Statistical Analysis Plan

Early Value of Eptinezumab in the Community (EVEC)

An exploratory, prospective, randomized, pragmatic open label cohort study to evaluate the comparative effectiveness of eptinezumab in the United States

Real World Effectiveness of Eptinezumab in Migraine

Eptinezumab

Study No.:	19766N
Sponsor:	Lundbeck LLC (Lundbeck) Deerfield, Illinois 60015, United States
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Table of Contents

List of Panels and Tables **5**

List of Abbreviations and Definitions of Terms **6**

1 Objectives and Endpoints **7**

2 Study Design **7**
2.1 Rationale for the Study Design 10
2.2 Study design justification 10

3 Definitions **11**
3.1 Definition of Periods 11
3.2 Definition of Baseline 12
3.3 Definition of Withdrawal 13
3.4 Definition of Planned versus Actual Treatment 13
3.5 Definition of Migraine and Headache Days 14
3.5.1 Headache Day 14
3.5.2 Migraine Day 15
3.5.3 Clear Day 15

4 Analysis Sets **15**

5 Descriptive Statistics **16**

6 Patient Disposition **16**
6.1 Summary of Patient Disposition 16
6.2 Withdrawals 16

7 Demographics and Baseline Characteristics **16**

8 Recent and Concomitant Medication **16**

9 Exposure **17**

10 eDiary Compliance **17**

11 Effectiveness Analysis **18**
11.1 Overview 18
11.2 Analysis Methodology for the Exploratory Endpoints 18
11.2.1 Estimand for the Number of Good Days (Week 1-4, 1-12, and 1-24) and Exploratory Endpoints 18
11.2.2 Analysis of the Exploratory Endpoints 20
11.2.3 Strategies for Addressing Intercurrent Events in the Exploratory Estimands 23
11.2.4 Rationale for Selected Analysis for the Exploratory Endpoints 24
11.2.5 Evaluation of Model Assumptions for the Analysis of Exploratory Endpoints 24
11.2.6 Sensitivity Analyses of the Exploratory Endpoints 25
11.2.7 Supplementary Analyses of the Exploratory Endpoints 25
11.2.8 Covariate Investigation and Subgroup Analyses of the Exploratory Endpoints 25

12 Safety Analyses 26
13 Data Reviews 27
14 Interim Analyses 28
15 Sample Size 28
15.1 Sample Size Rationale 28
16 Statistical Software 30
17 Changes to Analyses Specified in the Protocol 30
18 Details on Data Handling 30
18.1 Time from Scheduled Daily Report to Patient Reporting Time 30
18.2 eDiary 31
18.3 Good Day/Bad Day Scale (Week 1-4, 1-12, and 1-24) 31
18.4 PI-MBS (weeks 1-4, 1-12, and 1-24) 31
18.5 EQ-5D-5L (weeks 1-4, 1-12, and 1-24) 31
18.6 HCRU (weeks 1-4, 1-12, and 1-24) 31
18.6.1 Medical HCRU 32
18.6.2 Medication HCRU 32
18.7 HIT-6 (week 4, 12, and 24) 33
18.8 MIDAS (weeks 12 and 24) 33
18.9 Drug Switching 33
18.10 TSQM (week 24) 33
18.11 SDMQ-9 (screening and week 24) 34
18.12 SURE (screening) 34
18.13 PAM-10 (screening, week 12 and 24) 34
18.14 PSS 35
18.15 ISS (screening, week 12 and 24) 35
18.15.1 Weekly Migraine Days 35
References 36

Appendices

Appendix I Covariate Definitions 37

List of Panels and Tables

Panel 1 Objectives and Endpoints 7
Panel 2 Criteria for Chronic Migraine Diagnosis per International Headache Society (IHS) International Classification of Headache Disorders 3rd edition (ICHD-3). 8
Panel 3 Randomization Design..... 9
Panel 4 Patient Reported Outcomes Reporting Schedule..... 12
Panel 5 Effect Sizes Observed in Promise Trials 29
Panel 6 Sample size and Power from PROMISE Trials Assumptions 30

Table 1 Covariate Definitions..... 38

List of Abbreviations and Definitions of Terms

AE	Adverse events
APRS	All-patients-randomized-set
APTS	All-patients-treated-set
aCGRP	Anti-calcitonin gene-related peptide
CM	Chronic migraine
eCRF	Electronic case report form
EDC	Electronic data capture
EM	Episodic migraine
EQ-5D-5L	Euroqol 5 Dimension – 5 Levels
FAS	Full analysis set
HIT-6	Headache impact test – 6
HCRU	Healthcare resource utilization
ISS	Infusion Satisfaction Survey
MHDs	Monthly headache days
MIDAS	Migraine Disability Assessment
MMDs	Monthly migraine days
MMRM	Mixed model for repeated measures
MOH	Medication overuse headache
OTC	Over the counter
PAM-10	Patient Activation Measure – 10
PI-MBS	Patient-Identified Most Bothersome Symptom
PRO	Patient reported outcome
PSS	Perceived Stress Scale
QoL	Quality of life
SDM-Q-9	9-item Shared Decision-Making Questionnaire
SURE	Sure of myself; Understand information; Risk-benefit ratio; Encouragement
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States

1 Objectives and Endpoints

The study objectives and endpoints are summarized below in Panel 1.

Panel 1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To explore the effectiveness of eptinezumab on patient-centered outcomes	**Exploratory Endpoints** 1. Good Day/Bad Day scale at weeks 4, 12, and 24 2. Euroqol 5 Dimension – 5 Levels (EQ-5D-5L) at weeks 4, 12, and 24 3. Patient-Identified Most Bothersome Symptom (PI-MBS) at weeks 4, 12, and 24 4. Healthcare resource utilization (HCRU) at weeks 4, 12, 24 5. Headache Impact Test – 6 (HIT-6) change from baseline at week 4, 12, and 24 6. Migraine Disability Assessment (MIDAS) change from baseline at week 12 and 24 7. Treatment Satisfaction Questionnaire for Medication (TSQM) at week 24 8. Medication Switching at week 12 and 24 9. Shared Decision-Making Qeustionnaire-9 (SDMQ-9) at screening and week 24 10. SURE test at screening 11. Patient Activation Measure – 10 (PAM-10) at screening, week 12 and 24 12. Infusion Satisfaction Survey (ISS) at baseline and at week 12
Safety objective • To evaluate the safety and tolerability of eptinezumab	**Safety endpoints** • Reported adverse effects

2 Study Design

This is an exploratory, prospective, randomized, pragmatic, open-label cohort study of 200 participants receiving preventive treatment for episodic migraine (EM) or chronic migraine (CM) headache in the United States (US). Participants must have a history of $\geq$ 8 migraine days in two of the past three months prior to enrolment and have documented failure to at least two previous oral preventive treatments per the American Headache Society (AHS) Consensus Statement.

Panel 2 Criteria for Chronic Migraine Diagnosis per International Headache Society (IHS) International Classification of Headache Disorders 3rd edition (ICHD-3).

1.1 Migraine Without Aura

A. At least five attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours when untreated or unsuccessfully treated.

C. Headache has at least two of the following four characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache, at least one of the following:
1. nausea and / or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

1.2 Migraine With Aura

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

1.3 Chronic Migraine

A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C.

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine Without Aura and/or criteria B and C for 1.2 Migraine With Aura

C. On ≥8 days/month for >3 months, fulfilling any of the following:
1. criteria C and D for 1.1 Migraine Without Aura
2. criteria B and C for 1.2 Migraine With Aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

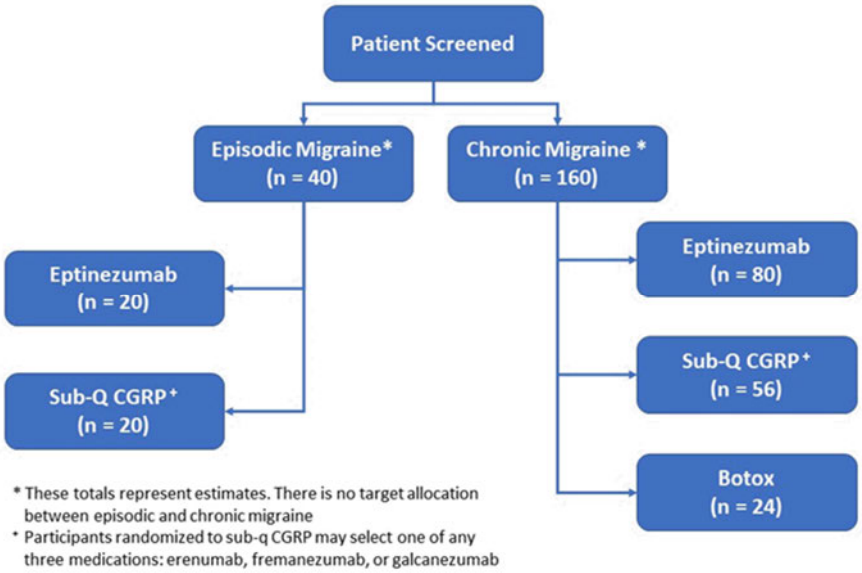
D. Not better accounted for by another ICHD-3 diagnosis

This study will be conducted in compliance with the protocol, *Good Clinical Practice* and applicable regulatory requirements.

Participants will be recruited from sites that can administer all therapies within the study in an outpatient setting.

After giving consent, participants will be classified as living with either EM or CM per International Classification of Headache Disorders 3rd edition (ICHD-3) guidelines (see Panel 2) based upon their medical history. Within these strata, the participants living with EM will be randomized to eptinezumab or subcutaneous (SC) anti-calcitonin gene-related peptide (aCGRP) (i.e., erenumab, fremanezumab or galcanezumab) in a 1:1 manner. Those experiencing CM will be randomized to eptinezumab, SC CGRP, or Botox in 3:2:1 manner. Participants randomized to the SC CGRP injectable arm will be free to select treatment with any aCGRP injectable of their choice (i.e., erenumab, fremanezumab or galcanezumab). Please see Panel 3 for further details on the randomization design.

Panel 3 Randomization Design



Participants will be followed prospectively for 24 weeks; a follow-up phone call will then be made to each participant 8 weeks after study completion at the End of Treatment/Early Termination Visit. At Screening, all participants will be trained to use an eDiary (a smartphone application) that will prompt participants to report their headache status on a daily basis, any related symptoms and any use of acute migraine medications. In addition, the eDiary will also prompt participants three times each week to report any interactions with the healthcare system (e.g., office visits, emergency room visits/urgent care visits, hospitalizations, prescription medication, etc.). The site staff will also follow-up with participants at each study visit to record additional details of healthcare resource utilization (HCRU) recorded in the eDiary, record HCRU not reported in the eDiary, and record reasons for any changes in prescription or over-the-counter (OTC) medications. Quality of life (QOL) data and HCRU data will be collected from participants via the smartphone application (app) and from the site staff via electronic data capture (EDC). QOL assessments include the EQ-5D-5L, HIT-6, Good Day/Bad Day scale, and MIDAS. Participants will complete the EQ-5D-5L and Good Day/Bad Day scale on a weekly basis, the HIT-6 monthly, and the MIDAS every 3 months via the eDiary.

Participant preferences in making a treatment selection will be measured using the SDM-Q-9 (at Screening and Week 24). Participant confidence in the treatment selection they made will be measured via the SURE test (at the Screening Visit only). Participants' knowledge, skill and confidence in managing their own health will be assessed at screening, week 12 and week 24 via the PAM-10 instrument. Participants' satisfaction with their treatment experience will be assessed at week 24 via the TSQM. The SDM-Q-9, SURE test, PAM, and TSQM will be completed electronically.

For participants on eptinezumab, satisfaction with their infusion experience will be assessed via the Infusion Satisfaction Survey after each infusion (at Visit 2 and Visit 5) using a paper questionnaire.

2.1 Rationale for the Study Design

EVEC is an exploratory, prospective, randomized, pragmatic, open-label study. This design allows for the collection of real-world data to better understand how eptinezumab compares to other advanced preventives for prevention of migraines.

2.2 Study design justification

Justification for two treatment groups

Eptinezumab is the fifth treatment option made available to people living with migraine for prevention of migraine attacks. As such the decision that insurers and prescribers must make is, “What benefit does this new treatment create over those options currently available?” Payers must consider whether to add eptinezumab to their formulary. Thus, whether eptinezumab improves efficacy over the basket of available treatments is the key question, rather than whether it is superior to a single treatment.

Justification for 6-month observation period

It is known that patients experience an early onset of efficacy with eptinezumab, and pooled analyses with other advanced preventives indicate that this early onset provides a comparative advantage to eptinezumab. However, less is known regarding the sustainability of this advantage. The durability of effect is a key element in the decision making of payers, thus 6-months is considered the minimum relevant period of observation.

Justification for an open-label study

EVEC is intended to be a real-world evidence study to answer the question for patients, prescribers and payers seeking to know the comparative effectiveness of eptinezumab in actual clinical practice. In the real-world, patients and their professional caregivers (physicians and staff) know what medication the patient receives; therefore, the same principle applies here. In addition, masking participants to treatment assignment in this study would require that every participant receive at least two of the following: 1) monthly sham injection; 2) 30 in-office sham injections in their head and face quarterly; or 3) a quarterly sham infusion. While this may reflect an internally valid study design, it is far from a real-world clinical experience.

Justification for use of an active comparator/no placebo

As noted above, this is a real-world study to evaluate the comparative effectiveness of eptinezumab against other advanced preventives for migraine. The justification for

comparison to a “market basket” of current treatments is noted above in the “Justification for two treatment groups.” We note here that we consider only an active comparator and no placebo because in a real-world setting no patient would receive a placebo. So only active comparators are considered.

3 Definitions

3.1 Definition of Periods

The study will have four periods:

- Screening (Visit #1) to Baseline (Visit #2)

At screening participants will complete the informed consent, review the patient decision aid describing the treatments, complete the SDMQ-9, SURE test, PAM-10, and receive training in use of the study eDiary app. During the period from Screening to Baseline, the participant will use the study app to report their daily experience. This will capture their compliance behavior to support the study analysis while also giving the participant training in use of the app. The site investigator will receive the treatment allocation and receive the participant’s first dose.

- Baseline to Week 12 (Visit #5)

During this period, participants will complete the daily diary, and the weekly and monthly patient-reported outcomes (PROs) as prompted by the study app. This period is the primary reporting period for the study. Participants randomized to receive eptinezumab or onabotulinumtoxinA will receive that treatment at Visit #5 at the study site. Those randomized to receive a subcutaneously injected aCGRP may visit the study site at Visit #5 for the follow-up visit or visit the study site.

- Baseline to Week 24 (Visit #8)

For reporting purposes, the period for visits 6-8 will be pooled with the previous period, so that results for week #24 will include all data since the Baseline visit. From the patient perspective there is no change in the required behavior.

- Safety Follow-up period (Week 25-33, Visit #9)

This is the two-month follow-up period required by Lundbeck to assess safety.

The reporting schedule is defined in the table that follows:

Panel 4 Patient Reported Outcomes Reporting Schedule

Assessments	Reporting Schedule				
	Daily	Weekly[a]	Monthly[b]	Quarterly[c]	Early Termination
Healthcare Resource Utilization	X[d]				X
EQ-5D-5L		X			X
Good Day/Bad Day Scale		X			X
PSS			X		X
HIT-6			X		X
PAM-10				X	X
MIDAS				X	X
SDM-Q-9				X	X
TSQM				X[e]	X

(a) Weekly = every 7 days, Visit 2 date = Day 0
(b) Monthly = every 28 days, Visit 2 date = Day 0
(c) Quarterly = every 84 days, Visit 2 date = Day 0
(d) Will be assessed 3 times per week
(e) Assessed at Day 168 only

Participants will report daily whether they have had a headache in the previous 24 hours, any migraine related symptoms (concurrent with the migraine or interictal) and use of rescue medication.

3.2 Definition of Baseline

The screening assessment (Visit 1) is to be conducted within 14 days of the participant's initial treatment at the Baseline Visit (Visit 2) to allow the investigator sufficient time to review the participant's medical history and determine if the participant is eligible for study participation.

The participant's first treatment occurs as the Baseline Visit. The day of the visit, the participant will be notified by the study app to complete the Baseline PROs and prior to initiating treatment the site will confirm the completion. The participant will also complete the Daily Headache Status Report in their eDiary on this date. Administration of the first treatment will consist of either the participant's first treatment with eptinezumab or Botox or the participant's first injection of a subcutaneous aCGRP mAb. For participants in the subcutaneous aCGRP arm, the first dose should be self-administered by the participant under the supervision of the site staff.

Where a study endpoint is based upon the change from baseline, the report at this visit will serve as that baseline.

3.3 Definition of Withdrawal

Withdrawal from the study is defined as termination of consent on or before Visit 8. Participants who withdraw from the study prior to Visit 8 will be asked to complete an Early Termination Visit. The visit must be scheduled as soon as possible after withdrawal. All information collected at an Early Termination Visit is to be recorded in the Visit 8 forms of the electronic case report form (eCRF). If the patient denies completing the Early Termination Visit, then no further data will be collected.

No participant will be withdrawn from the study due to non-compliance with treatment. As this is a pragmatic real-world study, the failure to comply with treatment is considered a real-world outcome. However, an investigator may withdraw a participant from the study based upon their medical judgement if they deem continued involvement in the study is detrimental to the participant's welfare.

No new information will be collected from participants who withdraw from the study, except information collected in relation to the scheduled Withdrawal Visit or needed for the follow-up of adverse events.

The reason for withdrawal must be recorded in the eCRF.

For a participant who withdraws consent:

- If the participant withdraws consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including that visit will be used
- If the participant withdraws consent during a telephone conversation, the investigator will ask the participant if they might attend a Withdrawal Visit. If the participant:
    - Agrees to attend a Withdrawal Visit, all the data collected up to and including that visit will be used
    - Refuses to attend an Early Termination Visit, the investigator should attempt to follow the participant's safety and future treatment; any information collected will only be recorded in the patient's medical records

If the participant explicitly requests that their data collected from the time of withdrawal of consent onwards not be used, this will be respected.

The end of the study for an individual participant is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study.

3.4 Definition of Planned versus Actual Treatment

As this is a pragmatic real-world study, there is no restriction on treatment pathways following randomization with the exceptions defined below. Note that all participants will be analyzed on an "intention to treat" basis, regardless of changes made to their treatment following the Baseline visit.

Participants may switch to an alternative preventive treatment in either treatment cohort after they have received their initial treatment with the medication to which they were randomized. Such a decision may be made upon recommendation of their treating clinician or participant preference. The site staff will investigate the reason for treatment change with both the treating clinician and participant. The use of medications, including gepants, for relief of acute migraine symptoms in either treatment arm is permitted and will be recorded in the smartphone application.

For all participants, the treatment to which they are initially assigned must be the treatment given at Baseline (Visit 2). Switching of medication is not permitted prior to administration of the first dose of medication. For participants who receive eptinezumab or Botox as their initial treatment and elect to switch to a subcutaneous aCGRP injectable (i.e., erenumab, fremanezumab or galcanezumab), they may not do so until week 12 (visit 5). Participants who receive eptinezumab or Botox at week 12 (Visit 5) will not be permitted to switch their treatment for the remaining duration of the study.

Participants initially treated with a subcutaneous aCGRP injectable may only switch to eptinezumab, or Botox at week 12 (visit 5) due to the design of the study. However, these participants may switch to another of the subcutaneous aCGRP injectable medications at any time, once the treatment window for their previous injection has ended.

No changes in treatment will be permitted after Visit 7.

All changes in treatment are to be documented in the eCRF.

If a participant wishes to switch their medication but does not meet the specified criteria to do so, as stated above, they should be withdrawn from the study and be treated as per standard of care by their physician.

3.5 Definition of Migraine and Headache Days

3.5.1 Headache Day

A headache day will be defined as a day in which the participant reports the following:

- Reported “yes” to having a headache in the past 24 hours and who do NOT report criterion A nor B:
    - Criterion A
        - Headache with ≥2 of the following features:
            - Moderate or severe pain intensity
            - Unilateral location
            - Pulsating quality
            - Aggravation by or causing avoidance of routine physical activity
        - During the headache, the patient reports ≥1 of the following symptoms:
            - Nausea and/or vomiting

        - Photophobia
        - Phonophobia
    - Criterion B
        - Reported acute medication use

3.5.2 Migraine Day

A migraine day will be defined as a day in which a patient reports the following features consistent with ICHD-3 criteria for migraine without aura (Panel 2):

- Reported "yes" to having a headache in the past 24 hours and who also report either criterion A or B:
    - Criterion A
        - Headache with ≥2 of the following features:
            - Moderate or severe pain intensity
            - Unilateral location
            - Pulsating quality
            - Aggravation by or causing avoidance of routine physical activity
        - During the headache, the patient reports ≥1 of the following symptoms:
            - Nausea and/or vomiting
            - Photophobia and
            - Phonophobia
    - Criterion B
        - Reported acute medication use

3.5.3 Clear Day

A clear day will be defined as a day in which the patient reports:

- Reported "No" to having a headache in the past 24 hours AND
    - Reports no residual symptoms between headaches AND
    - Reports no "warning" symptoms prior to a headache

4 Analysis Sets

The following analysis sets will be used for evaluation of the data:

- All patients randomized set (APRS) – all patients randomized to the eptinezumab and the other advanced migraine treatment arms
- All patients treated set (APTS) – all patients in the APRS who received at least one dose of eptinezumab or other advanced migraine therapy
- Full analysis set (FAS) – all patients in the APTS who completed at least one daily report after receiving eptinezumab or other advanced migraine therapy

Effectiveness analyses over the 24-week period will be based on the FAS. We will also evaluate baseline characteristics based on the APRS to assess the validity of the randomization strategy.

Safety analyses will be based on the APTS.

5 Descriptive Statistics

All assessment data, including demographics, will be summarised using descriptive techniques. Summary statistics (n, mean, standard deviation, median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables. Counts and percentages will be presented for categorical and binary variables.

6 Patient Disposition

6.1 Summary of Patient Disposition

Participant disposition will be reported overall and by treatment group. If needed, further tables summarizing disposition by site and treatment group can be added.

6.2 Withdrawals

For each period, the number of participants who withdrew from the study, will be summarized by treatment group, and primary reason for withdrawal, and by treatment group and all reasons for withdrawal.

If relevant, Kaplan-Meier failure plots of time to withdrawal in each period will be presented by treatment group. Participants who reach the end of follow-up without withdrawing from the study will be regarded as censored.

7 Demographics and Baseline Characteristics

Demographics; baseline characteristics (including baseline eDiary compliance); baseline disease characteristics; and baseline efficacy (i.e., MMD) variables will be summarized at Baseline by randomization group and study site.

8 Recent and Concomitant Medication

Concomitant medication is any medication other than the investigational medicinal products (IMPs) that are taken during the study from Screening up until the participant completes the study at Visit 8. This includes all prescription and OTC medications, as well as vitamins and

supplements. In addition, if a patient receives a COVID-19 vaccination while enrolled in the trial, each dose of the vaccine received should be entered as a concomitant medication.

Details of all concomitant medication being taken at the time of the Screening Visit must be recorded in the eCRF at the first visit. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit.

For any concomitant medication for which the dose was increased due to worsening of a concurrent disorder after enrollment in the study, the worsening of the disorder must be recorded as an adverse event and the medication with the increase dosage should be reported as a new concomitant medication.

For any concomitant medication initiated due to a new disorder after enrolment in the study, the disorder must be recorded as an adverse event.

9 Exposure

For each period, the total number of infusions (for eptinezumab) or injections (for onabotulinumtoxinA) received and total number completed as planned will be summarized by treatment group.

For participants randomized to the subcutaneously injected aCGRPs, dispensing information will be obtained from the speciality pharmacy providing the medication. The date the participant reported injecting the medication will be captured in the eDiary. The information that the participant has been dispensed medication will be reported by medication group. Similarly, the information that the participant has injected the medication will be reported by medication group.

10 eDiary Compliance

Participant compliance with eDiary use will be measured between the Screening and Baseline visits. This will be used in analysis as a model covariate to adjust for expected compliance. After Baseline, all data reported through the eDiary will be used in analysis as described in the section on Section 18 Details on Data Handling.

11 Effectiveness Analysis

11.1 Overview

All effectiveness analyses will be based on the FAS, unless specified otherwise, and patients will be analyzed according to the randomized group. Details of calculating values for outcome variables and assumptions regarding handling of missing data is described in section 18.

11.2 Analysis Methodology for the Exploratory Endpoints

11.2.1 Estimand for the Number of Good Days (Week 1-4, 1-12, and 1-24) and Exploratory Endpoints

A summary of the intercurrent events that will be addressed and the estimand attributes can be found below.

The estimand is the difference in the mean weekly number of good days within each specified time interval between eptinezumab compared to other advanced preventive therapies (erenumab, fremanezumab, galcanezumab, or onabotulinumtoxinA) in adults with migraine on concomitant acute migraine therapy who have failed ≥2 prior oral preventive therapies and who are naïve to advanced migraine therapy based on a treatment policy strategy in which patients are analyzed according to the randomized group and are included in the analysis regardless of discontinuation or switching of the index migraine therapy during the follow-up period.

Intercurrent events that will be addressed include:

- Discontinuing the index preventive migraine medication with or without initiation of a new preventive therapy (i.e., a treatment switch).
- Withdrawal from the study due to lack of efficacy, adverse event, participant request, physician request, or loss to follow-up.
- Interruption or termination of infusions.

Attributes of the estimand for the number of good days include:

- The index treatment of interest is eptinezumab (100 mg or 300 mg) compared to other advanced preventive therapies (erenumab 70 mg or 140 mg, fremanezumab 225 mg or 675 mg, galcanezumab 120 mg, and onabotulinumtoxinA 155 units)
- The population is all patients with migraine who fulfil the inclusion and exclusion criteria.
- The primary endpoint of interest is the mean number of good days across weeks 1-12 after randomization
- The population-level summary is the mean difference between eptinezumab and other advanced preventive therapies for the endpoint

Estimands for the remaining exploratory endpoints can be formulated similarly to the estimand for the number of good days described above.

EQ-5D (weeks 1-4, 1-12, and 1-24)

- The endpoint to be obtained is the weekly EQ-5D score in each specified time interval
- The population level summary is the difference in mean weekly EQ-5D score in patients on eptinezumab relative to advanced migraine therapies in each time interval

PI-MBS (weeks 1-4, 1-12, and 1-24)

- The endpoint to be obtained is the weekly most bothersome symptom and associated severity
- The population level summary is the weekly proportion of most bothersome symptoms and average severity of each symptom in patients on eptinezumab and advanced migraine therapies in each time interval

Cumulative healthcare resource use (HCRU) (weeks 1-4, 1-12, and 1-24)

- The endpoint to be obtained is the cumulative HCRU (stratified by medical and pharmaceutical HCRU) in each specified time interval
- The population-level summary is the difference in mean HCRU in patients on eptinezumab relative to advanced migraine therapies in each time interval

HIT- 6 change from baseline score (week 4, 12, and 24)

- The endpoint to be obtained is the HIT-6 change from baseline score at each specified time point
- The population level summary is the difference in mean HIT-6 change from baseline score in patients on eptinezumab relative to advanced migraine therapies at each time point

MIDAS change from baseline score (weeks 12 and 24)

- The endpoint to be obtained is the MIDAS change from baseline score at each specified time point
- The population level summary is the difference in mean MIDAS change from baseline score in patients on eptinezumab relative to advanced migraine therapies at each time point

TSQM score (week 24)

- The endpoint to be obtained is the TSQM score at week 24 for each domain
- The population level summary is the difference in mean TSQM score in patients on eptinezumab relative to advanced migraine therapies for each domain

Switching of index medication (weeks 1-12 and 1-24)

- The endpoint to be obtained is a binary outcome indicating if a patient discontinued the index therapy and initiated a new therapy in the specified time intervals
- The population-level summary is the odds ratio of switching from the index medication in patients on eptinezumab relative to advanced migraine therapies in each time interval

SDMQ-9 (screening and week 24)

- The endpoint to be obtained is the SDMQ-9 score at each specified time point
- The population level summary is the mean SDMQ-9 in patients on eptinezumab and advanced migraine therapies in each time interval

SURE score at screening

- The endpoint to be obtained is the SURE test score at screening
- The population level summary is the mean SURE test score in patient on eptinezumab and advanced migraine therapies at screening

PAM-10 score (screening, week 12 and 24)

- The endpoint to be obtained is the PAM-10 score at each specified time point
- The population level summary is the mean PAM-10 score in patients on eptinezumab and advanced migraine therapies in each time interval

ISS score (screening, week 12 and 24)

- The endpoint to be obtained is the score or item response for each item in the ISS at each specified time point
- The population level summary is the mean ISS score or proportion of responses for each item in patients on eptinezumab at each time point

11.2.2 Analysis of the Exploratory Endpoints

The analysis of exploratory endpoints assumes that we have ≤10% of patients with at least one missing outcome value. A complete case analysis will be used as a preliminary approach to establish the "baseline" results prior to using a mixed model for repeated measures (MMRM) or multiple imputation to account for missing values.

Number of good days (weeks 1-4, 1-12, and 1-24)

The weekly difference in mean number of good days will be estimated using a MMRM. The model will include the following independent variables:

- Week as a factor (week 1, week 2, week 3, week 4…week n)
- Treatment indicator (eptinezumab vs other advanced therapies)
- Interaction of treatment and week (i.e., treatment*week 1…treatment*week 2…treatment*week n)
- A vector of covariates identified to be significantly different between treatment groups after randomization.

We will assume that residuals are normally distributed, and we will also assume an unstructured covariance structure of the residuals. The Kenward-Roger approximation will be used to estimate standard errors. The hypothesis tested will be that the interaction term of treatment and week is significantly different from zero using a two-sided test at $p<0.05$. The

population level summary will be the difference in mean number of good days at weeks 1-4. The analysis will also be conducted for weeks 1-12 and 1-24. If the model fails to converge, then other covariance structures will be utilized.

EQ-5D score (weeks 1-4, 1-12, and 1-24)

The weekly difference in the EQ-5D score will be estimated using a MMRM. The model will include the following independent variables:

- Week as a factor (week 1, week 2, week 3, week 4…week n)
- Treatment indicator (eptinezumab vs other advanced therapies)
- Interaction of treatment and week (i.e., treatment*week 1…treatment*week 2…treatment*week n)
- A vector of covariates identified to be significantly different between treatment groups after randomization.

We will assume that residuals are normally distributed, and we will also assume an unstructured covariance structure of the residuals. The Kenward-Roger approximation will be used to estimate standard errors. The hypothesis tested will be that the interaction term of treatment and week is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the difference in mean EQ-5D score at weeks 1-4. The analysis will also be conducted for weeks 1-12 and 1-24. If the model fails to converge, then other covariance structures will be utilized.

HCRU (weeks 1-4, 1-12, and 1-24)

The difference in cumulative mean HCRU will be estimated using a negative binomial model. The analysis will be stratified by type of HCRU (i.e., outpatient, inpatient hospitalization, emergency department/urgent care visits, and migraine-specific medications such as triptans). Independent variables will include a treatment indicator (eptinezumab vs other advanced therapies) and a vector of covariates identified to be significantly different between treatment groups after randomization. The hypothesis tested will be that the treatment term is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the relative difference in mean HCRU at weeks 1-4. The analysis will also be conducted for weeks 1-12 and 1-24. If there are a substantial number of observations with a value of zero HCRU, then a zero-inflated negative binomial model will be explored.

HIT-6 change from baseline score (month 1, 3, and 6)

The mean HIT-6 change from baseline score will be estimated using a mixed model for repeated measures (MMRM). The model will include the following independent variables:

- Month as a factor (Baseline month 0, month 1, month 3, and month n)
- Treatment indicator (eptinezumab vs other advanced therapies)
- Interaction of treatment and month (treatment*baseline…treatment*month 1…treatment*month n)

- A vector of covariates identified to be significantly different between treatment groups after randomization.

We will assume that residuals are normally distributed, and we will also assume an unstructured covariance structure of the residuals. The Kenward-Roger approximation will be used to estimate standard errors. The hypothesis tested will be that the interaction term of treatment and month is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the difference in mean HIT-6 change from baseline score at month 1, month 3, and month 6. If the model fails to converge, then other covariance structures will be utilized.

MIDAS change from baseline score (month 3 and 6)

The mean MIDAS change from baseline score will be estimated using a MMRM. The model will include the following independent variables:

- Month as a factor (Baseline month 0, month 3 and month n)
- Treatment indicator (eptinezumab vs other advanced therapies)
- Interaction of treatment and month (treatment*baseline, treatment*month 3, treatment*month n)
- A vector of covariates identified to be significantly different between treatment groups after randomization.

We will assume that residuals are normally distributed, and we will also assume an unstructured covariance structure of the residuals. The Kenward-Roger approximation will be used to estimate standard errors. The hypothesis tested will be that the interaction term of treatment and month is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the difference in mean MIDAS change from baseline score at month 3 and month 6. If the model fails to converge, then other covariance structures will be utilized.

PI-MBS (weeks 1-4, 1-12, and 1-24)

Among daily headache reports, the weekly proportion of each most bothersome symptom (e.g., pain worsened by physical activity, throbbing head pain, nausea, vomiting, photophobia, phonophobia, difficulty concentrating, visual aura, other aura, or other) associated with a headache and proportions of reports with no headache will be calculated for the eptinezumab and advanced migraine therapy group. The average weekly severity associated with each most bothersome symptom will be calculated. The trend in the weekly proportion and severity of each most bothersome symptom will be descriptively compared between the eptinezumab and advanced migraine therapy group.

TSQM score (week 24)

The difference in mean TSQM score for each domain (effectiveness, side effects, convenience, and overall satisfaction) at week 24 will be estimated using an ordinary least

square model. Independent variables will include a treatment indicator (eptinezumab vs other advanced therapies) and a vector of covariates identified to be significantly different between treatment groups after randomization. The hypothesis tested will be that the treatment term is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the difference in mean TSQM score at week 24.

Index drug switching (weeks 1-12, and 1-24)

The difference in the odds of index drug switching will be estimated using a logistic regression model. Independent variables will include a treatment indicator (eptinezumab vs other advanced therapies) and a vector of covariates identified to be significantly different between treatment groups after randomization. The hypothesis tested will be that the treatment term is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the odds ratio of index drug switching in the eptinezumab group relative to other advanced therapies. The analysis will be conducted weeks 12 and 24.

SDMQ-9 (screening and week 24)

The average SDMQ-9 score will be calculated for each treatment group and descriptively compared at screening and week 24.

SURE score at screening

The average SURE score will be calculated for each treatment group and descriptively compared at screening.

PAM-10 score (screening, week 12 and 24)

The average PAM-10 score will be calculated for each treatment group and descriptively compared at screening, week 12, and week 24.

ISS score (screening, week 12 and 24)

The ISS score or item responses will be analyzed descriptively using averages and proportions in the eptinezumab group at screening, week 12, and week 24.

11.2.3 Strategies for Addressing Intercurrent Events in the Exploratory Estimands

The goal of this pragmatic trial is to measure the effectiveness of migraine preventive treatments in “real-world” conditions regardless of the occurrence of intercurrent events during the follow-up period. Therefore, all intercurrent events will be addressed using a treatment policy strategy, in which all patients will be analysed despite the occurrence of an intercurrent event. This strategy reflects the intent-to-treat principle in which patients are analyzed regardless of protocol deviations.

Use of acute medication to treat a migraine headache

A treatment policy strategy will be used to address acute medication usage during the follow-up period. Patients with available endpoint data will be analysed regardless of acute medication use during the follow-up period.

Discontinuing the preventive migraine medication with or without initiation of a new preventive therapy.

A treatment policy strategy will be used to address patients who switch or discontinue the index therapy. Patients with available endpoint data will be analysed according to their index therapy regardless of switch or discontinuing the index therapy.

Withdrawal from the study due to lack of efficacy, adverse event, participant request, physician request, or loss to follow-up.

A treatment policy strategy will be used to address patients who withdraw from the study for any reason. Imputation of missing data will aim to ensure that all observations with missing outcome values can be used in the analysis.

Interruption or termination of infusions.

A treatment policy strategy will be used to address patients who experience an interruption or termination of infusions. Patients with available endpoint data will be analysed regardless of infusion interruption or termination.

11.2.4 Rationale for Selected Analysis for the Exploratory Endpoints

The number of good days, EQ-5D score, HIT-6, and MIDAS are continuous longitudinal data (i.e., correlated observations across time on the same individual) that are approximately normally distributed. Therefore, a MMRM is optimal for these outcomes. HCRU are counts, which follows a right skewed distribution and values are restricted >0, therefore, a negative binomial model is appropriate. The TSQM is approximately normally distributed and ordinary least squares is appropriate. Index drug switching is a binary outcome measure, and a logistic regression is appropriate. Other patient reported outcomes such as the PI-MBS, SDMQ-9, SURE, PAM-10, and ISS are discrete or categorical variables and describing the endpoints by proportion, mean, or median is appropriate.

11.2.5 Evaluation of Model Assumptions for the Analysis of Exploratory Endpoints

The assumption of normality of the patient-reported outcomes will be evaluated by visual inspection of the distribution of the outcomes, residual Q-Q plots, and scatter plot of standardized residuals vs predicted values.

11.2.6 Sensitivity Analyses of the Exploratory Endpoints

Number of good days (weeks 1-4, 1-12, and 1-24), EQ-5D score (weeks 1-4, 1-12, and 1-24), HIT-6 change from baseline score (month 1, 3, and 6), and MIDAS change from baseline score (month 3 and 6)

To test the robustness of the results with respect to missing data, the missing data will be imputed using multiple imputation by chained equation assuming data is missing at random.[1] First, the proportion and pattern of missing outcome values will be evaluated, and descriptive statistics of variables with missing values will also be evaluated. Additionally, among outcome variables with missing data, the association of missingness with other variables will be measured. Missing values will be imputed using fully conditional specification imputation in which each variable with missing values is imputed using regression (type of regression dependent on the variable distribution). Imputation models will be specified to include all analytic variables and additional variables that are associated with missingness. A minimum of 20 imputed datasets will be generated.[2] Trace plots for continuous variables and tabulations for categorical variables of the imputed datasets will be evaluated to assess the validity of imputations methods. Methods to "penalize" missing values will also be explored. Only observations in the eptinezumab group will be used to impute missing data in patients randomized to eptinezumab, and only observations in the comparator arm will be used to impute missing data in patients randomized to the comparator arm.

A mixed model with repeated measures (MMRM) will be used to evaluate the association between treatment and patient reported outcomes and a generalized linear model (log link and gamma distribution) will be used to evaluate the association between treatment and HCRU across the imputed datasets. Coefficients and standard errors obtained from each imputed dataset will be pooled and combined for inference using PROC MIANALYZE in which regression coefficients are averaged across imputations and standard errors are estimated to incorporate uncertainty within imputations and between imputations.1 The hypothesis tested will be that the treatment term is significantly different from zero using a two-sided test at $p<0.05$. The population level summary will be the difference in means at each specified time interval.

11.2.7 Supplementary Analyses of the Exploratory Endpoints

The correlation between migraine days and patient reported outcomes will be evaluated visually by plotting the average number of weekly migraine days versus average weekly values of the PI-MBS severity, number of good days, and EQ-5D across the 24-week follow-up period based on the entire cohort. Weekly correlation values will be calculated using Spearman's rank correlation and plotted across time.

11.2.8 Covariate Investigation and Subgroup Analyses of the Exploratory Endpoints

Although patients are randomized to eptinezumab and advanced therapies, randomization may not produce balanced groups. Baseline covariates listed below will be compared across the treatment groups using descriptive statistics. Significant differences will be tested using the t-

test or the Mann-Whitney test for continuous variables and chi-square test for categorical variables (Appendix I).

Baseline covariates include:

- Demographic variables
  - Age
  - Sex
  - Marital status
  - Race/ethnicity
  - Zip code
  - Highest education level attained
  - Current employment status
- Clinical variables
  - eDiary compliance
  - Number of migraine days in each of the past three months (MMDs)
  - Previous use of oral preventive medications
  - Migraine symptoms experienced in the seven days prior to enrollment
  - Migraine history (including age at time of first attack and classification of migraine as CM, EM, and MOH)
  - Migraine related medication history
  - Vital signs (height, weight, blood pressure, pulse, respiration)
  - All current medications being taken (including prescription, OTC, vitamins/supplements, vaccinations)
  - Medication allergies
  - Medical and psychiatric history
  - Cardiac history
  - Family medical history of migraines (parents and siblings)
  - Use of tobacco or vaping products, or any other nicotine product
  - Perceived stress scale

No subgroup analyses are planned.

12 Safety Analyses

Adverse events (AEs) will be collected throughout the 6-month study period. Analyses of adverse events will be based on the APTS, and events will be reported according to the therapy the patient received (i.e., not the randomized group).

All AEs will be coded according to the MedDRA version 24.0 or higher. The incidence of AEs occurring in the 6-month study period will be analyzed using descriptive statistics by therapy received. Given sufficient sample size, AEs may also be evaluated by dose received to evaluate any AE trends by dose.

Adverse events will be recorded according to MedDRA system organ class and preferred term by therapy group and classified as pre-treatment adverse events (an adverse event that starts on or after the date the patient signed the Informed Consent Form and prior to the date and time of first dose of therapy) or treatment-emergent adverse events (TEAE; an adverse event that starts or increases in intensity on or after the date and time of first dose of therapy). Only TEAEs will be reported and will be tabulated as:

- Any AEs
- AEs probably related to the therapy received stratified by AE
- Severe AEs stratified by AE
- AE leading to treatment discontinuation stratified by AE
- Serious AE stratified by AE
- Serious AE probably related to the therapy received by AE
- Serious AE leading to treatment discontinuation stratified by AE
- Fatal AE
- Overall AEs
  - Any SAE
  - Any AE probably related to the therapy received
  - Any Severe AE
  - Any AE leading to treatment discontinuation
  - Any serious AE
  - Any serious AE probably related to the therapy received
  - Any serious AE leading to treatment discontinuation
  - Fatal AE

13 Data Reviews

Data quality is controlled throughout the study by study-specific edit checks programmed within the software platforms used to collect data (eCaseLink and eCaseLinkMe).

Edit checks are separated into the following categories:

- Programmed edit checks primarily checks programmed within the EDC system that allow for data to be checked in real time during the data entry process, and which assist sites during data entry. These checks may be divided into:
  - Database Check: The corresponding data field limits the entry to a specific format (e.g. time in “HH:MM” [hours:minutes]).
  - Programmed Soft Check: This check category allows a confirmation of the discrepant information and subsequent manual closing of the discrepancy by Xcenda.
  - Programmed Hard Check: This check category requires a correction of the entered value to close the discrepancy.
- Manual edit checks: Checks that are not pre-programmed within the EDC system and are performed by appropriate Lundbeck and/or Xcenda study personnel. Manual checks may

result in the need for manual queries to be recorded by Xcenda within the EDC system for site response and/or data correction.

It is the responsibility of Xcenda to check on a regular basis whether additional edit checks are necessary to achieve final clean database with an acceptable error rate. All additional checks following deployment of the EDC system to the LIVE environment have to be approved by Lundbeck prior to implementation. Subsequent changes to the edit checks after first version release are tracked within the data dictionary.

Data recorded within eCaseLinkMe will not be queried by Xcenda, however, site study personnel will be trained to review the ePRO data prior to their monthly touchpoint with the patient in order to address any data entry errors or missing data moving forward. Patients will not have the ability to modify data once it has been submitted within eCaseLinkMe. Data listings may be generated in order to inform the study team of erroneous, implausible, or missing data. Findings from data listings may be shared with study sites in order to retrain patients on the data entry process and requirements. Data will be checked in real time via pre-programmed edit checks that will assist the patient during the data entry process. Edit checks will be detailed in the data dictionary.

Lundbeck will conduct manual data reviews based on weekly data transfers from Xcenda which include but are not limited to:

- eCaseLink
  - Descriptive statistics to evaluate randomization group, baseline demographics, medical history, concomitant medications, adverse events, and treatment administration. Missing data will be flagged and monitored. Consistent missing data will be escalated to Xcenda.
- eCaseLinkMe
  - Descriptive statistics to evaluate daily headache status and associated symptoms, and trends in patient reported outcomes. Missing data will be flagged and monitored. Consistent missing data will be escalated to Xcenda.

14 Interim Analyses

No interim analyses are planned.

15 Sample Size

15.1 Sample Size Rationale

EVEC is an exploratory study, as such the sample size was considered secondary to the ability of the study to provide exploratory information concerning the objectives. In addition, we lack good preliminary data on the exploratory outcomes and PROs for assessing sample size. Therefore, for illustrative purposes we have limited our power analysis to an evaluation of monthly migraine days based upon the results observed in the PROMISE trials and Phase IIIa

studies of other medications to be evaluated in EVEC. In the Panel 5 below we describe the effect size observed in the PROMISE 1 and 2 trials:

Panel 5 Effect Sizes Observed in Promise Trials

Study	SD*	Epti dose vs placebo	Effect Size (ES; MMDs)	Standardized Effect Size (SES)
Promise 1 (episodic)	3.0	30mg	-0.82	0.27
		100mg	-0.69	**0.23**
		300mg	-1.11	0.37
Promise 2 (chronic)	5.7	100mg	-2.0	**0.36**
		300mg	-2.6	0.45

Note that in EVEC, it is expected that most patients will initiate treatment on the 100 mg dose.

The primary hypothesis will be tested using the following regression model:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_z x_z + \varepsilon$$

Where "Y" is the number of migraine days accumulated from treatment initiation to the final day of week 12 (and 24), This "area under the curve" (AUC) calculation will provide more power than the PROMISE calculations which were based upon the change between the baseline month and the final month of observation. β_1 is the coefficient associated with the number of migraine days reported in the month proceeding screening, and β_2 is the coefficient associated with treatment group assignment (i.e., eptinezumab or other advanced preventive medications). B_z is the coefficient associated with the vector of other covariates that might be considered for inclusion in the model to control other sources of variation (i.e., botox assignment, age, gender, etc.).

The loss to follow-up in the Promise trials was less than 10%. As this is a pragmatic real-world trial with patients receiving free medication and having the opportunity to change treatments without penalty, we expect to have a similarly modest loss to follow-up.

Panel 6 Sample size and Power from PROMISE Trials Assumptions

Standardized Effect size (SES)	N per arm	Power
0.23 (Promise 1)	100	37%
	150	51%
	200	63%
0.30 (average)	100	56%
	150	74%
	200	85%
0.36 (Promise 2)	100	72%
	150	88%
	200	95%

As would be expected in a pragmatic trial, the sample size of EVEC (100 persons per arm) is a function of the project budget and timeliness. In Panel 6 we illustrate the expected power based upon the assumptions developed from PROMISE 1 and 2. We have highlighted the 100 per arm for the PROMISE 2 effect size. If, as expected, we meet the PROMISE 2 assumptions, we will have at least 72% power to demonstrate a standardized effect of 0.45. Given that we believe that the effect size will be larger in EVEC than observed in PROMISE 2, even as we pool patients with episodic and chronic migraine, we expect to have a practical power in excess of 80% to find a difference between eptinezumab and the other advanced preventive medications with an alpha of 0.05.

16 Statistical Software

Analyses will be conducted using SAS®, Version 9.4 or later and R®, Version 4.2.1 or later.

17 Changes to Analyses Specified in the Protocol

N/A

18 Details on Data Handling

18.1 Time from Scheduled Daily Report to Patient Reporting Time

If the time from the scheduled daily report on the eDiary to the reporting time of the patient exceeds >24 hours, then the patient report will be considered invalid, and all relevant data are considered missing.

18.2 eDiary

Compliance to the eDiary between the Screening and Baseline visits will be measured as the proportion of days in which the patient accessed the eDiary and responded to the question "In the last 24 hours did you have a headache?" within the time interval between the Screening visit and Baseline visit (inclusive of the days of the Screening and Baseline visit).

18.3 Good Day/Bad Day Scale (Week 1-4, 1-12, and 1-24)

The Good Day/Bad Day Scale measures patients' global perception of the effect of symptoms on the life of people living with migraine by asking how many "good days" and "bad days" they had over the past week. The total number of days reported is required to total 7 (i.e, the sum of the number of good days and bad days must equal 7).

The Good Day/Bad Day scale is reported weekly. If the total number of days reported is <7 for a given week, then the number of good days will be considered as missing. Missing values will be imputed using multiple imputation methods based on the amount and pattern of missing data.

18.4 PI-MBS (weeks 1-4, 1-12, and 1-24)

Patients will report their most bothersome symptom associated with a headache including pain worsened by physical activity, throbbing head pain, nausea, vomiting, photophobia, phonophobia, difficulty concentrating, visual aura, other aura, or the patient may specify other symptoms. For the most bothersome symptom, patients will be asked to rate its severity ranging from mild (1) to severe (3). The PI-MBS data will be captured daily via the smartphone app when participants are prompted to report if they had a headache. The PI-MBS and severity will be descriptively summarized, and missing data will not be imputed.

18.5 EQ-5D-5L (weeks 1-4, 1-12, and 1-24)

The EQ-5D-5L is a patient-reported assessment designed to measure the patient's well-being.[3] It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems). The VAS is scored separately and ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). A single summary index (from 0 to 1) will be calculated based on item responses using the Unites States value set (EuroQoL).

The EQ-5D will be reported weekly, and a missing weekly value for the EQ-5D score will be imputed using multiple imputation methods based on the amount and pattern of missing data.

18.6 HCRU (weeks 1-4, 1-12, and 1-24)

All-cause medical HCRU will include outpatient physician visits, inpatient hospitalizations, urgent care visits, and emergency department visits. Medications (over-the-counter and

prescription) used for the acute relief and prevention of migraine will also be included. HCRU is reported by patients using the ePRO application on a daily basis and on the HCRU follow-up questionnaire, which is a comprehensive review of patient HCRU obtained by study coordinators during the monthly visits. Since the HCRU follow-up questionnaire contains more comprehensive information (i.e., patient reported HCRU and any that may not have been reported by the patient on the ePRO), the analysis will be based on the HCRU follow-up questionnaire. However, data reported in the ePRO and follow-up questionnaire will be compared to assess for inconsistencies. Missing values will not be imputed.

18.6.1 Medical HCRU

Medical HCRU will be ascertained based on the HCRU follow-up questionnaire. Reported counts of HCRU will be summed across weeks 1-4, 1-12, and 1-24 based on the date of reported healthcare utilization.

Reported HCRU will be stratified as outpatient (physician office visit, outpatient service use, outpatient surgery), urgent care visit, emergency room visit, and inpatient service.

18.6.2 Medication HCRU

Migraine medication HCRU (over-the-counter and prescription) will be ascertained based on the patient's reported medication use during the monthly follow-up visits in which the study coordinator reviews all reported medication use in addition to any unreported utilization. Reported counts of medications will be summed across weeks 1-4, 1-12, and 1-24 based on the reported start and discontinuation dates of the medication.

Medications will be classified as acute, or preventive stratified by drug class:

- Acute
    - Oral anti-CGRP
    - Triptans
    - Analgesics (opioids, non-narcotic, anti-inflammatory)
    - Barbiturate hypnotics
    - Ergots
    - 5-HT agonist
    - Isometheptene
    - Antiemetics
- Preventive
    - Anticonvulsants
    - Serotonin-norepinephrine reuptake inhibitor
    - Selective serotonin reuptake inhibitors
    - Tricyclic antidepressants
    - Antihistamines
    - Antihypertensives (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, alpha agonists, calcium channel blockers)

- NMDA antagonists
- Monoamine oxidase inhibitors

18.7 HIT-6 (week 4, 12, and 24)

The HIT-6 (v1.0) is a Likert-type, self-reporting questionnaire designed to assess the impact of an occurring headache and its effect on the ability to function normally in daily life.[4] The HIT-6 contains 6 questions, each item is rated from "never" to "always" with the following response scores: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13. The total score for the HIT-6 will be sum of each item score which ranges from 36 to 78.[5] The life impact derived from the total score is described as followed: Severe (≥60), Substantial (56-59), Some (50-55), Little to None (≤49).

The HIT-6 will be reported monthly and missing values will be imputed using multiple imputation methods based on the amount and pattern of missing data.

18.8 MIDAS (weeks 12 and 24)

The MIDAS Questionnaire was developed to assess headache-related disability.[6] It is a 5-item instrument which assigns a disability score to patients based on the number of days in the past 3 months that patients report activity limitations due to migraine. The MIDAS score will be the sum of days reported from questions 1 through 5.[7]

The MIDAS score may be categorized according to the following:[7]

Score	Grade	Disability
0-5	I	Little or no disability
6-10	II	Mild disability
11-20	III	Moderate disability
≥21	IV	Severe disability

The MIDAS will be reported quarterly (weeks 12 and 24), and missing values will be imputed using multiple imputation methods based on the amount and pattern of missing data.

18.9 Drug Switching

Drug switching will be based on monthly follow-up visits. In the case in which follow-up data is missing and it is unknown whether the patient received their treatment or switched, we will assume that the patient is still receiving their index therapy.

18.10 TSQM (week 24)

The TSQM (version 1.4) measures the satisfaction of patients with their treatment with respect to side effects, effectiveness, convenience, and global satisfaction.[8] The TSQM score ranges from 0 to 100 with high scores indicating greater satisfaction for each domain. Scores will for each domain will be calculated according to the following:

Effectiveness: ([(Item 1 + Item 2 + Item 3) − 3] divided by 18) × 100 If one item is missing: ([(Sum of Item 1? + Item 2? + Item 3?)) − 2] divided by (12) × 100

Side effects: ([Sum of Item 5 to Item 8) − 4] divided by 16) × 100 If one item is missing: ([(Sum of Item 5? to Item 8?)) − 3] divided by 12) × 100

Convenience: ([Sum of Item 9 to Item 11) − 3] divided by 18) × 100 If one item is missing: ([(Sum of Item9? to Item11?)) − 2] divided by (12) × 100

Overall satisfaction, first recode Item14_recode = (Item14 − 1) × 5/6 , then: ([Sum of Item 12 to Item 14) − 3] divided by (12) × 100 If any one Item is missing: ([Sum of Item 12? to Item 14?) − 2] divided by (8) × 100

The TSQM will be reported at week 24, and missing values will not be imputed.

18.11 SDMQ-9 (screening and week 24)

The SDM-Q-9 measures the extent to which patients are involved in the process of decision-making from the perspective of the patient.[9] The questionnaire contains nine items, each describing one step of the SDM process. It was developed to assess the degree to which patients feel involved in the decision-making process. The items are scored from 0 to 5 on a six-point Likert scale ranging from ″completely disagree″ (0) to ″completely agree″ (5).[10] Scores will be summed across the 9 items to calculate the raw total score ranging from 0 to 45 with higher scores indicating higher shared decision making.

The SDMQ-9 will be reported at screening and week 24, and missing values will not be imputed.

18.12 SURE (screening)

The SURE test is a brief 4-item screening questionnaire the patient uses to assess their readiness and capacity to decide or to determine whether they are comfortable with their decision.[11] An answer of “yes” to an item yields a value of 1 and an answer of “no” yields a value of 0. Item values are summed to calculate the total score. A score of 4 indicates that a patient should not be experiencing a clinically significant decisional conflict, whereas a value of <4 indicates the presence of a clinically significant decisional conflict.

The SURE score will be reported at screening, and missing values will not be imputed.

18.13 PAM-10 (screening, week 12 and 24)

The Patient Activation Measure evaluates the knowledge, skills, and confidence a patient has in managing his or her health conditions.[12] In this study the 10-item Patient Activation Measure (PAM) tool will be utilized. PAM-10 uses a four-point Likert scale of agreement-disagreement to respond to each item. PAM is scored on a scale from 0 to 100 from which four levels of activation have been identified: Level 1 (0.0–47.0) low activation suggesting

that the person does not yet understand their role in healthcare to Level 4 (72.5–100) indicating that the person is proactive and engaged in recommended health behaviors and management of health conditions.[13] Scores will be calculated based on item responses using a propriety algorithm.

The PAM-10 score will be reported at screening, week 12, and week 24, and missing values will not be imputed.

18.14 PSS

The Perceived Stress Scale (PSS) is a classic stress assessment instrument. The tool, measures how different situations affect feelings and perceived stress. The questions ask about feelings and thoughts during the last month.[14] The 10 items use a 5-point Likert scale ranging from 0 (never) to 4 (very often). Item scores are summed to arrive at a total score ranging from 0 to 40, with higher scores indicating greater perceived stress.

The PSS will be reported monthly, and missing values will be imputed using multiple imputation based on the amount and pattern of missing data.

18.15 ISS (screening, week 12 and 24)

All participants receiving eptinezumab (regardless of initial treatment assignment) will complete an eptinezumab-specific survey describing their satisfaction with the infusion experience after each infusion while on site using a paper questionnaire.

The ISS item responses will be reported at screening, week 12, and week 24, and missing values will not be imputed.

18.15.1 Weekly Migraine Days

For a 1-week period in which the eDiary is accessed (i.e., the patient reported the presence or absence of a headache) on at least 4 of the 7 days, the weekly number of migraine days will be prorated as follows:

7 eDiary Days(Reported Migraine Days/Reported eDiary Days)*

For a 1-week period in which the eDiary is accessed on less than 4 of the 7 days, then we will assume that the missing days are migraine days. The rationale is that patients will not fill out the eDiary while having a migraine, therefore, we assume that the missing days are migraine days. If the patient accesses the eDiary and does not report a headache, then we will assume that the patient did not have a migraine on that day.

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Appendix I
Covariate Definitions

Covariate Definitions

Table 1 Covariate Definitions

Variable	Time of measurement	Measurement	Definition
Treatment Group			
Randomized group	Screening visit	Categorical	- Eptinezumab - OnabotulinumtoxinA - Self-injectible anti-CGRP o Erenumab o Fremanezumab o galcanezumab
Eptinezumab dose			- 100 mg - 200 mg - 300 mg
Aimovig dose	Screening visit	Categorical	- 70 mg - 140 mg
Ajovy Dose	Screening visit	Categorical	- 225 mg - 675 mg
Emgality loading dose			- Yes - No
Demographics			
Age	Screening visit	Continuous	Age of patient at time of enrolment
Sex	Screening visit	Categorical	- Female - Male
Marital Status	Screening visit	Categorical	- Married, - Divorced/separated/widow/widower - Single - Not reported
Race	Screening visit	Categorical	- White - Asian - Black/African American - Native Hawaiian or Other Pacific Islander - American Indian or Alaska Native - Other or Unknown
Ethnicity	Screening visit	Categorical	- Hispanic or Latino - Not Hispanic or Latino - Unknown
Education	Screening visit	Categorical	- Did not complete high school - Highschool diploma or GED - Some college or certificate - College or university degree (2 year or 4 year)

Variable	Time of measurement	Measurement	Definition
			- Masters, doctorate, or other advanced professional degree - Not reported
Employment status	Screening visit	Categorical	- Full time employment - Not reported or Other - Homemaker - Part-time employment - Retired - Student - Unemployed - Volunteer - Disabled
Clinical Characteristics			
eDiary compliance	Screening visit to baseline visit		- A response to the question "In the last 24 hours did you have a headache?"
Age at onset of first migraine	Screening visit	Categorical	- 18-33 - 34-48 - 49-64 - >64 - Unknown
Migraine classification	Screening visit	Categorical	- Chronic - Episodic - Medication overuse headache
MHDs in the past 3 months	Screening visit	Categorical	(How many headache days did the patient have… [IN THE LAST MONTH] + How many headache days did the patient have… [IN THE MONTH BEFORE LAST] + How many headache days did the patient have… [TWO MONTHS BEFORE LAST])/3 months
MMDs in the past 3 months	Screening visit	Discrete	(How many migraine days did the patient have… [IN THE LAST MONTH] + How many migraine days did the patient have… [IN THE MONTH BEFORE LAST] + How many migraine days did the patient have… [TWO MONTHS BEFORE LAST])/3 months
Family history of migraine	Screening visit	Categorical	- Yes - No - Unknown
1st preventive oral drug failure	Screening visit	Categorical	- Yes (if the patient does not respond with "none") - No (if the patient responds with "none")

Variable	Time of measurement	Measurement	Definition
2nd preventive oral drug failure	Screening visit	Categorical	- Yes (if the patient does not respond with "none") - No (if the patient responds with "none")
Migraine symptoms experienced in the last 7 days (patients may respond with more than one answer)	Screening visit	Categorical	- Headpain that worsens with any movement or physical activity - Throbbing head pain - Nausea - Vomiting - Phonophobia - Photophobia - Difficulty concentrating or thinking clearly - Visual aura - Other aura - Other
1st preventive oral drug failure class	Screening visit	Categorical	- Advanced preventive o Aimovig o Ajovy o Emgality o onabotulinumtoxinA o Vyepti - Antihypertensive o Atenolol o Bisoprolol o Candesartan o Lisinopril o Metoprolol o Nadolol o Nebivolol o Pindolol o Propranolol o Timolol o Verapamil - Antidepressant o Amitriptyline o Desipramine o Desvenlafaxine o Doxepin o Duloxetine o Milnacipran o Nortriptyline o Protriptyline o Venlafaxine - Antihistamine

Variable	Time of measurement	Measurement	Definition
			○ Cyproheptadine ○ Flunarizine - Anticonvulsant ○ Divalproex sodium ○ Gabapentin ○ Pregabalin ○ Sodium valproate ○ Topiramate ○ Zonisamide - Other ○ Memantine ○ "other" - None
2nd preventive oral drug failure class	Screening visit	Categorical	Same as above
Acute medication use	Screening visit	Categorical	- Opioid analgesics (alone and in combination) - Non-narcotic analgesics (acetaminophen, aspirin, caffeine, alone or in combination) - Anti-inflammatory analgesics (NSAIDs) - Barbiturate hypnotics - 5-HT agonists - Oral anti-CGRPs (Rimegepant, ubrogepant) - Isometheptene containing products - Antiemetics (chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine)
All current medications	Screening visit	Categorical	- TBD
Medical history (psychiatric, cardiac, and etc)	Screening visit	Categorical	- TBD
Smoking history	Screening visit	Categorical	- Never - Current - Former
Smokeless tobacco history	Screening visit	Categorical	- Never - Current - Former
Vaping history	Screening visit	Categorical	- Never - Current - Former
Body mass index	Screening visit	Continuous	- Calculated as BMI = weight (kg) ÷ height^2 (meters)
Perceived stress scale	Baseline visit	Categorical	The total score will be defined as the sum of scores across all questions.

Variable	Time of measurement	Measurement	Definition
			Total score will be categorized as (PSS Calculator): - Low stress = 0-13 - Moderate stress = 14-26 - High stress = 27-40