Title Page

Protocol Title:	A Multicenter, Open Label Study Assessing the Efficacy of erenumab on Functional Impact of Migraine
Protocol Number:	19-001AM
Amendment Number:	N/A
Investigational Product:	140 mg erenumab-aooe
Study Phase:	Phase 4
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Regulatory Agency Identifier Number(s):

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Version History

This statistical analysis plan (SAP) for Study 19-001AM is based on the protocol dated 16-Sep-2020.

SAP Version	Date	Change	Rationale
1	13-Oct-2021	Not applicable	Original version
2	23-Mar-2022	Revised Section 4.1.1 Missing Data	Clarification of how to handle missing data

1. Introduction

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of erenumab-aooe on the overall functional impact of migraine.	Change in Migraine Functional Impact Questionnaire (MFIQ) overall impact on usual activities item score from baseline to the final 4-week treatment period within subjects treated with erenumab-aooe.
Secondary	
To evaluate the efficacy of erenumab-aooe on specific aspects of the functional impact of migraine	Change in Migraine Functional Impact Questionnaire (MFIQ) domain scores from baseline to the final 4-week treatment period within subjects treated with erenumab-aooe: • Impact on physical functioning • Impact on usual activities • Impact on emotional functioning • Impact on social functioning
To evaluate the efficacy of erenumab-aooe on the following parameters during each 4-week treatment period:	Change from baseline to each 4-week treatment month within subjects treated with erenumab-aooe on the following:
• Functional impact of migraine	Global Migraine Functional Impact Questionnaire (MFIQ) scores: • Overall impact on usual activities • Impact on physical functioning • Impact on usual activities • Impact on emotional functioning • Impact on social functioning
• Migraine interictal burden	• Migraine interictal burden scale (MIBS-4) scores
• Migraine days	• Number of migraine days
• Work Productivity and Activity Impairment	• Work Productivity and Activity Impairment- Migraine (WPAI-M) scores
• Sleep disturbance	• Neuro-QoL Sleep Disturbance Short Form (SDSF) scores
• Self-Efficacy	• General Self-Efficacy Short Form (GSE-SF) scores

Objectives	Endpoints
• Severity of worry	• Brief Measure of Worry Severity (BMWS) scores
Exploratory	
To evaluate the efficacy of erenumab on activity and sleep.	Change from baseline to each 4-week treatment month within subjects treated with erenumab-aooe on activity and sleep measured though a wearable device.
To evaluate the efficacy of erenumab on functional impact of migraine.	Change from baseline to each 4-week treatment month within subjects treated with erenumab-aooe on Functional Assessment of Migraine Scale (FAMS) scores.
To evaluate the correlation between the Functional Assessment of Migraine Scale (FAMS) and other migraine related Patient Reported Outcome (PRO) measures.	Correlation between Functional Assessment of Migraine Scale (FAMS) and the following migraine related Patient Reported Outcome (PRO) measures: • Global Migraine Functional Impact Questionnaire (MFIQ) • Migraine interictal burden scale (MIBS-4) • Work Productivity and Activity Impairment- Migraine (WPAI-M) • Neuro-QoL Sleep Disturbance Short Form (SDSF) • General Self-Efficacy Short Form (GSE-SF) • Brief Measure of Worry Severity (BMWS)
Safety	
To evaluate the safety and tolerability of participants treated with erenumab-aooe.	Safety and tolerability of erenumab-aooe in study participants via collection of adverse events and safety evaluations.

1.2. Study Design

This is a multicenter, open label study assessing the interictal impact of erenumab-aooe in participants with migraine. The study population will consist of 54 participants 18 to 65 years old, with at least 4 and up to 20 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. A physical and neurological examination (including vital signs) will be performed as well as a 12-lead Electrocardiography (ECG), screening CMP labs, and the PHQ-9 will be completed. Women of childbearing potential (WOCB) will complete a urine pregnancy test. All participants will complete the MFIQ 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 4-20 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, WOCB 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:

- MFIQ
- MIBS-4
- WPAI-M
- SDSF
- GSE-SF
- BMWS
- FAMS

Finally, all eligible participants will receive an injection of 140 mg erenumab-aooe. 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, WOCB 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:

- MFIQ
- MIBS-4
- WPAI-M
- SDSF
- GSE-SF
- BMWS
- FAMS

Finally, all eligible participants will receive an injection of 140 mg erenumab-aooe. Visit 5 (End of Study) will not include injections but will include comprehensive metabolic panel (CMP) laboratory.

1.2.1. 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					
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					
PHQ-9	X	X	X	X	X	X
Inclusion and exclusion criteria	X	X				
Dispense activity tracker	X					
Dispense diary URL and instructions	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**	
Migraine Functional Impact Questionnaire (MFIQ)	X	X	X	X	X	X
MIBS-4		X	X	X	X	X
Work Productivity and Activity Impairment-Migraine (WPAI-M)		X	X	X	X	X
Neuro-QoL Sleep Disturbance Short Form (SDSF)		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
Functional Assessment of Migraine Scale (FAMS)		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. Statistical Hypotheses

The null hypothesis of this study is that participants' global Migraine Functional Impact Questionnaire (MFIQ) overall impact on usual activities item score will not be statistically different from baseline (Visit 2) to end of study (Visit 5) after 3 months dose of 140 mg erenumab-aooe.

2.1. Multiplicity Adjustment

Given the small sample size and open-label nature of the study, no multiplicity adjustments will be made to control for family-wise type 1 error.

3. Analysis Sets

Participant Analysis Set	***Description***
Full	• *All* participants *enrolled and with at least one administration of IP, will be included in this analysis set. The Full Analysis set will be used to analyze the efficacy and safety endpoints.*

4. Statistical Analyses

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.
- Univariate post-hoc tests will utilize appropriate multiple comparison adjustments (Bonferroni, Tukey, etc.) as needed.
- If a variable name (e.g., from REDCap Cloud or Fitabase) is directly used in this document, it will appear in this format: **[VARIABLE]**
- 95% Confidence Intervals will be used when necessary.

4.1.1. Missing Data

Missing data for full analysis population participants will be imputed as follows:

- Missing values on questionnaire items will be handled according to the questionnaire's scoring manual. When no guidance is specified in a questionnaire scoring manual, missing items will be left null and the score and/or sub-score will be imputed using a last observation carried forward (LOCF) method. This type of imputation replaces the missing value with the last observation value obtained for the participant.
- Missing DHD entries (Monthly Migraine Days) will be imputed as follows:
    - $<$ 14 DHDs completed: Participant's average MMDs for that study period will be replaced with their last study period's MMD using the LOCF method.
    - $\geq$ 14 DHDs completed: Participant's average MMDs for that study period will be imputed based on the data available in that study period and prorated to 28 days.
- Missing Garmin data (Steps and Sleep) will be imputed as follows:
    - $<$ 14 days synced: Participant's average steps and/or sleep for that study period will be replaced with their last study period's steps and/or sleep using the LOCF method.
    - $\geq$ 14 days synced: Participant's steps and/or sleep for the missing day will be imputed using the participant's mean steps and/or sleep for the data available in that study period.

4.2. Primary Endpoint Analysis

Data for the primary endpoint will be statistically analyzed via a within groups, repeated measures *t*-test, comparing change in participant's MFIQ Global Item Overall Impact on Usual Activities (item # 16) scores from baseline (Visit 2) to the final 4-week treatment period (Visit 5).

4.2.1. Definition of Endpoint

The MFIQ is a 26-item self-report questionnaire. It is designed to measure the impact of migraine on physical, social, and emotional functioning over 4 domains: Physical Function (PF), Usual Activities (UA), Social Function (SF), and Emotional Function (EF). **A single global item, Overall Impact on Usual Activities, assessing overall difficulty doing everyday activities is scored separately.** Final transformed scores range from 0-100, with higher scores indicating more impact on the participant. For this endpoint we will be measuring changes in participant's response on the single MFIQ Global Item Overall Impact on Usual Activities (item # 16). The item's transformed score can range from 0-100, with higher scores indicating more impact on the participant.

4.2.2. Main Analytical Approach

The MFIQ Global Item Overall Impact on Usual Activities is defined as item #16 on the MFIQ. Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Missing data will be imputed as outlined in the Migraine Functional Impact Questionnaire User Manual and Scoring Guide Version 1.0 (Appendix 6.3.1). The scores used to measure the primary endpoint will be taken using the participant's self-reported data entered into the MFIQs administered at Visit 2 and Visit 5 (or Early Discontinuation). The null hypothesis of this study is that participants' global MFIQ overall impact on usual activities item score will not be statistically different from baseline (Visit 2) to End of Study (Visit 5 or Early Discontinuation) after 3 months dose of 140 mg erenumab-aooe.

4.3. Secondary Endpoint Analysis

Data for each of the secondary outcome measures will be statistically analyzed for within group changes using repeated measures *t*-tests and/or repeated measures analysis of variance (ANOVA) with follow-up univariate tests as appropriate.

4.3.1. Change in Migraine Functional Impact Questionnaire (MFIQ) Domain Scores from Baseline to the Final 4-Week Treatment Period

4.3.1.1. Definition of Endpoint

The MFIQ is a 26-item self-report questionnaire. It is designed to measure the impact of migraine on physical, social, and emotional functioning over 5 domains: Physical Function (PF), Usual Activities (UA), Overall impact on Usual Activities, Social Function (SF), and Emotional Function (EF). Final transformed scores range from 0-100, with higher scores indicating more impact on the participant. The specific domain scores to be analyzed for this endpoint include impact on Physical Functioning (PF), impact on Usual Activities (UA), impact on Emotional Functioning (EF), and impact on Social Functioning (SF).

4.3.1.2. Main Analytical Approach

MFIQ domain scores will be derived as outlined in the Migraine Functional Impact Questionnaire User Manual and Scoring Guide Version 1.0 (Appendix 6.3.1). Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Missing data will be imputed as outlined in the Migraine Functional Impact Questionnaire User Manual and Scoring Guide Version 1.0 (Appendix 6.3.1). Data will be statistically analyzed via within groups, repeated measures *t*-tests, comparing change in participant's specific MFIQ domain scores from baseline (Visit 2) to End of Study (Visit 5 or Early Discontinuation).

4.3.2. Change in Migraine Functional Impact Questionnaire (MFIQ) Global and Domain Scores from Baseline to Each 4-Week Treatment Period

4.3.2.1. Definition of Endpoints

The MFIQ is a 26-item self-report questionnaire. It is designed to measure the impact of migraine on physical, social, and emotional functioning over 5 domains: Physical Function (PF), Usual Activities (UA), Overall impact on Usual Activities, Social Function (SF), and Emotional Function (EF). Final transformed scores range from 0-100, with higher scores indicating more impact on the participant. For this endpoint we will be measuring participant's response on the single MFIQ Global Item Overall Impact on Usual Activities (item # 16), as well as impact on the Physical Functioning (PF), Usual Activities (UA), Emotional Functioning (EF), and Social Functioning (SF) domains.

4.3.2.2. Main Analytical Approach

Global as well as the specific MFIQ domain scores will be derived as outlined in the Migraine Functional Impact Questionnaire User Manual and Scoring Guide Version 1.0 (Appendix 6.3.1). Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Missing data will be imputed as outlined in the Migraine Functional Impact Questionnaire User Manual and Scoring Guide Version 1.0 (Appendix 6.3.1). Data will be analyzed via a repeated measures ANOVA comparing change in participant's global and specific MFIQ domain scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.3.3. Change in Migraine Interictal Burden Scale (MIBS-4) Scores from Baseline to Each 4-Week Treatment Period

4.3.3.1. Definition of Endpoint

The MIBS-4 is a 4-item, self-administered questionnaire which measures interictal migraine-related burden in 4 domains: impairment in work or school, impairment in family and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress. The MIBS-4 total score is derived from the summation of all four questions on each MIBS-4. Answer options for the MIBS-4 are coded as: 0 = *Don't know/NA*, 0 = *Never,* 1 = *Rarely*, 2 = *Some of the time*, 3 = *Much of the time*, 4 = *Most or all of the time*. The range of total MIBS-4 score for each

time point is 0 to 12 (with higher scores indicating severe interictal burden of migraine on the participant's daily activities).

4.3.3.2. Main Analytical Approach

See Appendix 6.3.2 for MIBS-4 scoring information. Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this secondary endpoint will be analyzed via a repeated measures ANOVA comparing changes in participant's Migraine Interictal Burden Scale (MIBS-4) scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.3.4. Change in Migraine Days from Baseline to Each 4-Week Treatment Period

4.3.4.1. Definition of Endpoint

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 using the participant's unique log in credentials. Site personnel will be responsible for instructing participants on the requirement for timely and daily completion of the DHD.

Clinic visits are to occur every 28 days throughout the study; however, in practice, there may or may not be an exact 28-day duration between two consecutive visits. As such, participants may have more or less than 28 diary entries between two consecutive visits. To account for this, the following will be utilized:

- **Baseline**: eDiary information entered during the *last* 28 continuous days of the run-in period will serve as the "baseline" for calculating change from baseline. For example, if a participant's run-in period is 31 days long, and the participant entered eDiary information for all 31 days, the last 28 days (leading up to first drug administration) will be used to calculate and derive endpoint variables, with the first three eDiary entries (days 1, 2, and 3) being discarded from the analysis datasets.

- **Treatment Months**: If a participant enters more than 28 days of eDiary information between clinic visits during the treatment phase of the study, the *first* 28 continuous day's eDiary entries for each period/month will be used for analyses. For example, if a participant has a duration of 31 days between Visit 2 and Visit 3, and the participant entered eDiary information for all 31 days, the first 28 days (following Visit 2) of eDiary information will be used to calculate and derive endpoint variables, with the last three eDiary entries (days 29, 30, and 31) being discarded from the analysis datasets.

Migraine headache days are defined in this study as an attack within a calendar day (00:00 to 23:59) that meet at least one of the two following criteria:

1. A headache attack that includes all of the following criteria:

A. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

B. 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)

C. During headache at least one of the following:

1. nausea and/or vomiting

2. photophobia and phonophobia

2. A headache attack of any duration with relief (defined as a "Yes" answer to the eDiary question "*Did you get relief from taking the above medication(s) yesterday?"* **[HD_RLFYN])** from the following migraine-specific acute medication(s):

- Advil (Ibuprofen)
- Aleve (Naproxen)
- Amerge (Naratriptan)
- Axert (Almotriptan)
- Butabitol
- Cafergot (Ergotamine Tartrate/Caffeine)
- Cambia (Diclofenac Potassium)
- Cefaly
- DHE 45 (Dihydroergotamine)
- Ergomar (Ergotamine Tartrate Sublingual Tablets)
- Excedrin Migraine
- Fioricet
- Fiorinal
- Frova (Frovatriptan)
- gammaCore Sapphire
- Imitrex (Sumatriptan)
- Indocin (Indomethacin)
- Maxalt (Rizatriptan)
- Midrin (Isometheptene Mucate, Dichloralphenazone and Acetaminophen)
- Migerot (Ergotamine Tartrate/Caffeine Suppository)
- Migranol
- Migril (Ergotamine, Cylizine, and Caffeine)
- Namenda (memantine)
- Onzetra (Sumatriptan Nasal Powder)
- Prednisone

- Relpax (Electriptan)
- Reyvow (Lasmiditan)
- Sumavel (Sumatriptan Needleless Injection)
- Tivorbex (Indomethacin)
- Treximet (Sumatriptan/Naproxen)
- Tylenol (Acetaminophen)
- Zembrace (Sumatriptan injection)
- Zomig (Zolmitriptan)
- Zorvolex (Diclofenac)

4.3.4.2. Main Analytical Approach

Only data from those participants who meet criteria for the Full Analysis set will be analyzed. 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.

This frequency of migraine days will be derived from the participants' eDiary entries. The eDiary entries are based on the count of days with migraine headaches for each 28-day time points (baseline, treatment month 1, treatment month 2, treatment month 3). Participants with less than 80% diary compliance for any study period (defined as <23 completed eDiaries during that study period/month) will be considered Missing Data for that entire study period/month. The number of migraine days for these study periods/months will be imputed using the LOCF method. Data for this secondary endpoint will be analyzed via a repeated measures ANOVA comparing participant's mean change in the number of migraine days from baseline to each of the 4-week treatment periods. Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.3.5. Change in Work Productivity and Activity Impairment – Migraine (WPAI-M) Scores from Baseline to Each 4-Week Treatment Period

4.3.5.1. Definition of Endpoint

The Work Productivity and Activity Impairment-Migraine (WPAI-M) is a 6-item self-administered questionnaire that measures work productivity and the amount of time missed from work due to migraine. Scores are based on a percentage, so the range of scores is 0-100%, with higher scores indicating greater impairment and less productivity.

4.3.5.2. Main Analytical Approach

See Appendix 6.3.3 for WPAI-M scoring information. Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this secondary endpoint will be analyzed via a repeated measures ANOVA comparing changes in participant's total WPAI-M scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.3.6. Change in Neuro-QoL Sleep Disturbance Short Form (SDSF) Scores from Baseline to Each 4-Week Treatment Period

4.3.6.1. Definition of Endpoint

The Neuro-QoL Sleep Disturbance Short Form (SDSF) is an 8-item, self-administered questionnaire which measures quality of sleep including difficulties and perception of sleep satisfaction. Possible scores range from 8 to 40, with higher scores indicating worse sleep habits.

4.3.6.2. Main Analytical Approach

See Appendix 6.3.4 for SDSF scoring information. The variable used to measure the secondary efficacy endpoint of change in Neuro-QoL Sleep Disturbance Short Form (SDSF) between treatment month scores will be calculated using the scales online scoring service (https://www.assessmentcenter.net). By using the online scoring service participants raw scores for this endpoint will be calculated into T-Scores which will allow for a standardized comparison between the treatment months. Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this secondary endpoint will be analyzed via a repeated measures ANOVA, comparing mean changes in participant's total SDSF scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.3.7. Change in General Self-Efficacy Short Form 4a (GSE-SF) Scores from Baseline to Each 4-Week Treatment Period

4.3.7.1. Definition of Endpoint

The General Self-Efficacy Short Form 4a (GSE-SF) is a 4-item, self-administered questionnaire where the participant is asked to rate their confidence in managing situations, problems, and events. Scores range from 4-20. Higher scores indicate the participant has more self-efficacy managing difficult situations.

4.3.7.2. Main Analytical Approach

See Appendix 6.3.5 for GSE-SF scoring information. The variable used to measure GSE-SF between treatment month scores will be calculated using the scales online scoring service (https://www.assessmentcenter.net). By using the online scoring service participants raw scores for this endpoint will be calculated into T-Scores which will allow for a standardized comparison between the treatment months). Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this secondary endpoint will be analyzed via a repeated measures ANOVA comparing mean changes in participant's total GSE-SF scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.3.8. Change in Brief Measure of Worry Severity (BMWS) Scores from Baseline to Each 4-Week Treatment Period

4.3.8.1. Definition of Endpoint

The Brief Measure of Worry Severity (BMWS) is an 8-item, self-administered questionnaire that measures various components of dysfunctional worry. The BMWS total score is derived from the summation of all eight questions. Answer options for the BMWS are coded as: 0 = *Not true at all,* 1 = *Somewhat true*, 2 = *Moderately true*, 3 = *Definitely true*. The range of total BMWS score is 0 to 24 (with higher scores indicating more worry within the participant).

4.3.8.2. Main Analytical Approach

See Appendix 6.3.6 for BMWS scoring information. Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this secondary endpoint will be analyzed via a repeated measures ANOVA, comparing mean changes in participant's total BMWS scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.4. Exploratory Endpoint Analysis

Data for each of the exploratory outcome measures will be statistically analyzed for within group changes comparing baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). via a repeated measures analysis of variance (ANOVA) and/or dependent *t*-tests tests as appropriate, as well as bivariate correlations.

4.4.1. Change in Activity and Sleep from Baseline to Each 4-Week Treatment Period

4.4.1.1. Definition of Endpoint

The variables used to measure change in activity and sleep will be derived from participant's activity tracker they are to wear and sync daily. The participants' data are collected throughout

the course of the study. The data are synced on their app from the activity tracker and all information is then sent to Fitabase (https://www.fitabase.com).

- **Activity** will be defined by totaling the participants steps **[Steps]** from each day per treatment period.
- **Sleep** will be defined by totaling the participant's seconds of sleep **[DeepSleepDurationInSeconds]** + **[LightSleepDurationInSeconds]** from each day per treatment period. Sleep seconds will be converted to minutes for reporting purposes.

4.4.1.2. Main Analytical Approach

All participant files from Fitabase will be downloaded and coded according to the current version of the Fitabase Garmin Data Dictionary (Last updated version 6/4/2020 as of time of writing). Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this exploratory endpoint will be statistically analyzed via a repeated measures ANOVA, comparing baseline changes in activity and sleep to each of the treatment month(s) activity and sleep. Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.4.2. Change in Functional Assessment of Migraine Scale (FAMS) Total Scores from Baseline to Each 4-Week Treatment Period

4.4.2.1. Definition of Endpoint

Two versions of the Functional Assessment of Migraine Scale (FAMS) were administered to participants, including Research (FAMS-R) and Research Supplement (FAMS-RS). FAMS total score consists of all 27-items from both FAMS-R and FAMS-RS, self-administered in the form of a questionnaire, which evaluates the complete patient with migraine and their response to treatment. The FAMS total score is derived from the summation of all 27 questions. The range of total FAMS score is 27 to 135 (with lower scores indicating greater daily life burdens due to migraine).

4.4.2.2. Main Analytical Approach

See Appendix 6.3.7 for FAMS scoring information. Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this exploratory endpoint will be analyzed via a repeated measures ANOVA, comparing mean changes in participant's Functional Assessment of Migraine Scale (FAMS) total scores from baseline (Visit 2) to each of the 4-week treatment periods (Visit 3, 4, and 5). Significant changes will be followed up using within groups, repeated measures *t*-tests as needed.

4.4.3. Correlation Between Functional Impact of Migraine Scale (FAMS) Total and Domain Subscale Scores and Other Migraine Related Patient Reported Outcome (PRO) Measures

4.4.3.1. Definition of Endpoint

See section 4.4.2.1 for full definition of FAMS total score. The FAMS-R consists of 18 items. Scores can be derived as the Total Score from the summation of all 18 items (range 18-90) or as the Functioning Subscale Score from the summation of all items except 10 and 17 (range 16-80). Both the Total and Functioning Subscale Scores interpret lower scores as an indication of greater daily life burdens due to migraine. Additionally, the FAMS-R includes a Medicine Subscale Score from the summation of only items 10 and 17 (range 2-10), which interprets lower scores as an indication of lower confidence in the efficacy of migraine medication.

The FAMS-RS consists of 9 items. Scoring is divided across three subscales: Finance/Insurance Score (summation of items 1-3), Doctor/Provider Score (summation of items 4-6), and Education Score (summation of items 7-9), all of which range from 3-15. All subscales interpret lower scores as a greater day-to-day burden across the related subscale items. The PRO measures include Global MFIQ (see section 4.2.1), MIBS-4 (see section 4.3.3.1), WPAI-M (see section 4.3.5.1), SDSF (see section 4.3.6.1), GSE-SF (see section 4.3.7.1), and BMWS (see section 4.3.8.1) scores.

4.4.3.2. Main Analytical Approach

Only data from those participants who meet criteria for the Full Analysis set will be analyzed. Data for this exploratory endpoint will be analyzed via bivariate correlations between FAMS (total and subscales) and each of the above listed PRO measures. See Appendix 6.3 for scoring information on each of the measures.

4.5. Safety Analyses

The protocol states safety analyses would evaluate the safety and tolerability of participants treated with erenumab-aooe via collection of adverse events and safety evaluations. However, there will not be a formal statistical analysis for safety endpoints; rather, all safety endpoints will be summarized via tables and descriptive statistics as appropriate. Planned time points for all safety assessments are provided in the SoA.

4.5.1. Adverse Events (AEs)

Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 will be used to code all adverse events. AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or identified by research staff during study safety assessment procedures. These AE descriptions will be updated in the final report via mapping to the MedDRA Naming Hierarchy, using verbatim terms (e.g., feeling

queasy) mapped to MedDRA Preferred Terms (PT) (e.g., Nausea), Highest Level Term (HLT), Highest Level Group Term (HLGT) and System Organ Class (SOC). Final AE tables will be created using the most appropriate MedDRA hierarchy for each AE class.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or serious adverse event (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 Appendix 4 for Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting AEs.

4.5.1.1. Adverse Events of Special Interest

Based on the known warnings and precautions identified in AIMOVIG (erenumab) prescribing information, summary tables will be created for the below adverse events of special interest reported by all participants regardless of frequency.

4.5.1.1.1. Injection Site Reactions

This will include the subset of adverse events with a MedDRA coded HLT of *Injection Site Reaction*.

4.5.1.1.2. Constipation

This will include the subset of adverse events with a MedDRA coded PT of *Constipation*.

4.5.1.1.3. Hypertension

This will include the subset of adverse events with a MedDRA coded PT of *Hypertension*.

4.5.2. Additional Safety Assessments

Additional adverse events grouped by MedDRA coded SOC (unless further specificity is listed below or required) with ≥5% occurrence in participants treated with erenumab-aooe will be supplemented with tables of the below evaluations.

4.5.2.1. Clinical Laboratory Evaluation

- 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.
- 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.

4.5.2.2. Electrocardiograms (ECG)

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.2.1). The heart rate, PR, QRS, QT, and QTc intervals will be measured/calculated. Investigators will read final ECG's and determine any abnormalities. The overall interpretation and determination of the clinical relevance of ECG findings will be the responsibility of the investigator.
- AE table will be supplemented if ≥5% of participants treated with erenumab-aooe have AEs reported due to an abnormal ECG finding that have a MedDRA coded SOC of *Cardiac disorders* or *ECG investigations*.

4.5.2.3. Physical and Neurological Examination Findings

- 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.
- AE table will be supplemented if ≥5% of participants treated with erenumab-aooe have AEs reported that have a MedDRA coded PT of *Weight increased* or *Weight decreased*.
- AE tables will be supplemented if ≥5% of participants treated with erenumab-aooe have reported AEs MedDRA coded as:
    - HLGT = *Neurological disorders not elsewhere classified (NEC)*
    - SOC = *Cardiac disorders*
    - SOC = *Respiratory, thoracic and mediastinal disorders*
    - SOC = *Gastrointestinal disorders*

4.5.2.4. Suicidal Ideation

Participants being treated with erenumab-aooe 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.

AE table will be supplemented if ≥5% of participants treated with erenumab-aooe have AEs reported that have a MedDRA coded HLGT of *Suicidal and self-injurious behaviours NEC*.

4.5.2.5. Vital Signs

The following vital signs will be collected during the study:

- Blood pressure and pulse measurements.
- 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.
- AE tables will be supplemented if ≥5% of participants treated with erenumab-aooe experience potentially significant vital sign change AEs including those outlined below:
    - AEs that have a MedDRA coded PT of:
        - *Blood pressure systolic decreased*
        - *Blood pressure systolic increased*
        - *Blood pressure diastolic decreased*
        - *Blood pressure diastolic increased*
    - AEs that have a MedDRA coded PT of *Heart rate decreased* or *Heart rate increased*.
    - AEs that have a MedDRA coded PT of *Body temperature decreased* or *Body temperature increased*

4.6. Other Analyses

Not Applicable, i.e., there are no other planned analysis for this study.

4.7. Interim Analysis

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

4.8. Changes to Protocol-planned Analyses

Not Applicable, i.e., there are no changes to the protocol-planned analysis for this study.

5. Sample Size Determination

A meta-analysis of commonly used patient reported outcome (PRO) effect sizes was conducted to determine the expected effect size for the primary endpoint[3]. The meta-analysis revealed participants on erenumab 140mg had an average change score on commonly used PROs with an effect size of $d = 0.87$. Additionally, prior research on the MFIQ showed an average correlation of $r = 0.59$ between the global MFIQ scores and these regularly utilized PROs[4]. Due to the differences in study design between this study and prior studies, the novelty of the MFIQ and the uncertainty of its effect size, and to correct for potential replication errors[5], we lowered the expected effect size to a more moderate effect size of $d = 0.50$.

To determine the needed sample size for this study we utilized G*Power Version 3.1.9.3 to conduct a power analysis for the primary endpoint analysis comparing baseline global MFIQ scores to the final 4-week treatment period's global MFIQ scores utilizing a within group, repeated measures *t*-test. We utilized the conservative effect size of $d = 0.50$, alpha set at 0.05, and a power of .95. With these parameters the power analysis indicated a total of 54 participants would need to be analyzed to detect this effect with .95 power.

6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
ANOVA	Analysis of variance
BMWS	Brief Measure of Worry Severity
CMP	Comprehensive metabolic panel
CRF	Case report form
DHD	Daily headache diary
ECG	Electrocardiography
EF	Emotional Function
FAMS	Functional Assessment of Migraine Scale
FAMS-R	Functional Assessment of Migraine Scale- Research
FAMS-RS	Functional Assessment of Migraine Scale- Research Supplement
GSE-SF	General Self-Efficacy Short 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)
IP	Investigational Product
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MFIQ	Migraine Functional Impact Questionnaire

Abbreviation or Term	Definition/Explanation
MIBS-4	Migraine Interictal Burden Scale
PF	Physical Function
PHQ-9	9-Item Depression Patient Health Questionnaire
PRO	Patient reported outcome
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SDSF	Neuro-QoL Sleep Disturbance Short Form
SF	Social Function
SoA	Schedule of Activities
UA	Usual Activities
WOCB	Women of Childbearing Potential
WPAI-M	Work Productivity and Activity Impairment- Migraine

6.2. Appendix 2: International Classification of Headache Disorders, 3rd edition: Migraine with and without aura

6.2.1. 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.

6.2.2. 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.

6.3. Appendix 3: Patient Reported Outcomes Scoring Manuals

6.3.1. Migraine Functional Impact Questionnaire (MFIQ)

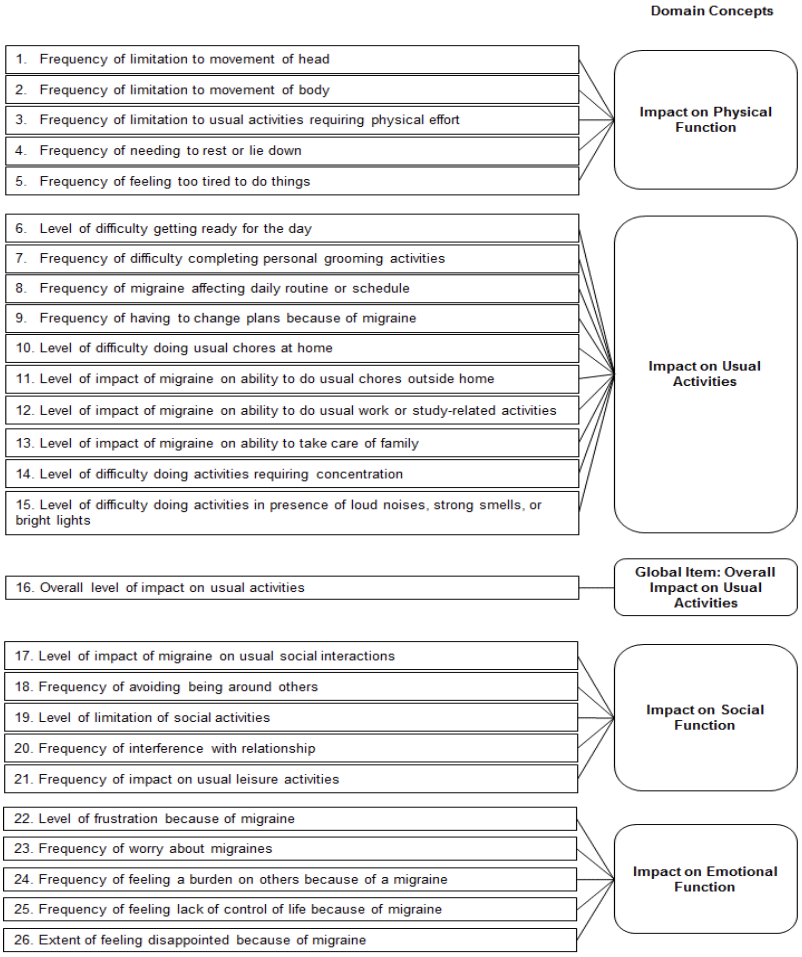


Figure 1. MFIQ Conceptual Framework

6.3.1.1. Scoring

MFIQ items are scored on a 5-point response scale. Items ask about "level of difficulty" with activities, "frequency of impact," or "level of impact." Five items also include a "does not apply" response option.

Item responses are summed to generate four domain scores: impact on Physical Function (PF; 5 items), Usual Activities (UA; 10 items), Social Function (SF; 5 items), and Emotional Function (EF; 5 items). A single global item assessing overall difficulty doing everyday activities is scored separately. A four-factor model showed the best fit to the data in an exploratory factor analysis. Five items were dropped from the draft version based on results from item-level analyses and qualitative interview results, resulting in the final 26-

item instrument (version 2.0). Item response theory and a unidimensional CFA confirmed the four-factor structure and unidimensionality of the domains.

Domain sum (raw) scores range from 5-25 for the PF domain, 10-50 for the UA domain, 1-5 for the global item, 5-25 for the SF domain, and 5-25 for the EF domain (Table 1). Scores are transformed to a 0–100 scale, where higher score values indicate greater impact of migraine. No total score is currently created for the MFIQ.

The formula below is used to transform raw domain score values into a 0–100 scale.

$$\text{Transformed score} = \frac{\text{(Raw score – lowest possible raw score)}}{\text{(Highest possible raw score – lowest possible raw score)}} * 100$$

Domain/ Global Item	*Number* of Items in Domain	*Sum* of Item Values	Lowest and Highest Possible *Sum* of Item Values (Raw Scores)	Final Domain/ Global Item Score Range
Physical Function (PF)	5	1+2+3+4+5	5, 25	0-100
Usual Activities (UA)	10	6+7+8+9+10+11+12+13+14+15	10, 50	0-100
Overall impact on UA	1	Score on item 16	1, 5	0-100
Social Function (SF)	5	17+18+19+20+21	5, 25	0-100
Emotional Function (EF)	5	22+23+24+25+26	5, 25	0-100

Table 1. MFIQ Domains and Scoring

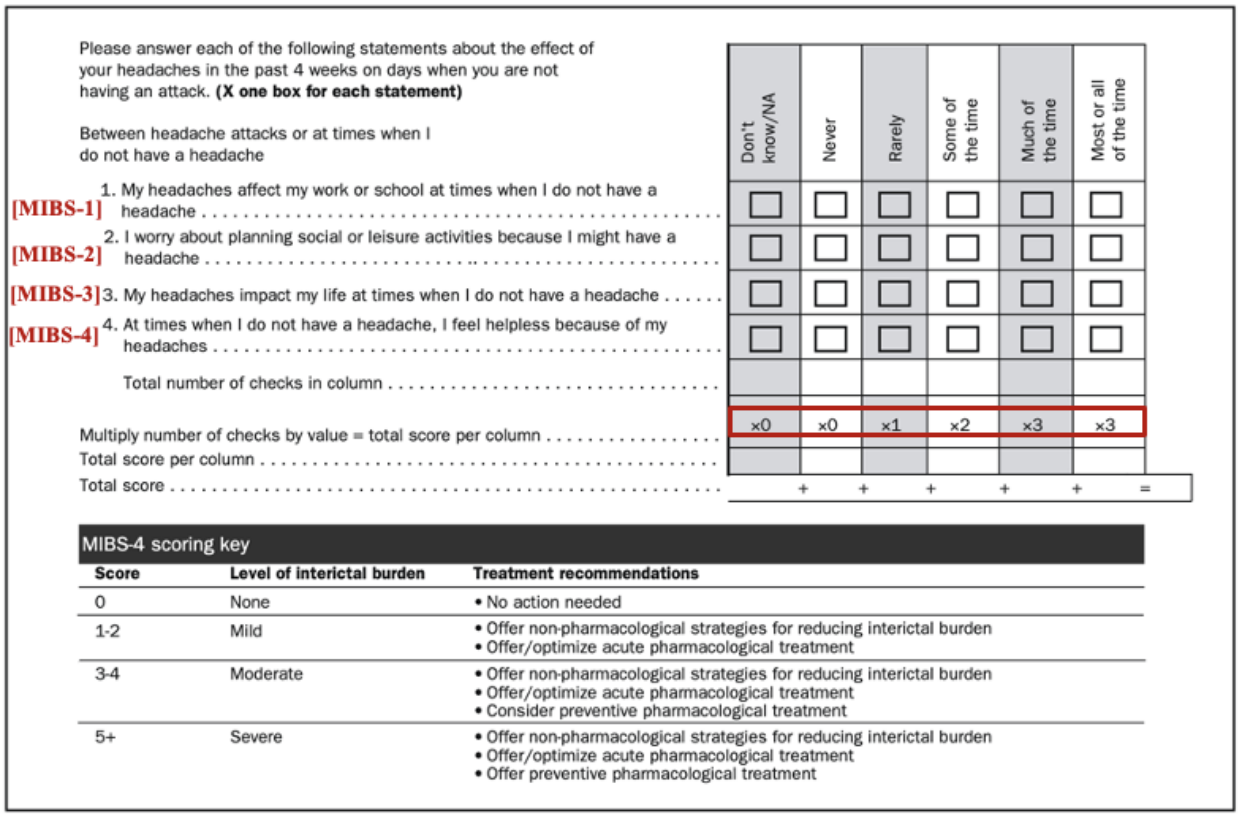
6.3.1.2. Missing Data Imputation Guidelines

6.3.1.2.1. Item-Level Missing Data

For each MFIQ domain, if <50% of the items within a domain are missing, the mean of the item scores that are present for that day is used to impute a score for the missing item(s). If ≥50% of the items that make up a domain are missing, no domain score is calculated; the domain score is considered missing.

For the purposes of domain scoring, "does not apply" (DNA response) are not considered missing and will be imputed with the mean of other non-missing items in the domain.

6.3.2. Migraine Interictal Burden Scale (MIBS-4)



Please answer each of the following statements about the effect of your headaches in the past 4 weeks on days when you are not having an attack. **(X one box for each statement)**

Between headache attacks or at times when I do not have a headache

		Don't know/NA	Never	Rarely	Some of the time	Much of the time	Most or all of the time
[MIBS-1]	1. My headaches affect my work or school at times when I do not have a headache	☐	☐	☐	☐	☐	☐
[MIBS-2]	2. I worry about planning social or leisure activities because I might have a headache	☐	☐	☐	☐	☐	☐
[MIBS-3]	3. My headaches impact my life at times when I do not have a headache	☐	☐	☐	☐	☐	☐
[MIBS-4]	4. At times when I do not have a headache, I feel helpless because of my headaches	☐	☐	☐	☐	☐	☐
	Total number of checks in column						
	Multiply number of checks by value = total score per column	×0	×0	×1	×2	×3	×3
	Total score per column						
	Total score		+	+	+	+	+ =

MIBS-4 scoring key

Score	Level of interictal burden	Treatment recommendations
0	None	• No action needed
1-2	Mild	• Offer non-pharmacological strategies for reducing interictal burden • Offer/optimize acute pharmacological treatment
3-4	Moderate	• Offer non-pharmacological strategies for reducing interictal burden • Offer/optimize acute pharmacological treatment • Consider preventive pharmacological treatment
5+	Severe	• Offer non-pharmacological strategies for reducing interictal burden • Offer/optimize acute pharmacological treatment • Offer preventive pharmacological treatment

Figure 2. MIBS-4 with scoring key: This shows how each item should be calculated into the total with the level of interictal burden. Below is an example of how each item will be calculated (Buse et al., 2009).

Example:

Item 1: Some of the time (x2)

Item 2: Never (x0)

Item 3: Much of the time (x3)

Item 4: Rarely (x1)

Total MIBS-4 score: 1x2 + 1x0 + 1x3 + 1x4 = 2 + 0 + 3 + 4 = 9. This would be Severe interictal burden

REDCap Cloud Variables used for this analysis: **[MIBS-1], [MIBS-2], [MIBS-3], [MIBS-4]**

REDCap Cloud values for each response are recorded as the participants answer, e.g., 'Rarely' instead of with the PRO's assigned value. In the figure above the red box indicates the value for each response. In R the biostatistician will programmatically recode the responses into the following values to match the PRO's:

- Don't Know/NA = 0
- Never = 0
- Rarely = 1
- Some of the time = 2
- Much of the time = 3
- Most or all of the time = 3

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

The WPAI-M outcomes are calculated into percentages, higher numbers indicate greater impairment and less work productivity.

Questions:	*Scores:*
1 = currently employed	Multiply scores by 100 to express in percentages.
2 = hours missed due to specified problem	
3 = hours missed other reasons	Percent work time missed due to problem: Question 2/(Question 2 + Question 4)
4 = hours actually worked	
5 = degree problem affected productivity while working	Percent impairment while working due to problem: Question 5 / 10
6 = degree problem affected regular activities	
	Percent overall work impairment due to problem:

	Question 2/(Question 2 + Question 4)+[(1-(Question 2/(Question 2 + Question 4)))x(Question 5/10)] Percent activity impairment due to problem: Question 6 / 10

Figure 3. WPAI-M questions and scoring key: This shows each question and how each outcome is assessed.

Example:

Question 1 = Yes (1) No (0)

Question 2 = 5 hours missed due to Migraine

Question 3 = 0 hours missed for other reasons

Question 4 = 35 hours worked

Question 5 = 6

Question 6 = 3

Percent work time missed due to migraine: Q2/(Q2+Q4) = 5/(5+35) = 5/40 = 0.125 x 100 = 12.5%

Percent impairment while working due to migraine: Q5/10 = 6/10 = 0.6 = 60%

Percent overall work impairment due to migraine: Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)] = 5/(5+35) + [(1-(5/(5+35)))x(6/10)] =

5/40+[(1-(5/(40)))x(0.6)] =

0.125+[(1-0.125)x(0.6)] =

0.125+[(0.875)x(0.6)] =

0.125+0.525=

0.525 x 100 = 52.5%

Percent activity impairment due to migraine: Q6/10 = 3/10 = .3 = 30%

Results from example: This participant missed 12.5% of work due to migraine and while working their impairment was 60%. Their overall work impairment due to migraine was 52.5%. They also experienced 30% migraine impairment for other activities.

REDCap Cloud Variables used for this analysis: **[WPAIM_1], [WPAIM_2], [WPAIM_3], [WPAIM_4], [WPAIM_5], [WPAIM_6]**

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

Table 12: Adult Sleep Disturbance

Sleep Disturbance 8-item Short Form (Adult)					
Raw Score	T-Score	SE	Raw Score	T-Score	SE
8	32.0	5.9	25	61.6	3.4
9	36.3	5.0	26	62.8	3.4
10	39.1	4.7	27	63.9	3.4
11	41.7	4.4	28	65.1	3.4
12	43.8	4.2	29	66.4	3.4
13	45.6	4.0	30	67.6	3.5
14	47.3	3.9	31	68.9	3.5
15	48.9	3.8	32	70.3	3.5
16	50.4	3.7	33	71.7	3.6
17	51.8	3.6	34	73.2	3.6
18	53.1	3.6	35	74.7	3.7
19	54.4	3.5	36	76.4	3.8
20	55.6	3.5	37	78.2	3.9
21	56.8	3.5	38	80.2	3.9
22	58.0	3.4	39	82.2	3.8
23	59.2	3.4	40	84.2	3.5
24	60.4	3.4			

Figure 4. SDSF scoring table: This shows the values of the total raw score converted into the T-Scores, outlined in the red boxes (NeuroQoL Quality of Life in Neurological Disorders Scoring Manual, 2015). These figures also allow data management to provide an accuracy check on the Health Measure output.

In order to use the HealthMeasures online scoring assessment the biostatistician will need to follow the Assessment Center Scoring Service User Manual attached in Appendix 4.

Answer options for the SDSF are coded as:

- 1 = *Never*
- 2 = *Rarely*
- 3 = *Sometimes*
- 4 = *Often*
- 5 = *Always*.

The range of total SDSF score for each time point is 8 to 40 (with higher scores indicating more sleep disturbance).

REDCap Cloud Variables used for this analysis: **[SDSF-1], [SDSF-2], [SDSF-3], [SDSF-4], [SDSF-5], [SDSF-6], [SDSF-7]**

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

PROMIS SHORT FORM V1.0 – GENERAL SELF-EFFICACY 4A

GENERAL SELF-EFFICACY 4-Item Short Form		
Short Form Conversion Table		
Raw Score	T-score	SE*
4	18.6	3.8
5	22.2	3.7
6	25.3	3.6
7	28.1	3.6
8	30.6	3.5
9	32.9	3.5
10	35.3	3.5
11	37.5	3.5
12	39.7	3.5
13	42.0	3.5
14	44.4	3.5
15	46.9	3.6
16	49.5	3.6
17	52.2	3.6
18	55.3	3.7
19	58.9	4.1
20	64.7	5.5

*SE=Standard Error on T-score metric

Figure 5. GSE-SF scoring key: This shows the values of the total raw score converted into the T-

Scores, outlined in the red boxes (General Self-Efficacy and Self-Efficacy for Managing Chronic Conditions Scoring Manual, 2017). These figures also allow data management to provide an accuracy check on the Health Measure output.

In order to use the HealthMeasures online scoring assessment the biostatistician will need to follow the Assessment Center Scoring Service User Manual attached in Appendix 4.

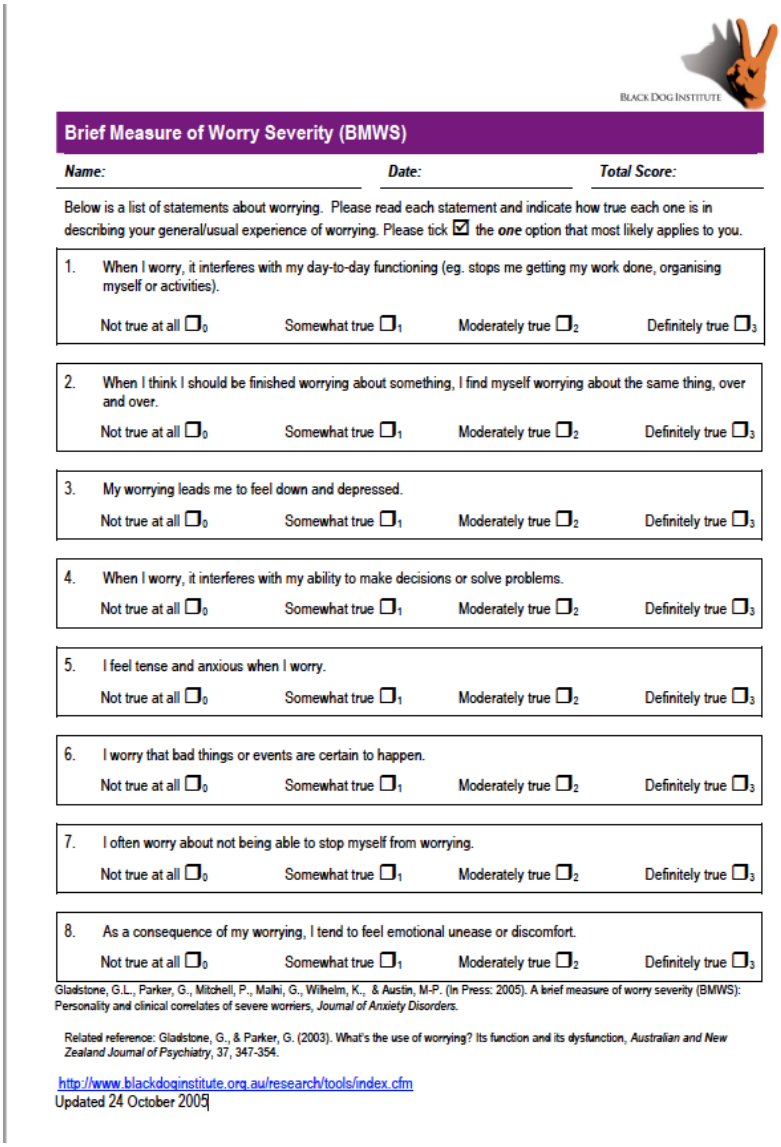
Answer options for the GSE-SF are coded as:

- 1 = *I am not at all confident*
- 2 = *I am a little confident*
- 3 = *I am somewhat confident*
- 4 = *I am quite confident*
- 5 = *I am very confident*

The range of total GSE-SF score for each time point is 4 to 20 (with higher scores indicate more self-efficacy managing difficult situations).

REDCap Cloud Variables used for this analysis: **[GSE14_C], [GSE19_C], [GSE11_C], [GSE20-C]**

6.3.6. Brief Measure of Worry Severity (BMWS)



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Brief Measure of Worry Severity (BMWS)

Name: *Date:* *Total Score:*

Below is a list of statements about worrying. Please read each statement and indicate how true each one is in describing your general/usual experience of worrying. Please tick ☑ the ***one*** option that most likely applies to you.

1. When I worry, it interferes with my day-to-day functioning (eg. stops me getting my work done, organising myself or activities).
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
2. When I think I should be finished worrying about something, I find myself worrying about the same thing, over and over.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
3. My worrying leads me to feel down and depressed.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
4. When I worry, it interferes with my ability to make decisions or solve problems.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
5. I feel tense and anxious when I worry.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
6. I worry that bad things or events are certain to happen.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
7. I often worry about not being able to stop myself from worrying.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3
8. As a consequence of my worrying, I tend to feel emotional unease or discomfort.
   Not true at all ☐0 Somewhat true ☐1 Moderately true ☐2 Definitely true ☐3

Gladstone, G.L., Parker, G., Mitchell, P., Malhi, G., Wilhelm, K., & Austin, M-P. (In Press: 2005). A brief measure of worry severity (BMWS): Personality and clinical correlates of severe worriers, *Journal of Anxiety Disorders.*

Related reference: Gladstone, G., & Parker, G. (2003). What's the use of worrying? Its function and its dysfunction, *Australian and New Zealand Journal of Psychiatry*, 37, 347-354.

http://www.blackdoginstitute.org.au/research/tools/index.cfm
Updated 24 October 2005

Figure 6. **BMWS Questionnaire**

6.3.6.1. Scoring

The BMWS total score is derived from the summation of all eight questions. Answer options for the BMWS are coded as: 0 = *Not true at all,* 1 = *Somewhat true*, 2 = *Moderately true*, 3 = *Definitely true*. The range of total BMWS score is 0 to 24 (with higher scores indicating more worry within the participant).

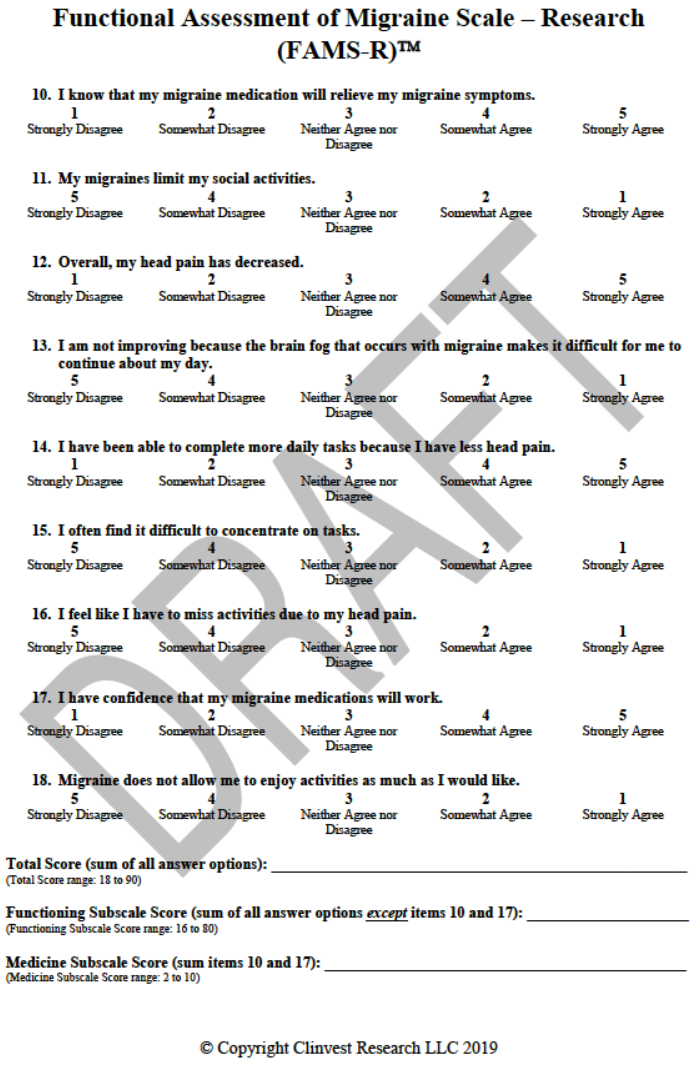
6.3.7. Functional Assessment of Migraine Scale (FAMS)

Functional Assessment of Migraine Scale – Research (FAMS-R)™

The purpose of this survey is to identify questions that would help assess your migraine treatment and improvement with your provider or for research purposes.

For each item mark (circle) your agreement with the statement from strongly disagree to strongly agree based on the ***last month*** of your migraine treatment and symptoms.

1. My migraine associated symptoms are negatively impacting my life.					
5 Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree	
2. The number of my head pain days have decreased.					
1 Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree	
3. My migraine associated symptoms prevent me from doing my normal activities.					
5 Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree	
4. My migraines prevent me from scheduling activities.					
5 Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree	
5. I now have fewer migraine attacks.					
1 Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree	
6. My migraines make me miss too much work.					
5 Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree	
7. My migraine attacks decrease my feelings of self-worth.					
5 Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree	
8. My number of severe head pain days has decreased.					
1 Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree	
9. My migraines negatively affect my relationships.					
5 Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree	



Functional Assessment of Migraine Scale – Research (FAMS-R)™

10. I know that my migraine medication will relieve my migraine symptoms.

1	2	3	4	5
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

11. My migraines limit my social activities.

5	4	3	2	1
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

12. Overall, my head pain has decreased.

1	2	3	4	5
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

13. I am not improving because the brain fog that occurs with migraine makes it difficult for me to continue about my day.

5	4	3	2	1
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

14. I have been able to complete more daily tasks because I have less head pain.

1	2	3	4	5
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

15. I often find it difficult to concentrate on tasks.

5	4	3	2	1
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

16. I feel like I have to miss activities due to my head pain.

5	4	3	2	1
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

17. I have confidence that my migraine medications will work.

1	2	3	4	5
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

18. Migraine does not allow me to enjoy activities as much as I would like.

5	4	3	2	1
Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree

Total Score (sum of all answer options): _____
(Total Score range: 18 to 90)

Functioning Subscale Score (sum of all answer options *except* items 10 and 17): _____
(Functioning Subscale Score range: 16 to 80)

Medicine Subscale Score (sum items 10 and 17): _____
(Medicine Subscale Score range: 2 to 10)

Figure 7. FAMS-R with scoring key: This shows how each item should be calculated for totals as well as subscales.

Functional Assessment of Migraine Scale – Research Supplement (FAMS-RS)™

The purpose of this survey is to assess associated migraine concerns that often arise that impact treatment but are not directly related to day to day functioning.
For each item mark (circle) your agreement with the statement from strongly disagree to strongly agree.

1. The cost of the medication to treat my symptoms is a burden.	**5** Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree
2. The cost of my migraine medication(s) makes it difficult for me to treat when I need to.	**5** Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree
3. Insurance limits my ability to choose an effective migraine medication.	**5** Strongly Disagree	**4** Somewhat Disagree	**3** Neither Agree nor Disagree	**2** Somewhat Agree	**1** Strongly Agree
4. I can communicate with my migraine provider effectively.	**1** Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree
5. My medical provider understands my migraine symptoms.	**1** Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree
6. I have adequate access to a migraine specialist.	**1** Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree
7. My friends understand my migraine symptoms and limitations.	**1** Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree
8. I am able to explain my migraine symptoms to my family and friends.	**1** Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree
9. My family understands my migraine symptoms and limitations.	**1** Strongly Disagree	**2** Somewhat Disagree	**3** Neither Agree nor Disagree	**4** Somewhat Agree	**5** Strongly Agree

Finance/Insurance Score (sum items 1 to 3): _____

Doctor/Provider Score (sum items 4 to 6): _____

Education Score (sum items 7 to 9): _____

All scores range from 3 to 15

Figure 8. FAMS-RS with scoring key: This shows how each item should be calculated for the subscales.

6.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

6.4.1. 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.

6.4.2. 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.

- 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.

6.4.3. 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.
- 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.
- 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.

6.4.4. 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.
- 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.

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