Title Page

Protocol Title: A Multicenter, Open Label Study Assessing the Efficacy of AJOVY® (fremanezumab-vfrm) on Interictal Migraine Related Burden

Protocol Number: 19-001TE

Amendment Number: NA

Investigational Product: 225 mg fremanezumab-vfrm

Study Phase: Phase 4

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Approval Date: 05-Oct-2020

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Principal Investigator Signatory:

Investigative Site Principal Investigator	**Date**

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multicenter, Open Label Study Assessing the Efficacy of AJOVY® (fremanezumab-vfrm) on Interictal Migraine Related Burden

Objectives and Endpoints:

Objectives	Endpoints
Primary	
1. To evaluate the efficacy of fremanezumab-vfrm on interictal migraine related burden between 50% responders and non-responders, via change in Migraine Interictal Burden Scale (MIBS-4) score during the 12-week treatment phase.	1. Change in monthly Migraine Interictal Burden Scale (MIBS-4) scores from baseline to each 4-week treatment period during the 12-week treatment period comparing between 50% responders and non-responders within subjects treated with fremanezumab-vfrm.
Secondary	
To evaluate the efficacy of fremanezumab-vfrm between 50% responders and non-responders on the following parameters during the 12-week treatment phase: 1. Change in migraine days 2. Change in Neuro-QoL Sleep Disturbance Short Form (SDSF) 3. Change in General Self-Efficacy Short Form (GSE-SF) 4. Change in PROMIS-29 5. Change in Work Productivity and Activity Impairment- Migraine (WPAI-M)	Change from baseline to each 4-week treatment period during the 12-week treatment period comparing between 50% responders and non-responders within subjects treated with fremanezumab-vfrm on the following: 1. Number of migraine days 2. Neuro-QoL Sleep Disturbance Short Form (SDSF) scores 3. General Self-Efficacy Short Form (GSE-SF) scores 4. PROMIS 29 scores 5. Work Productivity and Activity Impairment- Migraine (WPAI-M) scores

Objectives	Endpoints
6. Change in Brief Measure of Worry Severity (BMWS) 7. To evaluate the safety and tolerability of subjects treated with fremanezumab-vfrm	6. Brief Measure of Worry Severity (BMWS) scores 7. Safety and tolerability of fremanezumab-vfrm in study participants via collection of adverse events and safety evaluations.
Exploratory	
To evaluate the efficacy of fremanezumab-vfrm between 50% responders and non-responders on the following parameters during a 12-week treatment phase: 1. Change in activity and sleep measured though a wearable device	1. Change from baseline to each 4-week treatment period during the 12-week treatment period comparing between 50% responders and non-responders within subjects treated with fremanezumab-vfrm on activity and sleep measured though a wearable device.

Overall Design:

This is a single group, multicenter, open-label study with a study population of patients who meet International Classification of Headache Disorders 3rd edition (ICHD-III) criteria for migraine with or without aura and have 4 to 22 migraine days per month.

Disclosure Statement:

This is a single-group supportive care study with one arm and no masking.

Number of Participants:

A maximum of 40 participants will be enrolled to study intervention.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in the clinical study following completion of the informed consent process and the 4-week run-in period. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study via at least one administration of IP, are not considered enrolled.

Intervention Groups and Duration:

All participants in this single-group study will complete a 4-week run-in period. After the run-in period, eligible participants will be enrolled to study intervention and enter a 12-week treatment period.

Data Monitoring Committee: No

1.2. Schedule of Activities (SoA)

Procedure	Screening	Treatment				Early Discontinuation
	Visit 1 **Day -33 to Day -28**	**Visit 2 (Enrollment)** **Day 1**	**Visit 3** **Day 29 ± 3**	**Visit 4** **Day 57 ± 3**	**Visit 5** **Day 85 ± 3**	
Informed consent	X					
Height	X					
Weight	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Demography	X					
Physical examination	X	X	X	X	X	X
Neurological examination	X					
Medical history (includes migraine history and substance usage)	X					
Prior and concomitant medications history	X					
Urine pregnancy test (WOCBP only)	X	X	X	X	X	X
Laboratory assessments (CMP)	X				X	X
12-lead ECG	X				X	X

Procedure	Screening	Treatment				Early Discontinuation
	Visit 1 **Day -33 to Day -28**	**Visit 2 (Enrollment)** **Day 1**	**Visit 3** **Day 29 ± 3**	**Visit 4** **Day 57 ± 3**	**Visit 5** **Day 85 ± 3**	
PHQ-9	X	X	X	X	X	X
Inclusion and exclusion criteria	X	X				
Dispense activity tracker	X					
Dispense diary URL and instructions	X					
Migraine Interictal Burden Scale (MIBS-4)	X	X	X	X	X	X
Neuro-QoL Sleep Disturbance Short Form (SDSF)		X	X	X	X	X
PROMIS-29		X	X	X	X	X
Work Productivity and Activity Impairment-Migraine (WPAI-M)		X	X	X	X	X
General Self-Efficacy Short Form (GSE-SF)		X	X	X	X	X
Brief Measure of Worry Severity (BMWS)		X	X	X	X	X
AE review		X	X	X	X	X
SAE review		X	X	X	X	X
Diary review		X	X	X	X	X
Concomitant medication review		X	X	X	X	X
IP injection		X	X	X		

2. Introduction

2.1. Study Rationale

This study is being conducted to evaluate the efficacy and safety of fremanezumab-vfrm on interictal migraine related burden in adult participants age 18 to 65 years old, who meet International Classification of Headache Disorders 3rd edition (ICHD-III; Appendix 5) criteria for migraine with or without aura and have 4 to 22 migraine days per month.

2.2. Background

The burden of Migraine can extend well beyond the pain phase and affect more than just work and school attendance. Patients with frequent Episodic Migraine and Chronic Migraine are known to experience the impact of migraine even on days they do not have migraine pain or associated symptoms such as nausea, photophobia, or phonophobia. Most of the focus of migraine management is placed on migraine pain and associated symptom relief and the interictal burden of migraine is often overlooked.

Individuals experiencing frequent migraine attacks regularly find themselves engaged in preparatory or compensatory behaviors, hoping to minimize lost productivity or compromised quality of life, even before attacks begin. These types of behaviors originate from the fear and dread of the inevitable migraine attacks to come and lead to a significant diminution of quality of life before the pain has even started[1,2]. Patients frequently cancel plans with family and friends or avoid making commitments in the first place based on their anticipation of a migraine episodes. Even worse, these fears and behavior changes also tend to exacerbate co-occurring conditions such as anxiety, depression, and sleep disorders, further contributing to poor quality of life. Unfortunately, migraine prevention trials have traditionally focused on reduction of migraine days as a primary endpoint and have largely ignored the significant health and lifestyle burdens also associated with migraine and associated symptoms.

2.3. Significance

This study aims to capture changes in functional impact, including but not limited to the assessment of the interictal burden of migraine after participants begin treatment with fremanezumab-vfrm. In addition to using a variety of scales to capture these changes this study will use activity trackers to allow detailed monitoring of daily activity and sleep patterns. This approach has been used in a variety of clinical trials over a wide range of disease states with success and its addition will enrich the results obtained through administration of traditional questionnaires. Specific assessments of worry, work productivity, and self-efficacy will

complement the overall impact of patients' lives directly and indirectly related to response to CGRP blockade. It is hypothesized that participants treated with fremanezumab-vfrm will demonstrate improvements in a variety of measures of daily activity and attitudes. Results from this study will be a significant contribution to the medical literature and bring value to providers as they manage expectations with patients regarding the functional impact of fremanezumab-vfrm on migraine prophylaxis efforts. Moreover, this study aims to bridge the gap between the traditional focus on reduction of migraine days as a primary endpoint and the numerous other significant health and lifestyle burdens also associated with migraine and associated symptoms.

2.4. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of fremanezumab-vfrm may be found in the Package Insert.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
1. To evaluate the efficacy of fremanezumab-vfrm on interictal migraine related burden between 50% responders and non-responders, via change in Migraine Interictal Burden Scale (MIBS-4) score during the 12-week treatment phase.	1. Change in monthly Migraine Interictal Burden Scale (MIBS-4) scores from baseline to each 4-week treatment period during the 12-week treatment period comparing between 50% responders and non-responders within subjects treated with fremanezumab-vfrm.
Secondary	
To evaluate the efficacy of fremanezumab-vfrm between 50% responders and non-responders on the following parameters during the 12-week treatment phase: 1. Change in migraine days 2. Change in Neuro-QoL Sleep Disturbance Short Form (SDSF) 3. Change in General Self-Efficacy Short Form (GSE-SF) 4. Change in PROMIS-29 5. Change in Work Productivity and Activity Impairment- Migraine (WPAI-M) 6. Change in Brief Measure of Worry Severity (BMWS) 7. To evaluate the safety and tolerability of subjects treated with fremanezumab-vfrm	Change from baseline to each 4-week treatment period during the 12-week treatment period comparing between 50% responders and non-responders within subjects treated with fremanezumab-vfrm on the following: 1. Number of migraine days 2. Neuro-QoL Sleep Disturbance Short Form (SDSF) scores 3. General Self-Efficacy Short Form (GSE-SF) scores 4. PROMIS 29 scores 5. Work Productivity and Activity Impairment- Migraine (WPAI-M) scores 6. Brief Measure of Worry Severity (BMWS) scores 7. Safety and tolerability of fremanezumab-vfrm in study participants via collection of adverse events and safety evaluations.

Objectives	Endpoints
Exploratory	
To evaluate the efficacy of fremanezumab-vfrm between 50% responders and non-responders on the following parameters during a 12-week treatment phase: 1. Change in activity and sleep measured though a wearable device	1. Change from baseline to each 4-week treatment period during the 12-week treatment period comparing between 50% responders and non-responders within subjects treated with fremanezumab-vfrm on activity and sleep measured though a wearable device.

4. Study Design

4.1. Overall Design

This is a multicenter, open label study assessing the interictal impact of fremanezumab-vfrm in participants with migraine. The study population will consist of 40 participants 18 to 65 years old, with at least 4 and up to 22 migraine days per month (inclusive) following ICHD-III criteria for migraine with or without aura.

At Visit 1, the participant will sign the informed consent indicating they are willing to participate in the study and will provide basic demographic information, have a comprehensive review of their medical history and prior and concomitant medications. The subject's migraine history will be reviewed and confirmed in accordance with the ICHD-III, by the PI or an appropriately delegated and qualified sub-Investigator. A physical and neurological examination (including vital signs) will be performed as well as a 12-lead Electrocardiography (ECG), screening comprehensive metabolic panel (CMP) labs, and the PHQ-9 will be completed. Women of childbearing potential (WOCBP) will complete a urine pregnancy test. All participants will complete the MIBS-4 questionnaire. Inclusion and Exclusion criteria will also be reviewed. Participants who meet the study criteria will be dispensed the activity tracker and its associated phone application instructions, as well as their unique Daily Headache Diary (DHD) URL and its instructions. Participants will then enter into a 28-day run-in period. During the 28-day run-in period, all participants will be monitored through the use of electronic Daily Headache Diary (DHD) to ensure they continue to meet all inclusion criteria, and none of the exclusion criteria. During this run-in period, participants will continue treating their migraines and other defined conditions with their usual treatment providing it has been stable for a minimum of 3 months. Daily electronic diaries will be used to assess symptoms and treatment response throughout the run-in period.

Visit 2 will take place 28 to 33 days following Visit 1. Those participants who (1) continue to meet eligibility criteria (2) experienced 4-22 migraine days that meet ICHD-III criteria for migraine and (3) have completed at least 23/28 diary days will be eligible to be enrolled into the study. At this visit a physical examination (including vital signs) will be performed, WOCBP will complete a urine pregnancy test, and all participants will complete the PHQ-9. Medical history and/or adverse events and concomitant medications will be reviewed and updated as needed. Participant's DHD will be reviewed for compliance, and participants will complete the following questionnaires:

- MIBS-4

- SDSF
- PROMIS-29
- MPAI-M
- BMWS
- GSE-SF

Finally, all eligible participants will receive an injection of 225 mg fremanezumab-vfrm. Participants will continue completing diary headache diaries for the remainder of the trial.

Visits 3-5 will take place on days 29 (+/-3d), 57 (+/-3d), and 85 (+/-3d), following Visit 2. At each visit: a physical examination (including vital signs) will be performed, WOCBP will complete a urine pregnancy test, and all participants will complete the PHQ-9. Medical history and/or adverse events and concomitant medications will be reviewed and updated as needed. Participant's DHD will be reviewed for compliance, and participants will complete the following questionnaires:

- MIBS-4
- SDSF
- PROMIS-29
- MPAI-M
- BMWS
- GSE-SF

Finally, all eligible participants will receive an injection of 225 mg fremanezumab-vfrm at visits 3 and 4. Visit 5 (End of Study) will not include injections but will include comprehensive metabolic panel (CMP) laboratory.

4.2. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit (Visit 5) or the last scheduled procedure shown in the SoA.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. willing to participate and sign informed consent;
2. ability to read and understand informed consent and study procedures, including able to use the electronic Daily Headache Diary;
3. in good general health based on investigator's judgment;
4. must be between 18 to 65 years of age, inclusive, at time of Visit 2;
5. have migraine with and/or without aura meeting the diagnostic criteria listed in the International Classification of Headache Disorders 3rd edition (ICHD-III; Appendix 5);
6. verification of headache frequency through prospectively collected baseline information during the 28-day screening/baseline phase reporting 4-22 migraine days and no more than 22 total headache days;
7. onset of migraine before age 50;
8. able to differentiate migraine from other primary headache types allowed in the study (e.g., tension-type headache);
9. stable history of migraine at least 3 months prior to screening with at least some discreet headache free periods;
10. not currently taking a migraine preventive OR has been taking a stable dose of a preventive for at least 90 days prior to screening and agrees to not start, stop, or change medication and/or dosage during the study period;

    * * participants on migraine preventive should have stable headache pattern
11. women may be included only if they have a negative pregnancy test at screening and baseline, are sterile, or postmenopausal. Women of childbearing potential (WOCBP) engaging in potentially procreative intercourse must use highly effective birth control methods for the duration of the study (i.e., starting at screening). Definitions of WOCBP, sterile and postmenopausal women, male contraception, and highly effective and acceptable birth control methods are to be determined based on investigator's judgment;

12. demonstrated compliance with the electronic Daily Headache Diary during the 28-day screening/baseline phase as defined by entry of headache data on a minimum of 23 days;
13. is willing to wear activity/sleep tracker throughout the duration of the trial;
14. has a smartphone and willing to install activity tracker app on phone.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. unable to understand the study requirements, the informed consent, or complete headache records as required per protocol;
2. pregnant, actively trying to become pregnant, or breast-feeding;
3. history of substance abuse and/or dependence that would interfere study conduction, in the opinion of the Investigator;
4. history of impaired renal function that, in the investigator's opinion, contraindicates participation in this study;
5. suffers from a serious illness, or an unstable medical condition, one that could require hospitalization, increase the risk of adverse events, or compromise data integrity (ie, likely require changes in con meds or lead to other medical investigations or treatments during the study).
6. a psychiatric condition, in the opinion of the investigator, that may affect the interpretation of efficacy and safety data or contraindicates the participant's participation in the study;
7. received nerve blocks or trigger point injections in the previous 8 weeks or plans to receive them during the study;
8. prior exposure in the last 6 months, or 5 half-lives, to biologics or drugs specifically targeting the calcitonin gene-related peptide (CGRP) pathway;
9. has failed more than 3 classes of medications for the prevention of migraine or >6 migraine preventive medications of any type due to lack of efficacy;
10. received any investigational agents within 30 days prior to Visit 1 (6 months for any investigational biological products unless previous study blind has been broken and subject was known to have received placebo);
11. plans to participate in another clinical study at any time during this study;
12. history of medication overuse of opioids or butalbital, as defined by opioid or butalbital use ≥10 days/month in each of the previous 3 months or during run-in period; Medication

Overuse Headache (MOH) with other medication types will be allowed but must be documented;

13. unstable medication use for migraine prevention (changes in the last 3 months);
14. clinically relevant lab results at screening as determined by the investigator;
15. clinically relevant or significant ECG abnormalities as determined by the investigator, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 500 msec;
16. history of any of the following cardiovascular conditions:
    a. Moderate to severe congestive heart failure (New York Heart Association class III or IV);
    b. Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
    c. Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
17. Subjects known to have active HIV or untreated Hepatitis C infection;
18. score of > 0 on question 9 on Patient Health Questionnaire (PHQ-9) at any visit;
19. have any other condition, that in the judgment of the investigator, would make the participant unsuitable for inclusion, or would interfere with the participant participating in or completing the study.

5.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention at Visit 2. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be permitted in certain situations to rescreen, after discussion with the study medical monitor. However, participants that test positive, through urine testing, as pregnant, or are determined to be of significant suicide risk, are not allowed to be rescreened.

Rescreened participants should be assigned a new participant number (i.e., different than the initial screening participant number).

6. Study Intervention

6.1. Study Intervention(s) Administered

Description:

Fremanezumab-vfrm is a calcitonin gene-related peptide (CGRP) antagonist subcutaneous injection indicated for the preventive treatment of migraine in adults, see product insert for detailed information.

Dosing and administration:

225 mg/1.5 mL solution via single-dose prefilled syringe administered subcutaneously once monthly in the abdomen, thigh, or upper arm.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or appropriately trained and delegated designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the storage and final disposition of unused investigational product are provided in the Package Insert.
5. See the Package Insert for complete preparation, handling, storage, and accountability details.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study with one arm; potential randomization and/or blinding concerns are not applicable.

6.4. Study Intervention Compliance

All participants will be dosed at the site and will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the Case report form (CRF).

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants should not currently be taking a migraine preventive or have been taking a stable dose of a preventive for at least 90 days prior to screening and agrees to not start, stop, or change medication and/or dosage during the study period.

6.5.1. Prohibited Medications

Nerve blocks or trigger point injections in the previous 8 weeks prior to study or at any time during the study are prohibited. Prior exposure to biologics or drugs specifically targeting the CGRP pathway in the 6 months, or 5 half-lives, prior to or during the study are also prohibited.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will not remain in the study. See the SoA for data to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Migraine Interictal Burden Scale (MIBS-4)

Participants will complete an electronic version of the MIBS-4 within the clinic during visits outlined in the SoA.

8.1.2. Migraine Days via Daily Headache Diary (DHD)

Headache and Migraine data will be recorded by the participants into an electronic daily headache diary (DHD) throughout the study. The DHDs are web-based and can be completed on any internet enabled device. Participants will be given their unique DHD URL at Visit 1. Site personnel will be responsible for instructing participants on the requirement for timely and daily completion of the DHD. Participants will be asked to record diary data each day for the previous day (24-hour period). If a participant does not experience a headache in the previous 24-hour period, the diary must still be completed as instructed. Participant's diaries may vary day to day based on their responses. All participants should have at least 80% compliance with diary completion throughout the length of the study. Participants will record headache severity, symptoms, use of acute medications, as well as additional assessments as required.

8.1.3. Neuro-QoL Sleep Disturbance Short Form (SDSF)

Participants will complete an electronic version of the SDSF within the clinic during visits outlined in the SoA.

8.1.4. General Self-Efficacy Short Form (GSE-SF)

Participants will complete an electronic version of the GSESS within the clinic during visits outlined in the SoA.

8.1.5. PROMIS-29

Participants will complete an electronic version of the PROMIS-29 within the clinic during visits outlined in the SoA.

8.1.6. Work Productivity and Activity Impairment- Migraine (WPAI-M)

Participants will complete an electronic version of the WPAI-M within the clinic during visits outlined in the SoA.

8.1.7. Brief Measure of Worry Severity (BMWS)

Participants will complete an electronic version of the BMWS within the clinic during visits outlined in the SoA.

8.1.8. Activity and Sleep via wearable device

Participants' activity and sleep data will be recorded via a sponsor-provided wearable device (e.g., Fitbit or similar). Participants may also be required to install the wearable device's phone application on their personal phones in order for the data to be transferred to the sponsor. Site personnel will be responsible for instructing participants on the requirement(s) of the wearable device and its associated phone application if applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical and Neurological Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, and Gastrointestinal systems. Height and weight will also be measured and recorded.
- A complete neurological examination will be performed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3. Electrocardiograms

- 12-lead ECG's will be obtained as outlined in the SoA (see Section 1.3). The heart rate, PR, QRS, QT, and QTc intervals will be measured/calculated. Investigators will read final EKG's and determine any abnormalities. The overall interpretation and determination of the clinical relevance of ECG findings will be the responsibility of the investigator

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and Clinvest and the medical monitor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with fremanezumab-vfrm should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Baseline assessment of suicidal ideation and behavior/ intervention emergent suicidal ideation and behavior will be monitored during the study using PHQ-9.

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF) until Visit 5 as specified in the SoA (Section 1.3).

All AEs will be collected from the start of intervention until Visit 5 as specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively solicit reports of AE’s or SAE’s after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, within five half-lives after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, female partners of male participants will be collected after the start of study intervention and until 5 terminal half-lives after the last dose. Pregnancies will be followed until delivery.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

Not applicable, all treatments will be delivered in clinic by investigator or designee.

8.5. Pharmacokinetics

Not applicable, pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

Not applicable, genetics are not evaluated in this study.

8.7. Biomarkers

Not applicable, biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable, immunology assessments are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Not applicable, medical resource utilization and health economics are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis of this study is that participants' global Migraine Interictal Burden Scale (MIBS-4) scores will not be statistically different between 50% responders and non-responders from baseline (Visit 2) to any 4-week treatment period during the 12-week treatment period after 3 months dose of 225 mg fremanezumab-vfrm.

9.2. Sample Size Determination

To determine the needed sample size for this study we utilized G*Power[3] Version 3.1.9.3 to conduct a power analysis for the Primary Endpoint analysis (repeated measures ANOVA, within-between interaction) comparing baseline MIBS-4 scores to treatment month(s) MIBS-4 scores between 50% responders and non-responders. Based on prior research, we expect an approximate equal proportion of responders and non-responders in this open-label study. The power analysis indicated that a total of 36 subjects would be adequate to detect a medium effect ($f = 0.25$), with alpha set at 0.05, and a power of .95. To account for a 10% early withdrawal rate, a total of 40 subjects should be enrolled in the study.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Full Analysis Population	All participants enrolled and with at least one administration of IP, will be included in this study population. The Full Analysis Population will be used to analyze the primary efficacy and safety endpoints

Note: Other populations may be defined in the SAP.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. In case of a discrepancy, the SAP will supersede the protocol.

9.4.1. General considerations

An alpha of .05 will be used for statistical significance for all statistical tests. All statistically significant multivariate analyses will be followed by univariate post-hoc tests. Appropriate multiple comparison adjustments will be made if needed. A Last Observation Carried Forward (LOCF) method will be utilized to impute missing data where appropriate.

9.4.2. Primary endpoint

Data for the primary endpoint will be statistically analyzed via a repeated measures ANOVA, within-between interaction comparing baseline MIBS-4 scores to treatment month(s) MIBS-4 scores between 50% responders and non-responders.

9.4.3. Secondary endpoint(s)

Data for each of the secondary outcome measures will be statistically analyzed for within and between group changes via analysis of variance (ANOVA), *t*-tests, or chi-square tests as appropriate.

9.4.4. Tertiary/exploratory endpoint(s)

The Statistical Analysis Plan will describe any planned tertiary/exploratory analyses in greater detail.

9.4.5. Other safety Analyses

There will not be a formal statistical analysis for safety endpoints (adverse events, etc.); however, all adverse events will be summarized via tables and descriptive statistics as appropriate.

9.5. Interim Analyses

Not Applicable, i.e., there is not a planned interim analysis for this study.

9.6. Data Monitoring Committee (DMC)

Not Applicable, i.e., there is not a DMC for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred outside of study site will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the study team in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, the reported trial data are accurate, complete, and verifiable, and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization cGCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the Contract Research Organization (CRO).
- Details of clinical site monitoring are documented in a Monitoring Plan (MP). The MP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No

records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Data for this trial will be primarily collected in a web-based electronic data capture (EDC) REDCap platform. The EDC access will be supplied by the sponsor with relevant training support to sites. Sites will be responsible for training study subjects in the EDC system. All data specified should be captured by the site personnel or participants in the EDC system. When possible, all eCRFs are to be completely filled out by personnel administering the study procedures in real-time at the time of the visit. All eCRFs that are completed in real-time at the time of the visit will be considered source documentation for this study. When allowed by the site's IRB, any data entered on an eCRF which was not entered into REDCap in real-time at the time of the visit, or where such data originated from an external paper source document (e.g., signed Informed Consent Form (ICF) signature page, laboratory, procedure findings, etc.), will require paper source documents to be uploaded into the REDCap system to allow for source data verification monitoring. When a site's IRB does not allow for specific paper source documents to be uploaded into REDCap (e.g., the ICF signature pages, etc.), then those paper source documents will be reviewed during on-site monitor visits.
- It is the investigator's responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRF and confirmation the data is accurate, authentic, attributable, complete, and consistent. The investigator or sub-investigator must sign the CRFs within the EDC system to attest the information contained with the CRF is true and causality of any safety information has been assessed. All data must be reviewed and signed by the investigator or sub-investigator at the conclusion of the study for each subject. The CRFs should not be made available in any form to third parties, without written permission from the sponsor.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Teva (financial sponsor) before submission. This allows the financial sponsor to protect proprietary information and to provide comments.
- Teva (financial sponsor) will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the financial sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Urine Pregnancy Testing

Table 1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Other Screening Tests	The results of each test must be entered into the CRF.			

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

A SAE is defined as any untoward medical occurrence that, at any dose:
• Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.

AE and SAE Recording

- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

Assessment of Causality
• There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor and Medical Monitor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to sponsor and medical monitor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the sponsor and medical monitor by telephone.

SAE Reporting to Sponsor and Medical Monitor via an Electronic Data Collection Tool
• Contacts for SAE reporting can be found in the investigative site file.

SAE Reporting to Sponsor and Medical Monitor via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor and medical monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the investigative site file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Definitions of Woman of Childbearing Potential (WOCBP), sterile and postmenopausal women, male contraception, and highly effective and acceptable birth control methods are to be determined based on investigator's judgment; however, women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive AJOVY® (fremanezumab-vfrm).
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5. Appendix 5: International Classification of Headache Disorders, 3rd edition: Migraine with and without aura

1.1 Migraine without aura

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

1.2 Migraine with aura

Description: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
    1. visual
    2. sensory
    3. speech and/or language
    4. motor
    5. brainstem
    6. retinal
C. At least three of the following six characteristics:
    1. at least one aura symptom spreads gradually over ≥5 minutes
    2. two or more aura symptoms occur in succession
    3. each individual aura symptom lasts 5–60 minutes
    4. at least one aura symptom is unilateral
    5. at least one aura symptom is positive
    6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

10.6. Appendix 6: Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ANOVA	Analysis of variance
BMWS	Brief Measure of Worry Severity
CFR	Code of Federal Regulations
CGRP	Calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CMP	Comprehensive metabolic panel
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRO	Contract Research Organization
DHD	Daily headache diary
DMC	Data Monitoring Committee
ECG	Electrocardiography
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GSE-SF	General Self-Efficacy Short Form
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICHD-III	International Classification of Headache Disorders 3rd edition
IEC	Independent Ethics Committee(s)
IRB	Institutional Review Board(s)
LOCF	Last observation carried forward
MIBS-4	Migraine Interictal Burden Scale
MOH	Medication Overuse Headache
MP	Monitoring Plan
PHQ-9	9-Item Depression Patient Health Questionnaire
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SDSF	Neuro-QoL Sleep Disturbance Short Form
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
WOCBP	Women of Childbearing Potential
WPAI-M	Work Productivity and Activity Impairment- Migraine

11. References

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