare worker

In the past 14 days, have you experienced any of the following new, unusual, or worsening symptoms? (Unusual = not explained by a pre-existing condition such as allergies)

Fever, Chills, Shivering/Shakes (temp > 37.8o C/100o F) [YES / NO]
Cough [YES / NO]
Sore Throat [YES / NO]
Runny or congested nose [YES / NO]
Difficulty breathing or shortness of breath [YES / NO]
Unexplained muscle aches [YES / NO]
Feeling unusually weak or fatigued [YES / NO]
Loss of sense of smell or taste [YES / NO]
Diarrhea (defined as > 3 loose stools in 24 hours) [YES / NO]
Eye redness with or without discharge ("pink eye") [YES / NO]
Nausea or vomiting [YES / NO]

Do you live with someone who is waiting for COVID test results due to symptoms of a COVID type illness? [YES / NO]

In the past 14 days, have you returned from travel outside of the US? [YES / NO]

Do you confirm the answers you have provided are true, and that you understand the information is critical to your safety and to the safety of others? [YES / NO]

If participants answer YES to any of the above questions, they will be referred to their medical provider and asked to stay at home. Participants who recovered from COVID-19 may be eligible to participate in this study at the discretion of the PI. However, patients who are currently undergoing active workup for COVID-19 will not be recruited for this study.

If answer is NO to every question, we will tell the study participant "if you should develop ANY OF these symptoms before your appointment tomorrow, we're asking you to stay home and call us at 415-XXX-XXXX. We will further assess how you are doing and determine next steps to reschedule your appointment."

At the time of arrival onsite, study participants will be asked to use the self-screening digital tool that patients are asked to complete prior to entering a UCSF Health clinic. The tool is found by going to https://tiny.ucsf.edu/entry and participants will need to show the "cleared" screen in order to gain entry to the building of their visit. NOTE: if participants do not have a smart phone or otherwise have the ability to complete the digital screener, the CRC should conduct the screen verbally (using the digital screener on behalf of the participant).

Both participants and personnel will adhere to UCSF Social Distancing Protocols:

- Face coverings will be worn at all times during the study visit
- Study personnel will wash hands with soap for at least 20 seconds before putting on face coverings
- Physical distances (>6 feet) will be maintained whenever possible
- If an empty room is not available, participants will be asked to fill out questionnaires electronically at home

Informed consent will be conducted in-person by the PI. The clinical research coordinator will obtain signatures on the informed consent form and Bill of Rights from the PI and the

participant. The participants will be given a copy of the signed forms. Questionnaires will be administered electronically via a link generated from REDCap preferably during the study visit.

Data Management:
All study data will be kept in a secure online REDCAP database. Paper forms, such as study consents, will be kept in a locked file cabinet in a locked office in a secure building.

- **Data Management Procedures:**
    - The data will be entered into a REDCap database. The study team will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once data collection and quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Informed Consent:
Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records. Please refer to the section "COVID-19 Protocol Amendments" for an updated consent process.

Data Safety Monitoring Plan:
The Data Safety Monitoring Plan will be implemented by the PI and all key study personnel. The purpose will be to review data relating to safety and efficacy, to conduct and review interim analyses, and to ensure the continued scientific validity and merit of the study, according to the UCSF Data Safety Monitoring requirements. There will be 1 interim review(s) conducted by the PI for the purpose of monitoring study conduct and assessing patient safety. This will include a review of adverse effects, breaches of confidentiality, and unanticipated problems involving risk to participants and others. If there are any serious adverse effects, they will be reported to the IRB in an ongoing fashion. This study will also involve a DSMB, which will be formed by 3 members: a neurologist, an otolaryngologist, and a statistician. They will

review any serious adverse events within 5 days and perform 1 interval analysis once half of the target recruitment is achieved.

f. **Adverse Events:**

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

g. **Serious Adverse Experiences (SAE):**

SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed

Serious Adverse Experience Reporting:

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed. In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB, the site investigator will report SAEs to the IRB.

Privacy Protection:

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

Protocol Amendments:

Any amendment to the protocol will be written by the PI. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

IRB:

The protocol and consent form will be reviewed and approved by the UCSF IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Data Analysis Plan:

Subjects will be divided by study status into several groups.

1. Per Protocol Analysis
    a. Signed Consent
    b. 4 study visits (in person or virtual) within:
        i. SV2 (day 30) no earlier than day 23, and no later than day 44.
        ii. SV3 (day 60/day 30 after SV2) no earlier than day 23 after SV2, and no later than day 37 after SV2.
        iii. SV4 (day 120/day 60 after SV3) no earlier than day 50 after SV3, and no later than day 70 after SV3.
    c. Received same drug (galcanezumab or placebo) for all doses during the trial
    d. Completed Day 90 injection within 7 days of target date, so 23 to 37 days after SV3
    e. 80% or better adherence to text message
    f. Filled out all questionnaires
2. Intent to Treat
    a. Everyone who signed consent and got at least one dose of study drug who does not meet per protocol criteria
3. SV2 failure
    a. Signed consent but did not meet eligibility during the baseline month (less than 80% adherence to texting, or fewer than 4 definitive dizzy days or SV2 VM-PATHI less than 25
4. SV1 failure
    a. Signed consent but then VM-PATHI score too low on SV1

5. Screen failure
    a. Did not meet inclusion/Exclusion so did not sign consent

Responsibilities of Study Team Members:

Jeffrey D. Sharon, MD (Principal Investigator): Dr. Sharon is an Assistant Professor in the Department of Otolaryngology – Head and Neck Surgery, and the director of the Balance and Falls Center at UCSF. Dr. Sharon will serve as PI for this project, and will supervise experimental design, data analysis, and summarizing the result for public disclosures to the academic community.

Rebecca Michael, MD: Co-investigator: Dr. Michael is an Assistant Professor of Neurology, and a member of the UCSF Headache Center. She will assist will all aspects of the study.

Morris Levin, MD: Dr. Levin is the director of the Headache Center at UCSF, and will assist in all aspects of the study.

Roseanne Krauter, FNP-BC. Roseanne is a nurse practitioner within the department of Otolaryngology-Head and Neck Surgery, and specializes in vestibular disorders. She will assist with all aspects of the study.

Isabel E. Allen, PhD: Dr. Allen is a biostatistician, and will assist with study design, database management, data analysis, and manuscript preparation.

Clinical Research Coordinator: The clinical research coordinator will help with patient recruitment and enrollment, database management, and data entry.

Clinical Recruitment Team: The following providers at UCSF have all agreed to help screen patients for study inclusion, and they all see patients with vestibular migraine on a regular basis:

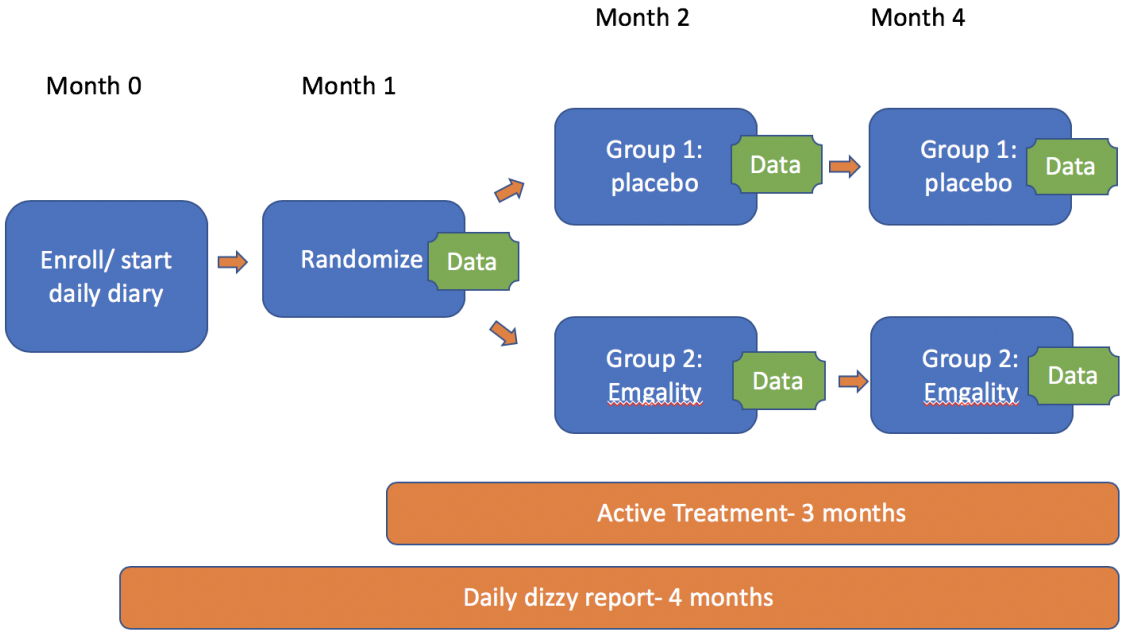
Department of Otolaryngology-Head and Neck Surgery: Roseanne Krauter, NP; Laura Kirk, PA; Charles Limb, MD; Aaron Tward, MD, PhD; Jeffrey D. Sharon, MD.

Department of Neurology: Rebecca Michael MD, Nina Riggins MD, Morris Levin MD

Appendix 1: Schedule of study events

Study month		0	1	2	3	4
Clinical Visit		√ (L5) **SV 1**	√ (L4) **SV 2**	√ (L4) **SV 3**		√ (L4) **SV 4**
Phase of study		Baseline Eval	Randomize/Start Treatment	First eval on Tx		Final eval for data/safety
Testing	CBC	√				√
	CMP	√				√
	EKG	√				√
	Pregnancy Test	√				
	Audio (if not previously done)	√				
	Vital signs	√	√	√		√
Questionnaires	VM-PATHI	√	√	√		√
	DHI		√	√		√
	HIT-6		√	√		√
	PROMIS SF v1.2- Global Health		√			√
	Med review	√	√	√		√
	Adverse Effects			√		√
	Medical history	√				
	Demographics	√				
	PHQ-9		√			√
	GAD-7		√			√
	Diagnosis form	√				
	Close-out form					√
Definitive Dizzy Day Text		√	√	√	√	√
Treatment			240 mg Emgality/Placebo	120 mg	120 mg	

Appendix 2: Schema of study design.



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Statistical Analysis Plan for a Pilot Trial of Galcanezumab for Vestibular Migraine

This is a single center, randomized double-blinded placebo-controlled trial comparing galcanezumab to placebo for treatment of vestibular migraine. Blocking was used in increments of 10 subjects to ensure equitable distribution of subjects into the two treatment arms. In addition, stratification by sex and definite versus probable vestibular migraine status was used to ensure equal allocation. Total duration of subject participation will be five months.

Primary Outcome:

Assess the efficacy of galcanezumab in treating vestibular migraine, as assessed by VM-PATHI (Vestibular Migraine Patient Assessment Tool and Handicap Inventory) score change between baseline (month 0) and after three months of treatment (month 4), comparing active treatment and placebo arms.

Secondary Outcomes:

Assess the efficacy of galcanezumab in treating vestibular migraine, as assessed by baseline definitive dizzy days (month 0 to 1), compared to during the third month of treatment (months 3 to 4), between active treatment and placebo arms. Definitive dizzy days will be assessed by a daily query via text message, and consist of any day where dizziness is rated as a 2 (moderate) or higher.

Assess the response rate of subjects to galcanezumab in vestibular migraine, as measured by a 100%, 75%, 50%, and 25% reduction in definitive dizzy days, comparing baseline data (month 0 to 1), to after treatment data (months 3-4), comparing between active treatment and placebo arms.

Assess the time course of response to galcanezumab in vestibular migraine, measured by definitive dizzy days per month, comparing active treatment and placebo arms, from months 0 to 4.

Assess the efficacy of galcanezumab in treating vestibular migraine, as assessed by DHI (Dizziness Handicap Inventory) score change between baseline (month 0) and after three months of treatment (month 4), comparing active treatment and placebo arms.

Assess the efficacy of galcanezumab in treating quality of life in vestibular migraine, comparing the change in baseline PROMIS SF v1.2- Global Health scores to scores after 3 months of treatment (at month 4), across active treatment and placebo arms.

Statistical Methods:

Descriptive statistics will be used to summarize all the clinical characteristics and demographic outcomes. These will be summarized overall, by treatment group, by assessment time, and by treatment group and time. Continuous variables will be summarized using means, medians, standard deviations and ranges. Categorical data will be summarized by number and percent. Bivariate analyses comparing groups and time points will be summarized using t-tests and one-way analysis of variance for continuous variables that are not extremely skewed and by Wilcoxon rank sum and the Mann-Whitney U test for variables requiring non-parametric statistics. Categorical analyses will use Chi-squared tests of independence, Fisher exact tests, and Z-tests of proportions.

Primary Endpoint:

VM-PATHI score changes between baseline and after treatment (month 4) will be compared between active treatment and placebo arms using a paired two-tailed t-test.

Secondary Endpoints:

Definitive dizzy days/month, comparing baseline to after treatment, between active treatment and control arms, will be assessed using Student's paired two-tailed t-tests.

Response rates will be reported per category (100%, 75%, 50%, 25%, and 0%) for both active treatment and control arms. Number of subjects who experience 50% or better reduction in dizziness days will be compared using chi-squared tests.

Dizziness Handicap Inventory will be compared between active treatment and control arms, looking at change in score from baseline to month 4, using Student's paired two-tailed t-tests.

PROMIS scores, comparing subdomain score changes from before (month 0) and after (month 4) treatment, across active and placebo arms, using Student's paired two-tailed t-tests.

Missing Data:

We minimized missing data by having the clinical trial coordinator present to help the study subject fill out all data. We anticipated a 15-20% loss to follow up and accounted for that in our sample size calculations. Outliers and non-compliant subjects will be included in the intent-to-treat analysis.