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.

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		

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.

- 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.

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.

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.

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.

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.

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.

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

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

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

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

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;

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.

- 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.

9.4.1. 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.

10.1.3. 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).

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.

11. References

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