Anti-CGRP neutralizing antibody for modulation of neurogenic inflammation in trigeminal and glossopharyngeal pain associated with small fiber neuropathy/fibromyalgia

A phase 1b clinical study

NCT04158752

Duke University Medical Center – Duke Health

PI Dr. Sweta Sengupta, Duke University Medical Center, Department of Neurology

Document Date: January 18, 2022

Investigator-Initiated Trial (IIT) protocol submitted to

Eli Lilly

Table of Contents

Title of Study:

Anti-CGRP neutralizing antibody for modulation of neurogenic inflammation in trigeminal and glossopharyngeal pain associated with small fiber neuropathy/fibromyalgia

Program Objective:
The primary objective of the proposed pilot study is to assess safety and effectiveness of galcanezumab in a 1b clinical trial setting when treating trigeminal and glossopharyngeal nerve pain. We propose to treat patients who suffer from trigeminal or glossopharyngeal nerve pain in the context of painful small fiber neuropathy.

Abstract
Neurogenic inflammation that critically depends on CGRP has been well-established in human migraine headaches, relying on data from clinical trials with –gepant compounds, and antibodies that block CGRP-signaling. Undoubtedly, migraine headaches are a highly prevalent human pain condition, which involves trigeminal pain transduction and –transmission.
That human migraine can be treated effectively with episodic injections of anti-CGRP antibodies begets the question whether these newly prescribe-able medications can be repurposed for other trigeminal pain conditions and the related glossopharyngeal cranial nerve pain which are known to involve neurogenic inflammation. Another pain condition with poor treatment options for sufferers is fibromyalgia, especially fibromyalgia with associated small fiber neuropathy which leads to systemic de-afferentiation of patients' sensory system. In this condition, there is strong evidence for presence of neurogenic inflammation, and it is a rational concept that neurogenic inflammation contributes to disease pathogenesis and especially to the dominating clinical symptom of pain.

We propose to treat patients (targeting enrollment of n=20) who suffer from trigeminal or glossopharyngeal nerve pain in the context of painful small fiber neuropathy. We predict that recruitment of these patients will not be a challenge in the PI's clinics, based on previous experience and ongoing referral practice. Primary criterion is to establish an excellent safety profile that recapitulates the favorable data recorded in migraineurs. The primary pain-related objective is reduction of pain and reduced use of rescue and other anti-pain medications.
Secondary pain-related objectives are improvement of circadian rhythm impairment by galcanezumab, improvement of serum markers for chronic inflammation including protein/peptide as well as small non-coding RNA molecules, and discovery of DNA polymorphisms that predispose treated patients to accentuated responses of either lack of response or particularly potent response.

Clinical Collaborators
Timothy Collins MD, Duke Neurology
Wolfgang Liedtke MD

Hypothesis/ Purpose

We hypothesize that the proposed galcanezumab regimen will be found safe in our patient population, and that provisionary evidence of its effectiveness will become apparent. We envision galcanezumab to target neurogenic inflammation in the trigeminal territory and neurogenic inflammation associated with small fiber neuropathy/fibromyalgia.

Treatment with a CGRP-neutralizing antibody, galcanezumab in this specific patient group, being seen in the PI's clinics on a regular basis, is rooted in the rationale of unmistakable presence of clinical signs of neurogenic inflammation in the painful territory, such as episodic swelling combined with redness/hyperemia, also relief by external cold application which typically patients with trigeminal or glossopharyngeal nerve pain abhor.

Primary Outcome Measures

Primary criterion is to establish an excellent safety profile that recapitulates the favorable data recorded in migraineurs. The primary pain-related objective is reduction of pain and reduced use of rescue and other anti-pain medication.

Inclusion Criteria

• G50.1 diagnosis (can encompass an add-on G50.0 and other headache G43…. codes), or G52.1 diagnosis code (with explicit mentioning of pain of glossopharyngeal origin) **AND** small fiber neuropathy diagnostic codes G63.3, G60.8, G62.8 (can encompass fibromyalgia diagnostic code M79.7)
• 18-80 years old
• not allergic to galcanezumab and other hu mAb biologics

Exclusion Criteria

• allergic to galcanezumab and other hu mAb biologics
• pregnancy

Study Design / Overview

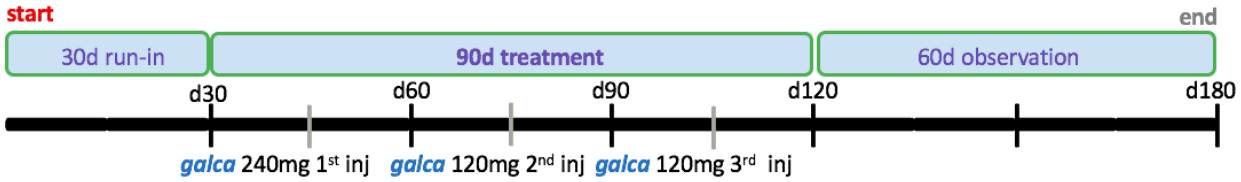
We propose to treat patients open label for 12 weeks, with galcanezumab, supplied by Eli Lilly, as add-on to all other therapeutic measures. We propose to use a 240mg/120mg/120mg regime, with subcutaneous (self-)injections every 4 weeks.

To reflect pain experienced by patients, the primary read-out is pain level on a 0-10 visual analog scale. We will be prompting patients to record a daily summary read at the end of each day.

The second criterion is reduction of intake of anti-pain medication (rescue PRN or regular) which the patients will record.

Chronic pain, especially fibromyalgia pain combined with trigeminal or glossopharyngeal nerve pain, is a potent disruptor of circadian rhythm. We strongly believe that this is an important and hitherto under-appreciated contributor to individual disease burden. Therefore, the third criterion is assessment of circadian rhythm function. We will assess this by having the patient rate subjectively how energetic they feel during awake day-time. Wearable activity monitors will be used to address how many hours patients sleep per

24h period, with detailed focus on total duration of sleep/rest and duration of night-time sleep only.
Before treatment, there will be a 4 week observation-only period, and another one 8 weeks post-treatment, so that the total study period will be 6 months.
We aim for 20 patients to be included in this study.



see more detailed graphics in the next section

In terms of ancillary, laboratory-based studies, we intend to draw blood before treatment and at the 45-, 75-, 105- and 135-day of treatment time-points. We will measure cytokine/chemokine/lipid pain- and inflammation markers in patients' serum, also determine microRNA in their serum, and genomic DNA polymorphisms, the latter only at baseline. Please see next section for more detail.

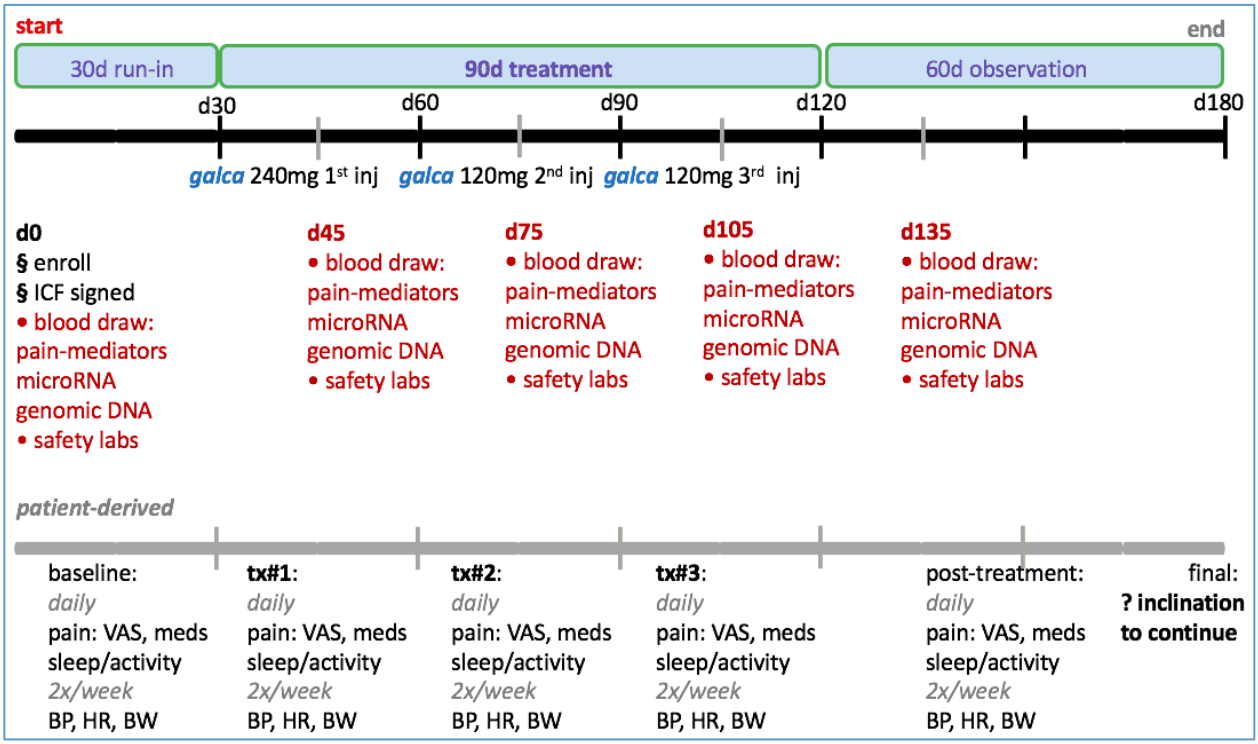
To establish safety of the anti-CGRP treatment in this patient cohort, blood draw at baseline and at the 45-, 75- , 105- and 135-days of treatment time-points will also include routine systemic sentinel/surveillance markers, namely comprehensive metabolic panel and complete blood count with differential, and complete urinalysis. No more than 45 ml of blood will be collected at any given visit.
In terms of additional safety parameters, we propose an open, patient-kept side-effect log, plus home-based recordings of blood pressure, heart rate and weight at a frequency of 2x/week.

We will set up a data and safety monitoring board for proper management and oversight of data handling and patient safety-related issue; see next section.

We expect to observe effective treatment, at least in a significant subgroup of patients. Effectiveness of treatment, also magnitude of any observed therapeutic effect will be correlated with the pain/inflammation proteinaceous, lipid and RNA-based biomarkers in patients' serum, also with any polymorphisms in the patients' genomic DNA.
We also expect galcanezumab treatment to show another record of safe treatment, our expectation sculpted by analysis of in-depth data from treatment of migraineurs. Yet we will remain vigilant and implement the proposed safety sentinel measures in order not to miss adverse effects. This appears prudent because trigeminal or glossopharyngeal nerve pain plus small-fiber neuropathy is a different underlying disorder than migraine, likely representing a higher prevalence in peri-menopausal female patients. We also believe it is likely that level of chronic pain suffering-associated stress will be higher in our study population than in migraineurs.
We also expect that the proposed studies will be very important for guiding future, more in-depth studies involving larger patient cohorts, placebo-controlled/double-blinded studies, which will possibly lead us toward a personalized-medicine approach.

Study Design Detail

1) Schedule of Activities over Time



2) Blood draw: detailed analysis

Before treatment, and at 45th, 75th, 105th and 135th day of treatment, we propose to assess the following blood parameters, related to pain-associated biomarkers in the systemic circulation.

For this, we propose to study cytokine/chemokine pain- and inflammation markers in patients' serum, using commercially available protein multiplex detection assays. In serum, the following 39 cytokines/chemokines/lipid mediators/peptides will be measured: EPO, GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, IL-17A/F, IL-17C, IL-17E/IL-25, IL-17F, IL-21, IL-22, IL-23, IL-27p28/IL-30, IL-31, IL-33, IP-10, KC/GRO, MCP-1, MIP-1α, MIP-1β, MIP-2, MIP-3α, TNF-α, VEGF-A, TGF-ß, CGRP, Resolvin-D1, Prostaglandin-E2. For these measurements, we will be using a human 35-plex ELISA (U-PLEX Biomarkers) and single ELISAs (Signosis; Cayman).

These are key mediators and indicators of pain and inflammation. We believe it will be feasible to conduct these assays. For each marker there is sufficient evidence supporting its role in pro-algesic inflammation or organismal response to tissue damage. We are

convinced that their ensemble will prove a powerful source of mechanistic data that will elucidate treatment responses to galcanezumab in our patient population.

In addition, we propose to detect systemic circulatory microRNAs. These molecules will be identified by RNA-seq starting with small RNA-preparation from patients' serum. This approach is preferred over a candidate approach since it is maximally unbiased. We believe that an unbiased approach will be more suitable because pain-associated circulatory miRNA markers are not firmly established, therefore a "candidate approach" is not even feasible. With an open, unbiased discovery approach of miRNAseq we minimize the risk to miss anything of relevance. The number of miRNAs is considered currently slightly >2000, thus very roughly 1/10 of the number of all protein-coding genes. MicroRNAs have been established robustly as biomarkers in specific malignancies, also with chronic inflammation, so that a tentative association with specific pain conditions appears an appealing opportunity to make these discoveries in our patient population.

Baseline blood draw (and only at that time point because it will not change through treatment) will also include preparation of genomic DNA from white blood cells to sequence the patients' genomic DNA whole-exome. Having these data available will position us favorably so that we can identify any genetic abnormalities (e.g. in pain-associated voltage-gated sodium channels, pain-TRP channels, inflammation-associated genes) in our patients. First we will be analyzing the genomic DNA profile for presence of pain susceptibility genes in known genes and their respective families, such as voltage-gated sodium channels, neurogenic inflammation pathway, opioid receptor signaling, MRGPR-X related pathway, pain-TRPs and associated proteins, ß-adrenergic signaling, COMT pathways, algogenic lipid mediator pathways, and more. After identification of particular high-responders and low/non-responders, we will try to identify association of these particular response patterns with any measured biomarker, including DNA polymorphisms, miRNA, lipid, protein/peptide markers.

3) Data Safety Monitoring Board (DSMB)

A DSMB (Data Safety Monitoring Board) will be set up headed by Dr David Pisetsky MD, Duke Dept of Medicine, who has no relationship with this study. Dr Pisetsky is a renowned clinician who has been involved with several clinical trials, was the Division Chief of Rheumatology for many years in the Duke Department of Medicine. The DSMB will also include Dr Richard L Boortz-Marx MD, of the Duke Dept of Anesthesiology, who is an experienced clinical trial physician and organizer, and a nationally renowned practitioner of pain medicine, in addition Beth Parente PA-C, a very experienced provider in painful cranial neuropathies, of the Duke Dept of Neurosurgery.

The Data and Safety Monitoring Board (DSMB) serves as an independent group of experts that advises the team that runs this study. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and advise on continuation of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the pain condition, galcanezumab, and the specific patient population

under study. During the trial, the DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. The DSMB should also assess the performance of overall study operations and any other relevant issues, as necessary.
Items reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Data quality, completeness, and timeliness;
- Adequacy of compliance with goals for recruitment and retention;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The DSMB should conclude each review with their recommendations to the Research Management Team (RMT). Recommendations regarding modification of the design and conduct of the study could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study because of serious concerns about subjects' safety.

Confidentiality must always be maintained during all phases of DSMB review and deliberations. DSMB members must maintain strict confidentiality concerning all privileged study results provided to them.

DSMB membership reflects appropriately involved medical disciplines, also takes into account the pilot nature of our study.

No member of the DSMB has direct involvement in the conduct of the study. No member has financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB.

Meetings are set once a year and will be scheduled more frequently in case adverse effects occur more than 2x/ month of a severe AE per quarter.

The initial DSMB meeting should occur preferably before the start of the trial or as soon thereafter as possible. At this meeting the DSMB will discuss the protocol and its roll-out, mandatory triggers set for data review or analyses. Guidelines will address stopping the study for safety concerns.

Once a study is implemented, the DSMB will convene as often as necessary, but at least once annually, to examine the accumulated safety and enrollment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed. A DSMB meeting may be requested by DSMB members, the PI, the Duke University IRB, or study Principal Investigator at any time to

discuss safety concerns. Decisions to hold ad hoc meetings will be made by the PI and DSMB Chair. Meetings may be held by conference calls or videoconferences or as face-to-face meetings. In the event a DSMB member cannot attend a meeting, he/she may participate by conference call, in addition can provide written comments to the DSMB Chair for consideration at the meeting.

4) Necessary patient equipment/materials to generate data-points when home

Patients will be provided with a 200-page paper booklet.
Each page is intended for 1 day. For each day, they will record a summary pain rating on a visual analog scale (VAS) from 0-10. Also for each day, they will document all medications taken, listing analgesic medication first, both prescription as well as over-the-counter. On another 0-10 VAS they will rate their subjective level of how energetic they felt. They will record length of sleep, night-time and daytime.
Patients will also be wearing wearable activity monitors. In case they already have such a device, it will be used (e.g iWatch, fitbit). In case they do not have one, they will be provided with such a device, a Huawei Terra-B19 Band 3 Pro. Instructions for use will be provided.

After final data acquisition by the RMT, the Huawei device will be left to the patient for their own future use.

The d180 page of the subjective rating protocol will contain the question "*Do you want to continue using Emgality (galcanezumab) for s.c. injection?*"
Importantly, handling and acquisition of these data will not record any HIPAA-pertinent PHI because the activity monitor will not record or store any of these. The 200-page booklet will be tagged with a unique ID number in front, back and on the side of the pages, being mindful not to include any PHI.

For 2x/week measurement of blood pressure, heart rate and body weight, patients will be supplied with the following devices so that these metrics can be acquired in their domestic environment:
home scale for body-weight
blood pressure and heart rate monitoring device

5) Patient Training and Instructions

At the initial visit, patients will receive detailed instructions how to fill out the subjective rating booklet, how to self-inject, and how to wear, use and handle the activity monitors, in case they will be provided with one, or how to make sure that their own activity monitor will record activity and sleep as intended.
Training how to self-inject Emgality will be provided by the study staff. Patients will also be provided with written instructions.

It will be verified that they understand the need to record and document blood pressure, heart rate and body weight 2x/week, to be documented on their daily log page.

6) Research Management Team (RMT)

The Research Management Team will consist of Principal Investigator, Sub-Investigators, Regulatory/Data Coordinator and Research Coordinator/Research Nurse
Dr Liedtke will be the Principal Investigator. He has the primary responsibility for ensuring the ethical conduct of this research study. This includes protecting human subjects' rights, safety and welfare, protocol compliance, and adherence to institutional, state and federal regulations and guidance, and for proper communication with the financial support source. He is responsible for ensuring informed consent is appropriately obtained from each participant and for appropriately maintaining study records. He is also responsible for complying with the financial and administrative policies and regulations associated with the award, overall fiscal management of the project, and conflict of interest disclosure. He will oversee all aspects of this trial, but some tasks can be delegated to other research team members. He will be responsible for ensuring that all research team members have appropriate education, training and qualifications to assume delegated study tests. All study team members are responsible for ensuring that the conduct of the study is compliant with institutional, state and federal regulations.
Dr Sweta Sengupta and Dr Timothy Collins will serve as sub-investigators.

Data entry and management will rely on a RedCap database that will be set up specifically for this study.,The Research Coordinator/Research Nurse will be provided by Duke's Neurology Clinical Research Unit at Morreene Road.

7) Risks and Adverse Reactions – Adverse Event (AE) management

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Duke University IRB to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The PI is responsible for the appropriate medical care of subjects during the study.
Investigators must document their review of each safety report.
The PI remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to galcanezumab or the study, or that caused the patients to discontinue galcanezumab before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained.
The frequency of follow-up evaluations of the AE is left to the discretion of the PI.
Lack of drug effect is not an AE.
After the informed consent form (ICF) is signed, study site personnel will record via case report form (CRF) the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the pain condition under treatment in this study. In addition, site personnel will record any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to galcanezumab and/or protocol procedure via CRF.
The PI will interpret and document whether or not an AE has a reasonable possibility of being related to galcanezumab, its injection, or a study procedure, taking into account the disease, co-morbid conditions, concomitant treatment or pathologies.

A “reasonable possibility” means that there is a cause and effect relationship between galcanezumab, and/or study procedure and the AE.
The PI answers “yes/no” when making this assessment.
Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.
If galcanezumab is discontinued for a given patient as a result of an AE, study site personnel must report this to the Duke IRB via CRF, clarifying if possible, the circumstances leading to discontinuations of treatment.

A severe AE (SAE) is any AE from this study that results in one of the following outcomes:
• death
• initial or prolonged inpatient hospitalization
• a life-threatening experience (that is, immediate risk of dying)
• persistent or significant disability/incapacity
• congenital anomaly/birth defect
• important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for fulfilling criteria of SAE. SAE reports are forwarded to the Duke University IRB. For each SAE, the Duke University IRB safety commission will decide within 48h whether the case will be forwarded to Eli Lilly immediately.
Study site personnel must alert the Duke IRB of any SAE within 24 hours of PI or any other member of the clinical team becoming aware of the event.
If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.
Pregnancy does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.
Investigators are not obligated to actively seek AEs or SAEs in subjects once they have completed the 90-day treatment period. However, if the investigator learns of any SAE, including a death, during the 60 day observational period, the PI must promptly notify the Duke IRB. This will also apply to an SAE after finishing the study if the PI considers the event reasonably possibly related to treatment with galcanezumab or study participation.

Suspected unexpected serious adverse reactions (SUSARs) are serious events that the investigator identifies as related to galcanezumab or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. The Duke IRB has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with

global regulations and the associated detailed guidances.

Enrolled patients will be instructed to contact the PI and his study team as soon as possible if the patient has a complaint or problem with galcanezumab so that the situation can be assessed.

AE reporting will be conducted as detailed in this section. To remember, this is an Investigator Initiated Trial (IIT) meaning that the PI, his clinical team and their institutional safety board (Duke IRB) are/represent the Investigator and Sponsor, resulting in the above AE, SAE, SUSAR and other reporting requirements and mandatory chains of communication. Updating and reporting of IIT progress to Eli Lilly will be conducted under separate agreement. Effective communication between the PI, his clinical team, the Duke IRB and Eli Lilly will be implemented. This will help minimize risk and enhance safety for study participants, also by leveraging the wealth of information that Eli Lilly has gathered on galcanezumab.

8) Inclusion/exclusion criteria detail

Inclusion criteria, in terms of diagnosis are: the patient has an assigned diagnosis of non-neuralgic trigeminal nerve pain G50.1, with all its permutations listed in the ICD10 explicitly allowed. Co-morbid trigeminal neuralgia G50.0 and G43. … related headache codes are allowed. As an alternative to trigeminal nerve pain G50.1, glossopharyngeal nerve pain will be another inclusion criterion, with a G52.1 diagnosis and explicit mentioning of pain mediated by or in the innervation territory of the glossopharyngeal nerve. In addition, patients have to be diagnosed with a painful small fiber neuropathy. This diagnosis is based on a skin biopsy or biopsy of an innervated surface epithelium with nerve fiber density count. The required ICD10 diagnostic codes are G63.3, G60.8, G62.8. Co-morbidity with a fibromyalgia-related disorder will be allowed, typically summarized under a diagnosis code of M79.7.

Importantly, the PI's clinics and referring clinics to his clinics encounter patients with this diagnosis on a high frequency.

For the rationale to have the above specific inclusion criteria, see "Abstract" on p3, and "Purpose" on p4. Very briefly, (i) access to the respective patient population appears not limited, (ii) neurogenic inflammation is strongly considered to function pro-algesically in trigeminal nerve pain (and by inference in glossopharyngeal nerve pain) **and** in small fiber neuropathy-associated pain, (iii) trigeminal or glossopharyngeal nerve pain associated with small fiber neuropathy/ fibromyalgia appears to be a hitherto unrecognized particular variant of painful cranial nerve disorder. Re point (i), this could be related to the development that the PI's clinics have become US national go-to centers for painful cranial nerve disorders. Especially re argument (iii), the phase Ib treatment study as proposed here will help us to define better this new pain disorder, which we strongly feel deserves separate and explicit recognition, also in terms of treatment response.

Age-wise, the protocol applies to patients between 18 and 80 years old.

Patients that have a history of allergy or allergy-like incompatibility with a biologic that contains a human or humanized monoclonal antibody will be excluded.

Likewise female patients of child-bearing age who are or want to become pregnant will be excluded. In case such a patient intends to participate, then she has to commit to a pregnancy prevention regimen that is based on hormonal contraceptive or intra-uterine device. This is stated explicitly in the Informed Consent Form.
These exclusion/ inclusion-relevant points will be ascertained and discussed explicitly during the initial visit. Agreement between patient seeking enrollment and investigator will be documented in the patient's electronic health record and in the ICF. As for the pregnancy issue, in female patients of child-bearing age, a pregnancy test will be administered at first visit.

9) Standard-of-care vs activities to be carried by the protocol
All activities related to the study as listed under **1) Timeline** will be carried by the protocol. In case safety-related laboratory parameters (comprehensive metabolic panel, complete blood count and urine-analysis) will be needed under a standard-of-care approach, then this will be followed and resulting data will be perused for this study. In all other cases and circumstances, the clinical activities will be carried by this protocol.

10) Recruitment plan
Patients will be recruited via the PI's clinics at Duke University, the Duke Clinics that typically refer to her attention and outside clinics and providers that refer to her as well, and DEDUCE database. In case of slow recruitment patient self-help and patient advocacy associations in the facial pain arena will be informed of the ongoing study to assist with recruitment. These organizations (Facial Pain Research Foundations, Facial Pain Association) are well-known to the PI.

11) Brief Statistical Analysis Plan
Only patients who complete the study will be included in the statistical analysis.

Response to treatment will be assessed by comparing pain metrics during the 90-day treatment period vs averaged 30 day "run-in". Outcome variables will consist of selected readout parameters of "pain metrics", namely pain subjective rating on VAS (0-10) and medication co-use. Additional outcome variables include circadian rhythm-associated metrics. A daily readout for each variable will be entered into their log by each patient, or by automatic activity reads from their motion tracking device. In similar manner, we will compare pain metrics during the 90-day treatment period vs 60-day post-treatment observation.

We intend to conduct the study with an n=20 patients to successfully complete the study. This selected number appears the most feasible and practicable number. We are confident that with an n=20 we will be in a position to do justice to the objective of initial assessment of the safety of galcanezumab in the condition under study, trigeminal or glossopharyngeal pain in the context of painful small fiber neuropathy/fibromyalgia.
Following completion of the study, we will have estimates of effect sizes and corresponding 95% confidence intervals providing information on the precision of the statistical estimates of treatment effect. Power analysis will be performed based on these estimates and will provide us with guidance for sample sizes of follow-up studies that aim for demonstrating effectiveness.
The statistical analysis will be based on a linear mixed model for repeated measures. The

time course of pain metrics reported during the treatment period will be compared with metrics during the run-in baseline. The covariance matrix describing the nature of correlations between repeated measures will be selected based on Akaike information criterion and Bayesian information criterion, as guided by our statistics software, SAS/STAT15.1. p-values <0.05 will be considered statistically significant. Effects of treatments will be investigated with the introduction of treatment as a binary covariate (we will evaluate the effects of pre- and post-treatment in two different models).

Patients' anti-pain treatment response will be correlated with blood markers for pain, inflammation and miRNA, and also for genomic markers. This approach will be pursued in order to identify candidate biomarkers that pre-dispose patients to experience an effective or non-effective treatment response. In case of recording any particular safety-related parameters, correlation of these markers to safety metrics will also be conducted. Association between molecular biomarkers and pain- and activity-related metrics will be evaluated (i) at each time point separately using a linear regression model; (ii) by modeling the association across all time points and including time covariate in the linear regression model. The ensemble of these approaches will help determine the periods when pain or activity-related metrics and molecular markers co-evolve and become highly correlated.

Appendix

Informed Consent Form

The PI and her team are responsible for:
• ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
• ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of galcanezumab
• answering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue her participation in the study.
• ensuring that a copy of the ICF is provided to the patient and is kept on file.
• ensuring that the medical record includes a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized study team-member obtaining the informed consent must also sign the ICF.