

PART B STUDY DESCRIPTION

TITLE OF PROTOCOL	Novel insight into migraine pathophysiology and galcanezumab mechanisms of action
Principal Investigator	Rami Burstein, PhD

B1. PURPOSE OF PROTOCOL

The purpose of this study is to understand better the mechanisms of action of calcitonin gene related peptide (CGRP) targeted monoclonal antibodies in migraine prevention. Specifically, the protocol will allow us to determine whether the main site of action of this novel and recently-approved class of migraine prophylactic drugs act inside or outside the brain and if so, where.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

The migraine brain exhibits unique sets of structural and functional changes involving multiple nuclei in the brainstem, thalamus, hypothalamus, and basal ganglia as well as cortical areas that mediate many of the migraine associated symptoms, prodrome and auras. Currently, there is an ongoing academic debate over cause and effect in the pathophysiology of chronic migraine. This debate is based on 2 different hypotheses: (a) hypothesis one suggests that the migraine brain is inherently hyperexcitable, and that this inherent hyperexcitability is the cause of the headache as well as all the changes seen in migraine brain imaging. In contrast, (b) hypothesis two suggests that the continuous bombardment of the brain by pain signals that originate in the meninges and transferred to the dorsal horn, brainstem, thalamus, hypothalamus, basal ganglia and cortex is the cause of all the changes seen in the structure and function of the migraine brain.

Until recently, it was not possible to resolve this debate as no research tools existed that allowed us to distinguish clearly between peripheral and central contributions to the state of the migraine brain. The introduction of anti-CGRP monoclonal antibodies (anti-CGRP-mAbs) to our clinical ammunition against chronic migraine, however, have changed this situation. Because CGRP-mAbs are too large to cross the blood brain barrier - at least to the extent that their concentration and distribution in the different brain areas are large enough to generate a therapeutic effect – but nevertheless, can effectively render a significant number of patients completely or almost completely headache-free (i.e., the super-responders: defined as those whose migraine days per month decrease by 75, 90 or 100%), it is now generally acceptable that while migraine attack (prodromes, aura, sensory sensitivities) can originate in abnormal brain functioning, the headache itself depends entirely on activation of pain fibers that carry pain signals from the meninges and potentially other pain-sensitive structures in the head, to the spinal cord and brain.

Our working hypothesis is that many of the structural and functional abnormalities observed in the migraine brain are secondary to the continuous bombardment of the brain with pain signals that originate in the meninges. To test this hypothesis, we propose to determine whether structural and functional brain changes seen in individual chronic migraine (CM, ≥ 15 headache days/month) and high-frequency episodic migraine (HFEM, 10 to 14 headache days/month) patients are reversed in those cases in which galcanezumab therapy was super-effective but not in those in which galcanezumab therapy was ineffective (part 1 – imaging). We also propose to determine whether galcanezumab therapy eliminated interictal hypersensitivities, prodromes and auras as well as common triggers in patients in which this therapy was super-effective vs. patients in which it was not effective et al (part 2 – neurological evaluation). The importance of these studies is that they can help us understand better the migraine brain, migraine pathophysiology, and anti-CGRP-mAbs mechanisms of action in the prevention of migraine.

To test our working hypothesis more thoroughly, we will also determine whether the extent of structural and functional brain changes seen after 3 months of treatment; the reduction in interictal hypersensitivities; and/or the ability of prodromes, auras, and common triggers to predict or initiate attacks continue to improve over time in the responder group.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

a.

- *A brief overview of the study:* To test our working hypothesis, we propose to study 160 CM/HFEM patients in up to 14 visits to the Beth Israel Deaconess Medical Center (BIDMC) Comprehensive Headache Center and up to 4 visits to the research MRI center in the Ansin Building at BIDMC. The first 2 visits to the BIDMC Comprehensive Headache Center and the first visit to BIDMC research MRI center will take place before treatment and the 5th visit to BIDMC Comprehensive Headache Center and the second visit to the research MRI center will take place 3 months after initiation of treatment. In these visits, we will collect medical and headache history, perform a physical examination, administer and review subjects' e-diary, and perform functional and structural MRI of the brain. As a precaution for COVID, patients will have the option of choosing to conduct the 3rd and 4th study visits (2nd and 3rd study medication injections) remotely via StarLeaf or over the phone instead of coming to the headache clinic. Participants who reach certain thresholds over the course of their three months of treatment with the study medication may also continue with a study extension of up to nine months, where they will continue to receive monthly doses of the study drug while continuing the e-diary. Participants who end the study treatment either prior to the end of the third dose or during the study extension will be asked to conduct an end of treatment visit, where they will complete a final MRI scan and attend a study conclusion visit with the PI.
- Overall study design: Experimental prospective study involving identification of neurological effects after treatment of CM and HFEM with galcanezumab – an anti-CGRP-mAb.
- Design methodologies: Open-label treatment study comparing the effects of galcanezumab on neurological functioning and brain structure in super-responders, responders and non-responders among CM and HFEM patients.
- Primary goal: (1) To determine whether galcanezumab – a drug that acts mainly outside the brain - reverses abnormal brain functioning in CM and HFEM patients. For this study, signs of abnormal brain functioning include triggering of migraine by deviation from homeostasis (prodromes, sleep deprivation, skipping meals) and abnormal sensitivity to sensory stimuli (light, noise, smell, auras). (2) To determine whether the extent of structural and functional brain changes seen after 3 months of treatment; the reduction in interictal hypersensitivities; and/or the ability of prodromes, auras, and common triggers to predict or initiate attacks continue to improve over time by comparing results seen at 3 and 6 months after treatment initiation in the responder and super-responder groups. For ethical reasons, we will not continue with treatment (beyond 3 months) in the non-responders.
- Key details of study implementation: The study includes CM and HFEM patients. The intervention is galcanezumab (Emgality™). Galcanezumab is an anti-CGRP-mAb approved by the FDA for the prophylactic treatment of migraine. Because this is not an efficacy study, the primary endpoint will not include reduction in number of migraine/headache days per month. Rather, the primary endpoints of the study will include the following: incidence of prodromes, incidence of triggers, sensitivity to light, noise and smell during and in between attacks, and incidence of aura (as determined by filling the e-diary), gray mater thickness and connectivity strength between brain areas involved in migraine (as determined by MRI). Each patient will be scheduled to visit the headache clinic at BIDMC up to 8 times and the BIDMC research MRI center for three of those visits. The initial baseline visit at the Headach Center will take 1 hour. Follow up visits at the headache clinic, during which participants will receive doses of the study drug, will take 30 min. Visits that include an MRI scan (which take place before treatment, as well as 3, 6, and 12 months after treatment, will take 2 and a half hours. In addition, each patient will have to fill a daily diary for up to 13 months (estimated to take 5 minutes per day) and will receive a 5 minute weekly phone call from a study coordinator.
 - Note: Subjects that completed the first four months of the study prior to the approval of the study extension will be asked to sign a new consent form that includes information about the study extension prior to continuing with their study participation. These participants, all of whom are patients of Dr. Ashina, had been clinically prescribed with the medication after completion of the initial study treatment, which is in accordance with what the doctor would

typically prescribe. This only applies to the first eight enrolled patients, who concluded their initial study participation between 12/7/20 and 1/4/21.

b. Participants will undergo the following procedures:

1. Medical and Headache history at the Headache Center (questionnaire filled by patients and reviewed by Drs. Ashina and Burstein)
2. Physical examination including measurements of vital signs at the Headache Center (performed by Dr. Ashina)
3. Undergo Quantitative Sensory testing (QST) at the beginning of the study and after each MRI scan (performed by Dr. Ashina)
 - a. 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 mm² 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.
- b. 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.
4. E-diary education and administration by study coordinator at the Headache Center
 - a. The e-diary will be administered in the form of a REDCap survey using an email link that participants can access from their personal computer/electronic device
 - b. The e-diary will consist of a questionnaire that will ask questions concerning any headaches that the participant has experienced that day and any remedies that they undertook to relieve their pain
5. Undergo urine pregnancy testing at the research MRI center prior to the MRI scans
6. Up to 4 MRI sessions at the research MRI center run by Dr. Nicolas Bolo. We will recruit a healthy volunteer to do a phantom run of the imaging protocol.
 - a. During the two month research MRI shutdown starting in August, we will increase the scanning window by a month to compensate for the unavailability of the scanner. This change will not negatively impact the research, as subjects will remain on study treatment.
 - b. Any scans projected to occur during this time span that cannot be pushed back by a month will be performed using the clinical MRI on the West campus. The research MRI team will help coordinate these scans.
7. Administration of galcanezumab loading dose by Dr. Ashina at the Headache Center.
8. Self administration of galcanezumab maintenance doses at home. These doses will be shipped to subjects' residences ahead of their monthly dosage days. The study team will obtain the study medication from the Research pharmacy via the usual SOP and mail it to the subjects via a traceable method at ambient storage. As the study medication may be stored at room temperature for 7 days,

supply will be mailed within close proximity to the “visit” day. The sponsor has approved the aforementioned plan. Subjects will have the option to come in to the headache clinic for the visit if they so wish.

c. Imaging part of the study:

Patients recruited to the study and deemed eligible to participate (per the results of visit 1), will have MRI visits scheduled at the research MRI center for the MRI scanning. All MRI scanning will take place at BIDMC under the supervision of our Co-investigator Dr. Nicolas Bolo. Subjects will be met by the study coordinator and be escorted to the MRI scanning area. The BIDMC MRI staff will review the subject's MRI safety checklist and prep the subjects for scanning. As per the chart flow above, each patient will be scanned at least twice, once before initiation of treatment with galcanezumab and a second time on day 120 of the study, after being on galcanezumab for about 3 months. Participants that continue with the study extension will undergo two additional scans, one on day 210 and another on day 390.

Image acquisition will be performed with a General Electric 3 Tesla MRI scanner (GE Discovery MR750) equipped with a 32-channel proton head coil. For each patient, a series of high resolution structural, functional and metabolic imaging and spectroscopy scans of the brain will be acquired. Image acquisition will take 1-hour scanning time, including patient preparation and positioning.

Processing and analyses of brain imaging and spectroscopy scans will be performed with specialized software packages to yield morphometric, functional and metabolic brain measures.

Analysis of the brain images obtained from the MRI scans may be conducted by either Dr. Borsook at Boston Children's Hospital or Dr. Bolo at BIDMC. A data transfer agreement has been arranged between BIDMC and Boston Children's for the transfer of these images.

Study Timeline	Day 0: Screening (Headache Center)	Day 30: MRI scan and initial dosing (BIDMC)	Days 60 and 90: Maintenance dose (Home/BIDMC)	Day 120: MRI scan and maintenance dose/study conclusion visit for non-responders (BIDMC)	Day 150 and 180: Maintenance dose (Home/BIDMC)	Day 210: MRI scan and maintenance dose/study conclusion visit for non-responders (BIDMC)	Day 240, 270, 300, 330, 360: Maintenance dose (Home/BIDMC)	Day 390: MRI scan and study conclusion visit (BIDMC)	End of Treatment Visit
Informed consent	X								
Physical examination	X			X		X		X	X
Vital signs	X			X		X		X	X
Review of medical and headache history	X			X		X		X	X
QST	X			X		X		X	X
Administration of e-diary	X								
Review of e-diary		X		X		X		X	X

Review of inclusion / exclusion criteria		X							
Urine pregnancy testing		X		X		X		X	
MRI scan		X		X		X		X	X
Drug administration		X ¹	X ¹	X ¹	X ¹	X ¹	X ¹		
e-diary completion	X ²								

1. Home dosing will be assisted over the phone by the PI or subjects have the option to come into the clinic
2. Subjects will receive weekly phone calls and a reminder email from the coordinator about completing the diaries.

Incidental findings: Participants will be informed of any findings, such as inter-cranial abnormalities, and the PI will make the necessary referrals.

B. Statistical Considerations

- a. **Sample Size Justification:** This study will enroll a total of 160 patients with chronic and high-frequency episodic migraine and 1 additional volunteer to complete a dry run of the scanning sequences.

Overall Clinical Assessment: The required sample size estimate has been obtained to provide sufficient power to evaluate several inferences estimated within two statistical models. The overall alpha level ($\alpha = 0.05$) is preserved through sequential omnibus testing of the proposed hypotheses. Essentially, we are evaluating whether there is an association between degree of response and the probability of experiencing four equally important binary outcomes: 1) photophobia, (2) phonophobia, (3) nausea, and (4) at least one or more triggers. In model 1, inferences will be conducted based on the association of the degree of response to treatment (i.e., 0 to 100% response in headache frequency) and changes in these outcomes over time (0 vs 3 months). In model two, individuals who respond to treatment at 3 months will be further observed at 6 months to examine differences in the outcomes over time.

In a study by Rasmussen et al, 83.2% of migraine patients experienced photophobia, 82.4% of migraine patients experienced nausea and 85.7% experienced phonophobia. Additionally, in a 2007 study by Kelman et al, 75.9% of patients reported one or more trigger using an unstructured recall. Thus, the event rates for each of the primary outcomes are expected to be in the interval of 76% to 86%. To test our working hypotheses, we will enroll 160 CM/HFEM patients. This sample size is selected because it is anticipated that a substantial number of participants will be lost to screen failures, attrition or other drop-out. Based on previous studies it is expected that of the enrolled patients, 67% will be responders (> 50% improvement) and 33% will be non-responders. These patients will undergo the repeated brain scans and the identification of changes in neurological functioning, associated symptoms, prodromes and triggers. These patients will be scanned at week 12, while still on the galcanezumab therapy and then interviewed regarding their neurological functioning (Visit 3). Our goal is to have at least n = 30 responders who belong to the >75% super-responder group, n= 30 > 50% but less than 75% responders, and n = 20 non-responders.

Enrolling N = **160** individuals is expected to yield N = **80** evaluable individuals at 3 months. This sample size provides 80% power to detect an absolute difference in paired proportions (i.e., baseline vs 3 months) of **11%**, assuming a baseline proportion of 80%, two-sided alpha = 0.05, and a within-subject correlation of $r = 0.75$. Using these assumptions, this sample size also provides 80% power to detect an odds ratio from the continuous headache frequency change predictor of **OR \geq 1.95**.

- **Sample Size Justification (fMRI):** We estimated the sample size for the proposed work using previous pseudo-continuous arterial spin labelling data collected in migraine patients (N=17) and matched, healthy control (HCs, N=17) (Hodkinson et al., PlosOne, 2015). We calculated cerebral blood flow (CBF) in primary somatosensory cortex [means \pm standard deviations (SD), ml/100g/min] in migraine (44.59 ± 9.67) and HCs (33.03 ± 10.97); effect size (Cohen's d) = 1.12). We used the larger SD of the two cohorts to calculate the sample size and estimated 15 patients per group to detect a difference in CBF in primary somatosensory cortex with 80% statistical power at the 5% significance level. Similarly, Based on or prior data for a 6-year bracket, the expected variability in volumes is of the order of 1.8 and 1.5%, respectively. For SI, with an effect size of 0.83, to achieve 80% power while maintaining 95% confidence we need to acquire 20 subjects per group.
- b. **Data Collection and Analysis:** The following data will be collected before and after treatment: triggers, prodromes, associated symptoms, cortical thicknesses, and visual cortex activation magnitude. Of these, primary endpoints include freedom from triggers and prodromes, and cortical thickness recovery. Secondary endpoints include reduction in migraine associated symptoms (defined as sensitivity to light, noise and smell) and reduction in activation magnitude of the visual cortex. For each of these parameters, analyses will compare between the groups (>75% responders, >50% responders, non-responders).
- c. Details of data collection in the imaging study:

1. 3-Plane Localizer – 3 min

Fast Gradient-Echo sequence

Parameters: Slices = 5 in each of the sagittal, coronal, axial planes, slice thickness = 5 mm, no gap, FOV = 260 mm.

The localizer scan is used to determine the position of the subject's head in the scanner, readjust the subject's position to the magnetic center of the scanner if needed, and position the subsequent images.

2. Calibration scan – 2 min

SPGR (Spoiled Gradient) sequence

Parameters: FOV = 300 mm, slice thickness = 9.4 mm.

This scan is used to calibrate the transmit/receive channels for parallel imaging using the ASSET option of the GE scanner.

3. T1-weighted Structural – 7 min

MPRAGE (Magnetization Prepared Rapid Gradient Echo) sequence / Accelerated sagittal IR-FSPGR (Inversion Recovery – Fast Spoiled Gradient) sequence

Parameters: Sagittal slices = 176, slice thickness = 1 mm, no gap, FOV field of view = 256 x 256 mm, TE echo time = 1.74 ms, TI inversion time = 400 ms, TR repetition time = 2520 ms, flip angle = 11°, resolution = 1 x 1 mm, voxel size = 1 x 1 x 1 mm, receiver bandwidth = 31.25 Hz.

The T1-weighted image is used for morphometric analyses (primary outcome = regional cortical thickness).

This iso-voxel GE implementation of the MPRAGE sequence follows the ADNI-3 protocol.

4. T2-weighted FLAIR – 6 min

FLAIR (Fluid Attenuated Inversion Recovery) / Cube T2 FLAIR sequence

Parameters: Sagittal slices = 176, FOV = 256 x 256 mm, slice thickness = 1 mm, no gap, voxel size = 1 x 1 x 1 mm, TE = 119 ms, TR = 4800 ms, TI = 1473 ms, receiver bandwidth = 31.25 Hz.

The FLAIR image is used for morphometric analyses by providing a high-resolution T2-weighted contrast image to resolve dura and vessels from cortical gray matter. This improves the reliability of the cortical thickness analyses. It is also used to detect lesions and help identify the nature of incidental findings of structural anomalies. Follows the ADNI-3 protocol.

5. Single voxel MRS – 10 min

PRESS (Point Resolved Spectroscopy) sequence.

Parameters: Single voxel located in the occipital lobe centered on the primary visual area, oblique voxel size = 24 x 25 x 35 mm (21 mL), TE = 30 ms, TR = 2000 ms, 128 averages. For each water-suppressed scan, a water non-suppressed scan is acquired for use in water scaling to obtain absolute concentrations of metabolites (units of mmol/kg wet-weight brain). Time takes into account ~5 minutes for positioning of voxel and adjusting field homogeneity and transmitter power.

The single voxel MRS is used for regional brain metabolite analysis (17 metabolites including glutamate, N-acetylaspartate, total creatine, choline containing compounds and myo-inositol). GABA is not reliably determined.

6. Single voxel GABA-edited MRS – 11 min

MEGA-PRESS (Mescher-Garwood PRESS) sequence

Parameters: Single voxel with same location as scan 5, TE = 68 ms, TR = 2000 ms, 256 averages (128 ON – 128 OFF), editing pulses applied at 1.9 (ON) and 1.5 (OFF) ppm, macromolecule suppression on. For each water-suppressed scan, a water non-suppressed scan is acquired for use in water scaling to obtain absolute concentrations of metabolites (units of mmol/kg wet-weight brain).

The MEGA-PRESS MRS is used for regional brain GABA concentration analysis.

7. Cerebral Blood Flow (CBF) – 6 min

PCASL (Pseudo-Continuous Arterial Spin Labeling) 3D stack of spirals sequence

Parameters: Aaxial slices = 34, FOV = 240 x 240 mm, slice thickness = 4 mm, no gap, voxel size = 3.75 x 3.75 x 3.75 mm, TE = 9.8 ms, TR = 6000 ms, labeling duration = 1800 ms, post-labeling delay = 1800 ms, flip angle = 90°, spin labeling slab located 10 mm below cerebellum.

This PCASL scan is used for whole brain quantitative CBF analyses.

Total scan time = 45 min (leaves required 15 min for scanner setup and break-down in 1 hour slot)

Descriptive statistics of the data will be performed and presented. Continuous data will be reported as means \pm standard deviations or medians (interquartile ranges) and assessed with a parametric t-test or non-parametric equivalent. Differences before and after treatment will be assessed in paired tests, as appropriate. Additionally, in subgroup analyses, differences between all three groups (>75% responders, >50% responders, non-responders) will be assessed using analysis of variance (ANOVA) or Kruskal-Wallis tests. Categorical data will be presented as frequencies and proportions and assessed with a chi-square or Fisher's Exact test.

In order to assess our four primary outcomes over time and in relation to the differences observed conditional on the degree of response to galcanezumab, multivariate generalized linear modeling will be employed using generalized estimating equations (GEE). These models will consider the four binary outcomes simultaneously by specifying a binary outcome with a log link function. Fixed effects for time (0, 3, 6, 12 months), degree of response (headache frequency: coded as number of headache days), baseline headache frequency, and time x degree of response will be specified in the model. Participants will be the unit of clustering (to account for the repeated measures) with an AR1 covariance matrix to account for the expected degree of autocorrelation in the measurement occasions. An omnibus test for a shared effect (i.e., a joint change in all outcomes) will be conducted with sensitivity analyses considering measure-specific effects (i.e., a degree of change x outcome interaction). In this way, we will be able to examine the change in the outcomes over time, examine time-varying associations with degree of change in headache frequency, and consider if any of the outcomes are especially impacted by changes in headache frequency.

Although the associations will be conducted while treating degree of change in headache frequency as a continuous predictor, reporting of the effects will also be conducted using dichotomized versions of this predictor. Specifically, the associations will be reported for three groups of responders: non-responders (< 50% reduction), responders (> 50% reduction to \leq 75% responders), and super-responders (> 75% reduction).



The model estimates should be robust to missing data due to attrition. All data will be analyzed, with sensitivity models used to adjust the associations for additional prognostic predictors thought to be related to chance of attrition. If necessary, multiple imputation will be used as an additional sensitivity analysis.

Data will be stored on password protected computers behind the BIDMC firewall or in REDCap directly. Analyses will be conducted by a statistician at BIDMC within the Department of Anesthesia, Critical Care and Pain Medicine. Statistical analyses will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC).

d. **Data Interpretation**

- If galcanezumab treatment reduced prodromes, auras, interictal hypersensitivities to light and sound, and the number of triggers (such as skipping meals, sleeping too little, stress or post-stress, etc.) in patients in which it also reduced migraine days per month by more than 75% (the super-responders), we will conclude that the abnormal sensitivity of the migraine brain to deviation from homeostasis (hypothalamus) and to external stimuli is a result of the continuous bombardment of the brain with pain signals that originate outside the brain.
- If galcanezumab treatment shrinks the thickness of the somatosensory or reduces the enhanced BOLD signal in the visual cortex in patients in which it also reduced migraine days per month by more than 75% (the super-responders), we will conclude that the abnormal structural and functional changes seen previously in the migraine brain are caused by the continuous bombardment of the brain with pain signals that originate outside the brain.
- If galcanezumab treatment did not reduce occurrence of prodromes, auras, interictal hypersensitivities to light and sound, and the number of triggers (such as skipping meals, sleeping too little, stress or post-stress, etc.), or if it did not shrink the somatosensory cortex and reversed the hyperactivity in the visual cortex in patients in which it reduced migraine days per month by more than 75% (the super-responders), we will conclude that the abnormal sensitivity of the migraine brain to deviation from homeostasis (hypothalamus) or to external stimuli is a result of a condition that is internal to the brain (could be inherited or not) and that the reduction in the headache days was achieved due to the drug ability to block the activation of the nociceptors.
- If galcanezumab treatment did not eliminate aura in patients in which it reduced migraine days per month by more than 75% (the super-responders), we will conclude that galcanezumab acted on the trigeminovascular nociceptors – outside the blood brain barrier (BBB) – but not on the cortex – inside the bbb.
- If galcanezumab treatment reduced the occurrence of prodromes, auras, interictal hypersensitivity to light and sound in patients, and the number of triggers (such as skipping meals, sleeping too little, stress or post-stress, etc.) in which it did not reduce migraine days per month by more than 75% (the super-responders), we will conclude that the abnormal sensitivity of the migraine brain to deviation from homeostasis (hypothalamus) and to external stimuli are independent of pain signals that continue to invade the brain. In such case, we will conclude that galcanezumab mechanism of action is mainly central, inside the CNS. We will also conclude that the headache itself is likely to be independent of activation of meningeal nociceptors during migraine.
- If galcanezumab treatment shrinks the thickness of the somatosensory or reduces the enhanced BOLD signal in the visual cortex in patients in which it did not reduce migraine days per month by more than 75% (the super-responders), we will conclude that the abnormal structural and functional changes seen previously in the migraine brain are driven by mechanisms that are internal to the brain itself, its neurons, or reciprocal pathways.
- If the 3-month long galcanezumab treatment reduced incidence of prodromes, auras, and interictal hypersensitivities to light and sound, as well as cortical thickness and bold signal magnitude in the visual cortex (in responders) – and continue to reduce the monitored symptoms and triggers even further after 6 months treatment period, we will conclude that the brain requires a period that is longer than 3 month of being partially or completely 'pain-free' to allow neuronal plasticity to settle in and the brain to return to near normal functioning. If, however, the changes we monitor after 3 month remain similar at the 6 month post-treatment, we will conclude that a 3-month period is a sufficient time to allow galcanezumab to 'heal' the migraine brain.

This study design ensures that whatever the findings are, we will learn much about migraine pathophysiology and galcanezumab mechanisms of action.

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

- a. Between the ages of 18 and 65 years
- b. Been previously diagnosed with migraine (with or without aura), in accordance with the ICHD-3 criteria
- c. Experiences between 8 to 25 headache 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
- d. Onset of migraine at age 50 years or younger
- e. 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.)
- f. Participants need to have access to the internet and have their own device to complete the eDiary.
- g. 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. Currently using marijuana (including medical marijuana) or has used 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. 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. Contraindication to MRI

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

Migraine is common and disabling neurological disease. Migraine has been ranked 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, galcanezumab has been shown to be safe and efficacious in preventing migraine in EM and CM patients, and reduced disability and functional impairment. Galcanezumab 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 galcanezumab. Investigators believe that subjects with symptoms associated with migraine may benefit from monthly regimen of galcanezumab. 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 galcanezumab in this study are acceptable given the potential benefits of treatment.

HYPERSENSITIVITY REACTIONS

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

ANTICIPATED ADVERSE EVENTS

The most common adverse reaction of galcanezumab are constipation and 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 galcanezumab and placebo on any safety or tolerability outcomes with exception of injection site reaction, pruritus and swelling.

IMMUNOGENICITY

There is a potential for immunogenicity because galcanezumab is a therapeutic protein. In controlled studies with galcanezumab up to 6 months the incidence of anti-galcanezumab antibody was 4.8% (mostly neutralizing antibodies). In a 12 month open-label study, up to 12.5% of patients developed anti-galcanezumab antibodies (mostly neutralizing antibodies). Based on limited data, presence of anti-galcanezumab antibodies was not shown to affect pharmacokinetics, safety or efficacy of galcanezumab.

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.

IMAGE-RELATED RISKS

Metal of any kind is unsafe for the MRI procedure. Participants must remove all metal from their clothing and all metal objects from their person. They will not be allowed to bring any metal objects into the magnet room at any time. As such, the MRI is also not safe for people who have pacemakers, some ear implants, shrapnel injuries, or some types of metal or electric devices in their body; such persons will not be allowed to participate in the study. The study doctor will decide if participants who have undergone operations that have left metal in their bodies will be able to proceed with the scan.

People with a history of claustrophobia will also be excluded from the study, as lying in the MRI may trigger the phobia due to the sides and top of the scanner being very close to the participant's face and body.

REPRODUCTIVE RISKS

Because of the effects of this study medication on the developing fetus is not known, participants cannot be enrolled while pregnant and must refrain from becoming pregnant during the course of the study. Participants will be required to take a standard urine pregnancy test to verify that they are not pregnant before receiving the first dose of the study medication and before each MRI session.

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 the 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 be utilized 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.

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 the PI's primary clinic location in the BIDMC Comprehensive Headache Center at 1 Brookline Place 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 Comprehensive Headache Center at 1 Brookline Place in 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.

The study will be performed in standard patient rooms in the BIDMC Comprehensive Headache Center at 1 Brookline Place in Suite 406. This location provides 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 in Suite 406 as outpatient visits. The clinic visits will occur in the BIDMC Comprehensive Headache Center at 1 Brookline Place in Suite 406 and the MRI visits will occur at the BIDMC MRI center in the Ansin Building of 330 Brookline Avenue. Pregnancy testing will occur in the BIDMC MRI center.

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

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.

References

Lipton RB, Serrano D, Pavlovic JM, Manack AN, Reed ML, Turkel CC, Buse DC.
Improving the classification of migraine subtypes: an empirical approach based on
factor mixture models in the American Migraine Prevalence and Prevention (AMPP)
Study. *Headache*. 2014 May;54(5):830-49.

Torres-Ferrús M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich
P. When does chronic migraine strike? A clinical comparison of migraine according
to the headache days suffered per month. *Cephalalgia*. 2017 Feb;37(2):104-113.